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Evidence-based guidelines

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Pan American League of Associations for Rheumatology recommendations for the management of axial spondyloarthritis

In the format provided by the authors and unedited

Pan American League of Associations for Rheumatology recommendations for the management of axial spondyloarthritis: SUPPLEMENTARY INFORMATION

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B. METHODS

The entire methodological process was performed to develop recommendations in axial and peripheral spondyloarthritis, which ultimately concluded in two guideline documents: 1) *Clinical practice guideline for the treatment of patients with Axial Spondyloarthritis* and 2) *Clinical practice guideline for the treatment of patients with Psoriatic Arthritis* (see the guideline in the corresponding document).

Parts of this document correspond to material adapted from the source guideline *"The American College of Rheumatology / Spondylitis Association of America / Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis"*[1].

Update of this CPG

This clinical practice guideline (CPG) will be reviewed in 3 years' time as of its publication date to evaluate the need for an update, or before that if the current scientific evidence or clinical practice require an amendment of its content. The update process must be conducted by a team of experts (thematic and methodological) through a process involving a selection of topics and the update of bibliographic searches based on the strategies used in this CPG and using GRADE (Grading of Recommendations Assessment, Development and Evaluation) methodology. The implementation and patient perspective aspects must be evaluated according to the healthcare scenario in the region at the time of the update.

Management of conflicts of interest

The disclaimers of the participants involved in the development of this guideline have been declared according to the instructions of the journal.

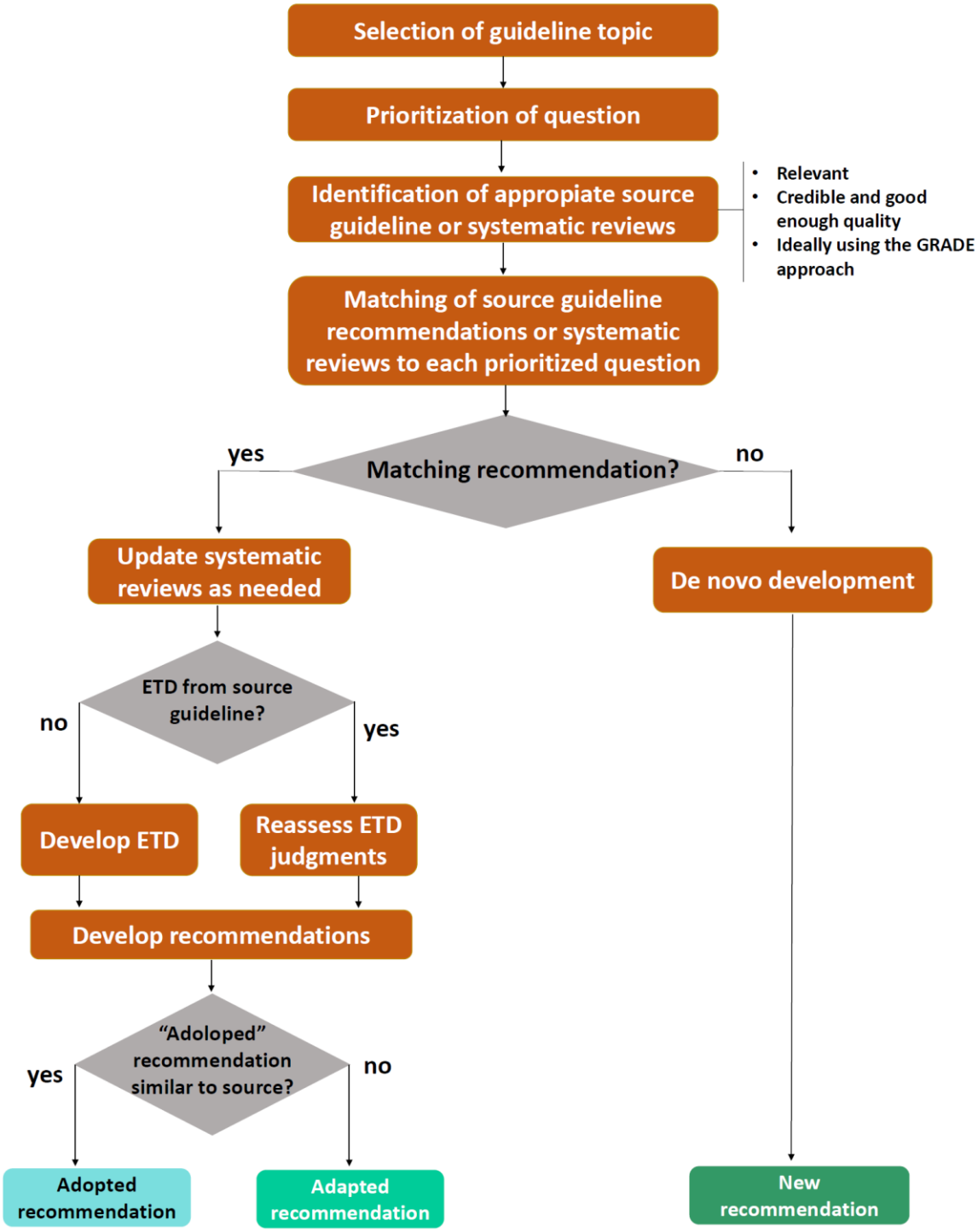
The conflicts of interest of all of the participants were managed in accordance with PANLAR's policies. The methodological team reviewed the statements and issued judgements of conditional participation in relation to any relevant participation of any of the panel members in the pharmaceutical industry. Academic training event funding was permitted.

Two experts from the voting panel (AGS and CFP) disclosed their participation in studies with biological medication in rheumatology and were therefore excluded from the voting session on the subject of biologics. No other panel member disclosed any interests regarded as conflicting for the purposes of this guideline.

Methodological framework

The methodological team performed the corresponding processes according to the GRADE ADOLOPMENT methodology (see Supplementary Figure 1), harmonising coincident questions and recommendations, updating searches based on the strategies reported by the source guideline, and updating the decision-making frameworks based on the discussion sessions held by the experts of the development group. The data from the original guidelines and additional supporting information were summarised by the methodological team using the GRADEpro guideline development tool (www.gradepro.org, McMaster University and Evidence Prime, Inc., Krakow, Poland).

Supplementary Figure 1: Methodological framework



Supplementary Figure 1 reproduced from Schunemann, H.J. et al.[2] ETD, Evidence to Decision; GRADE, Grading of Recommendations Assessment, Development and Evaluation.

Selection of the source guideline

Based on the scope established for the clinical practice guideline, and according to the GRADE ADOLOPMENT methodology, a systematic and exhaustive search was performed in clinical guidelines, using documents available as full-text publications in English and Spanish language press or grey literature between 2015 and 2020.

Documents of previous versions of a guideline already included were excluded, as were guidelines produced through the adaptation or adoption of other CPG and documents corresponding to guidelines dating from years before the search date.

Searches were performed in databases and in guideline compilation sites, namely:

Compiling entities

- Collaboration GIN (Guideline International Network)
- GuiaSalud: www.guiasalud.es

Organisations that produce CPG

- Scottish Intercollegiate Guidelines Network: www.sign.ac.uk
- National Institute for Clinical Excellence: www.nice.org.uk
- Australian National Health and Medical Research Council: https://www.clinicalguidelines.gov.au/§
- Geneva Foundation for Medical Education and Research: www.gfmer.ch§
- World Health Organization (WHO): http://www.who.int/publications/guidelines/en/
- Pan-American Health Organization (PAHO): http://www.paho.org/hq/index.php?option=com_content&view=article&id=1245&Itemid=1497&lang=es
- ICSI Health Care Guidelines: https://www.icsi.org/guidelines__more/§
- Singapore MoH Guidelines Project: https://www.moh.gov.sg/content/moh_web/home/Publications/guidelines.html

In addition, a search was performed for clinical practice guidelines, consensus documents and systematic reviews in electronic databases (Pubmed, Embase, Ovid, Scielo, LILACS), using filters to search for clinical practice guidelines adapted from the strategies proposed by the Capacity Enhancement Program of the University of McMaster, Canada (http://fhs.mcmaster.ca/cep/). Finally, an additional manual search was performed, using an advanced search in Google Scholar.

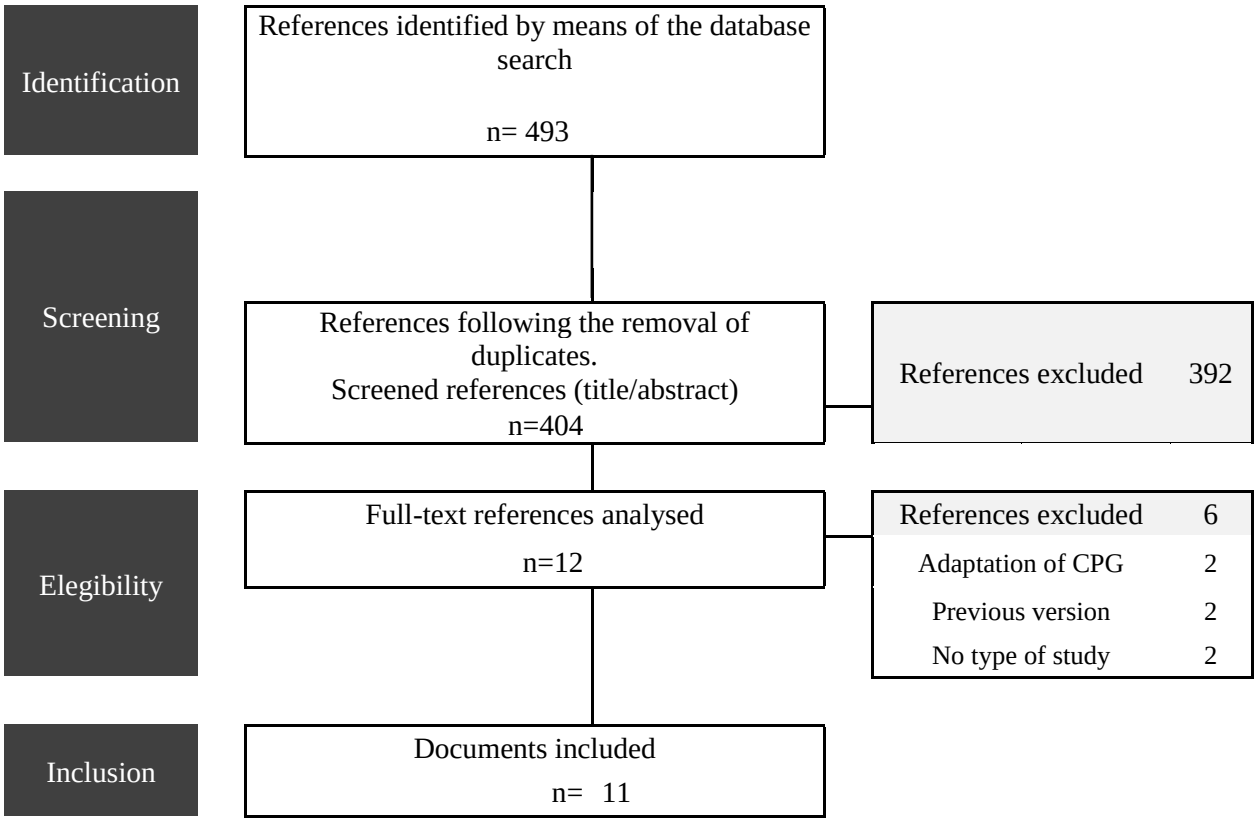
The population considered comprised patients aged 18 years or older with a diagnosis of axial spondyloarthritis (radiographic axial spondyloarthritis and non-radiographic axial spondyloarthritis) and psoriatic arthritis (focusing on arthritis, enthesitis, dactylitis and axial involvement).
A generic search strategy was designed, based on the key terms “spondyloarthritis” and “psoriatic arthritis”. The search strategy was comprised of controlled vocabulary (MeSH, Emtree and DeCS) and free language, taking synonyms, abbreviations, acronyms, spelling variations and plurals into account. Syntax was completed by the expansion of controlled terms, field identifiers, truncations, proximity operators and Boolean operators and was limited by using validated filters (database-specific) for clinical practice guidelines. This strategy was adapted for the different sources of information.

A report was generated for each search, thus guaranteeing reproducibility and transparency. The search strategies and results were stored in electronic format. The search results were recorded in a reference manager. The references were screened by two reviewers (LI, SM) independently, examining the titles and abstracts compared to the predefined eligibility criteria. In the event of any doubt regarding fulfilment

of the eligibility criteria, the entire study text was reviewed in order to inform the decision. Disagreements between peer reviewers were resolved by consensus.

The studies were selected based on the group of preselected references; to this end, one reviewer (SM) checked that the study fulfilled the eligibility criteria (inclusion and non-exclusion) by reviewing the full text of each publication. The adjusted search strategies for each database and a complementary manual search yielded a total of 493 references, reduced to 404 following the removal of duplicates. Following screening by means of review of title and abstract, 17 references were selected for full-text review, and 11 of these documents were chosen for inclusion.

Supplementary Figure 2: Study search and selection flowchart



The members of the development group were asked about other CPG that fulfilled the eligibility criteria described in this protocol.

The quality of the CPG selected was evaluated with the AGREE-II tool independently by two investigators (SM, LI).

Subsequently, CPG evaluated as being high-quality were selected and the other criteria were applied to evaluate the viability of their being used as a source guideline in a GRADE ADOLOPMENT process: published in the last 5 years, GRADE methodology, responds to clear questions, evaluates risks and benefits, rated the evidence according to GRADE, suitable for updating, access to evidence tables and abstracts, has a bias risk assessment. On the basis of these criteria, and according to the judgement of the experts, the *"2019 Update of the American College of Rheumatology/Spondylitis Association of America/Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of*

Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis"[1] was selected as a source guideline for the subject of axial spondyloarthritis.

Before the GRADE ADOLOPMENT process, authorisation was obtained to use content from the selected guideline.

Consensus thresholds

During the sessions held for building the recommendations, a consensus based on discussion was sought. However, in the event of persistent lack of agreement, the options were submitted to an open vote in which the will of the majority of the participants was decisive.

During the voting sessions, in order to measure the degree of agreement of the participants on the panel of experts, a 9-point Likert scale was used, ranging from totally disagree (1) to totally agree (9). A score of 1 to 3 represents a certain degree of disagreement with the recommendation, a score of 4 to 6 denotes an area of uncertainty, and a score of 7 to 9 indicates a certain degree of agreement with the statement in question. Consensus was defined if ≥70% of the voters assigned scores between 1 and 3 (disagree with the recommendation) or between 7 and 9 (agree with the recommendation); if this criterion was not met, a second round of voting was held following a discussion of the reasons for the lack of consensus and fit with the recommendation, with a maximum number of three rounds of voting being permitted.

Interpretation of recommendations

The recommendations made in this CPG may be interpreted according to the following terms:

Term	Definition
High-quality evidence	Studies that provide high confidence in the effect estimate, and new data from future studies are thought unlikely to change the effect.
Moderate-quality evidence	Studies that provide confidence that the true effect is likely to be close to the estimate but could be substantially different.
Low-quality evidence	Studies that provide limited confidence about the effect, and the true effect may be substantially different from the estimate.
Very low-quality evidence	Studies that provide very little certainty about the effect, and the true effect may be quite different from the estimate.
Strong recommendation in favour	Action should be favoured in almost all patients, usually requiring high quality evidence, high confidence that future research will not alter the conclusion, and an assessment that the desirable effects of the intervention outweigh the undesirable effects. Should not be taken to imply that the intervention has large clinical benefits. The strong recommendation is known as "it is recommended".
Strong recommendation against	Action should be favoured in almost all patients, usually requiring high-quality evidence, high confidence that future research will not alter the conclusion, and an assessment that the undesirable effects of the intervention outweigh the desirable effects. The strong recommendation against is known as "it is not recommended".
Conditional recommendation	Action should be followed in only selected cases, often limited by low-quality evidence, or when the desirable and undesirable consequences of an intervention are more balanced, or if patients' preferences for the intervention are thought to vary widely. The conditional recommendation is known as "it is suggested".

C. LITERATURE SEARCH

Parts of this document correspond to material adapted from the source guide *The American College of Rheumatology / Spondylitis Association of America / Spondyloarthritis Research and Treatment Network Recommendations for the Treatment of Ankylosing Spondylitis and Nonradiographic Axial Spondyloarthritis* [1].

1. SEARCHES:

All searches were run in April 2021 and updated to November 2021.

Databases

MEDLINE/PubMed

Web link: https://pubmed.ncbi.nlm.nih.gov/

Search strategy: The search strategy was done in the following databases.

PubMed searches.

Syntax Guide for PubMed	
[MeSH] = Medical Subject Heading	[Text Word] = Includes all words and numbers in the title, abstract, other abstract, MeSH terms, MeSH Subheadings, Publication Types, Substance Names, Personal Name as Subject, Corporate Author, Secondary Source, Comment/Correction Notes, and Other Terms - typically non-MeSH subject terms (keywords)…assigned by an organization other than NLM
[MeSH subheading] = a Medical Subject Heading subheading, e.g. drug therapy	[Title/Abstract] = Includes words in the title and abstracts
mh:noexp = a command to retrieve the results of the Medical Subject Heading specified, but not narrower Medical Subject Heading terms	
Boolean Operators	
OR = retrieves results that include at least one of the search terms	AND = retrieves results that include all the search terms
NOT = excludes the retrieval of terms from the search	

(((((((("SPONDYLARTHRITIS"[MESH:NOEXP] OR SPONDYLARTHRITIS[TIAB] OR SPONDYLOARTHRITIS[TIAB]) OR ("SPONDYLARTHROPATHIES"[MESH:NOEXP]) OR (SPONDYLARTHROPATH*[TIAB] OR SPONDYLOARTHROPATH*[TIAB]) OR ("SPONDYLITIS"[MESH:NOEXP] OR SPONDYLITIS[TIAB]) OR ("SPONDYLITIS, ANKYLOSING"[MESH] OR ANKYLOSING SPONDYL*[TIAB]) OR (BECHTEREW DISEASE*[TIAB] OR BECHTEREW'S DISEASE*[TIAB] OR BECHTEREW S DISEASE*[TIAB] OR MARIE STRUMPELL DISEASE*[TIAB] OR MARIE STRUMPELL DISEASE*[TIAB]) OR (AXIAL JOINT DISEASE*[TIAB] OR ENTHESITIS[TIAB]) OR ("SACROILIITIS"[MESH] OR SACROILITIS[TIAB] OR SACROILIITIS[TIAB] OR SACROILEITIS[TIAB]) OR (PERIPHERAL ARTHRITIS[TIAB]) AND (ENGLISH[LANG]))

NOT ("ANIMALS"[MESH] NOT ("ANIMALS"[MESH] AND "HUMANS"[MESH]))) NOT ((((("ADOLESCENT"[MESH]) OR "CHILD"[MESH]) OR "INFANT"[MESH]) NOT ((((("ADOLESCENT"[MESH]) OR "CHILD"[MESH]) OR "INFANT"[MESH]) AND ("ADULT"[MESH])))) NOT (EDITORIAL*[PT] OR LETTER*[PT] OR COMMENT*[PT]) AND (("2014/07/09"[PDAT] : "2017/09/09"[PDAT]))) AND ((PROCTOCOLITIS[TIAB]) OR ("COLITIS"[MESH] OR COLITIS[TIAB] OR INTESTINAL INFLAMMAT*[TIAB] OR BOWEL INFLAMMAT*[TIAB] OR IRRITABLE BOWEL*[TIAB]) OR ((IBD[TIAB]) OR (IRITIS[TIAB] OR IRIDOCYCLITIS[TIAB]) OR ("UVEITIS"[MESH] OR UVEITIS[TIAB] OR UVEITIDES[TIAB]) OR (CROHN'S ENTERITIS[TIAB] OR REGIONAL ENTERITIS[TIAB] OR CROHN'S DISEASE[TIAB] OR CROHNS DISEASE[TIAB] OR GRANULOMATOUS ENTERITIS[TIAB] OR ILEOCOLITIS[TIAB] OR GRANULOMATOUS COLITIS[TIAB] OR TERMINAL ILEITIS[TIAB] OR REGIONAL ILEITIS[TIAB]) OR (IDIOPATHIC PROCTOCOLITIS[TIAB] OR COLITIS GRAVIS[TIAB]) OR ("INFLAMMATORY BOWEL DISEASES"[MESH] OR INFLAMMATORY BOWEL DISEASE*[TIAB] OR ULCERATIVE COLITIS[TW] OR CROHN DISEASE[TW]))) AND ((("USTEKINUMAB"[TW] OR STELARA[TIAB] OR CNTO 1275[TIAB] OR CNTO-1275[TIAB]) OR (ACTEMRA[TIAB] OR ATLIZUMAB[TIAB]) OR (TOCILIZUMAB[TIAB]) OR ("TOCILIZUMAB"[SUPPLEMENTARY CONCEPT]) OR (IDEC-C2B8*[TIAB] OR IDEC C2B8*[TIAB] OR GP2013[TIAB]) OR ("RITUXIMAB"[TW] OR MABTHERA[TIAB] OR RITUXAN[TIAB]) OR (ANAKINRA[TIAB]) OR (BMS-224818[TIAB] OR BMS 224818[TIAB] OR LEA29Y[TIAB] OR NULOJIX[TIAB] OR ORENCIA[TIAB] OR BMS 188667[TIAB] OR BMS-188667[TIAB] OR BMS 188667[TIAB] OR CTLA-4-LG*[TIAB] OR CTLA4-LG*[TIAB] OR CTLA4 LG*[TIAB]) OR ("ABATACEPT"[TW] OR BELATACEPT[TIAB]) OR ("SECUKINUMAB"[SUPPLEMENTARY CONCEPT] OR COSENTYX[TIAB] OR AIN 457[TIAB] OR AIN457[TIAB] OR AIN-457[TIAB])) OR (KINERET[TIAB]) OR (SECUKINUMAB[TIAB]))) OR ((((((("SPONDYLARTHRITIS"[MESH:NOEXP] OR SPONDYLARTHRITIS[TIAB] OR SPONDYLOARTHRITIS[TIAB]) OR ("SPONDYLARTHROPATHIES"[MESH:NOEXP]) OR (SPONDYLARTHROPATH*[TIAB] OR SPONDYLOARTHROPATH*[TIAB]) OR ("SPONDYLITIS"[MESH:NOEXP] OR SPONDYLITIS[TIAB]) OR ("SPONDYLITIS, ANKYLOSING"[MESH] OR ANKYLOSING SPONDYL*[TIAB]) OR (BECHTEREW DISEASE*[TIAB] OR BECHTEREW'S DISEASE*[TIAB] OR BECHTEREW S DISEASE*[TIAB] OR MARIE STRUMPELL DISEASE*[TIAB] OR MARIE STRUMPELL DISEASE*[TIAB]) OR (AXIAL JOINT DISEASE*[TIAB] OR ENTHESITIS[TIAB]) OR ("SACROILIITIS"[MESH] OR SACROILITIS[TIAB] OR SACROILIITIS[TIAB] OR SACROILEITIS[TIAB]) OR (PERIPHERAL ARTHRITIS[TIAB]) AND (ENGLISH[LANG])) NOT ("ANIMALS"[MESH] NOT ("ANIMALS"[MESH] AND "HUMANS"[MESH]))) NOT ((((("ADOLESCENT"[MESH]) OR "CHILD"[MESH]) OR "INFANT"[MESH]) NOT ((((("ADOLESCENT"[MESH]) OR "CHILD"[MESH]) OR "INFANT"[MESH]) AND ("ADULT"[MESH])))) NOT (EDITORIAL*[PT] OR LETTER*[PT] OR "HISTORICAL ARTICLE"[PT] OR COMMENT*[PT]) AND (("2014/07/09"[PDAT] : "2017/09/10"[PDAT]))) AND (((TOFACITINIB[TIAB]) OR ((TOFACITINIB[TIAB]) OR ((("AZATHIOPRINE"[TW] OR AZOTHIOPRINE[TIAB] OR IMUREL[TIAB] OR IMURAN[TIAB] OR IMMURAN[TIAB]) OR ("THALIDOMIDE"[TW] OR THALOMID[TIAB]) OR (N- AND (4-TRIFLUOROMETHYPHENYL) AND -5-METHYLISOXAZOLE-4-CARBOXAMIDE[TIAB] OR HWA 486[TIAB] OR HWA-486[TIAB] OR SU101[TIAB] OR ARAVA[TIAB]) OR ("LEFLUNOMIDE"[SUPPLEMENTARY CONCEPT] OR LEFLUNOMIDE[TIAB]) OR (ANTIRHEUMATIC DRUG*[TIAB] OR ANTI-RHEUMATIC AGENT*[TIAB] OR ANTI RHEUMATIC AGENT*[TIAB] OR ANTI-RHEUMATIC DRUG*[TIAB] OR ANTI RHEUMATIC DRUG*[TIAB] OR DMARD*[TIAB] OR ANTIRHEUMATIC DISEASE-MODIFYING SECOND-LINE DRUG*[TIAB] OR ANTIRHEUMATIC DISEASE MODIFYING SECOND LINE DRUG*[TIAB] OR DISEASE-MODIFYING ANTIRHEUMATIC DRUG*[TIAB] OR DISEASE MODIFYING ANTIRHEUMATIC DRUG*[TIAB]) OR ("ANTIRHEUMATIC AGENTS"[MESH] OR ANTIRHEUMATIC AGENT*[TIAB]) OR ("APREMILAST"[SUPPLEMENTARY CONCEPT] OR APREMILAST[TIAB]) OR (OTEZLA[TIAB] OR CC 10004[TIAB] OR CC-10004[TIAB]) OR (ORAL SMALL MOLECULE*[TIAB]) OR ("TOFACITINIB"[SUPPLEMENTARY CONCEPT] OR TASOCITINIB[TIAB] OR XELJANZ[TIAB] OR CP 690,550[TIAB] OR CP690550[TIAB] OR CP-690550[TIAB] OR CP 690550[TIAB] OR CP-690,550[TIAB])) OR ((JAK INHIBITOR*[TIAB] OR JANUS TYROSINE KINASE INHIBITOR*[TIAB]) OR (JANUS KINASE ANTAGONIST[TIAB] OR JANUS KINASE INHIBITOR*[TIAB] OR JANUS KINASE BLOCKER*[TIAB] OR ANTI-JANUS KINASE*[TIAB]) OR ("JANUS KINASES/ANTAGONISTS AND INHIBITORS"[MESH])))) OR (("CT-P13"[SUPPLEMENTARY CONCEPT] OR CT-P13[TIAB] OR INFLEXTRA[TIAB] OR REMSIMA[TIAB]) OR ((INFLIXIMAB[TW] OR MAB CA2[TIAB] OR MONOCLONAL ANTIBODY CA2[TIAB] OR REMICADE[TIAB] OR

ETANERCEPT*[TW] OR TNF RECEPTOR TYPE II-IGG FUSION PROTEIN*[TIAB] OR TNF RECEPTOR TYPE II IGG FUSION PROTEIN*[TIAB] OR ENBREL[TIAB] OR TNFR-FC FUSION PROTEIN*[TIAB] OR TNFR FC FUSION PROTEIN*[TIAB] OR TNR-001[TIAB] OR TNR 001[TIAB] OR TNT RECEPTOR FUSION PROTEIN*[TIAB] OR ADALIMUMAB*[TW] OR D2E7 ANTIBOD*[TIAB] OR HUMIRA[TIAB] OR "CERTOLIZUMAB PEGOL"[MESH] OR CERTOLIZUMAB[TIAB] OR CIMZIA*[TIAB] OR CDP 870*[TIAB] OR "GOLIMUMAB"[SUPPLEMENTARY CONCEPT] OR GOLIMUMAB[TIAB] OR SIMPONI[TIAB]) OR ((ANTI TUMOR NECROSIS FACTOR AGENT*[TW] OR ANTI TUMOUR NECROSIS FACTOR AGENT*[TW] OR TNF ALPHA INHIBITOR*[TW] OR TNF INHIBITOR*[TW] OR TUMOUR NECROSIS FACTOR ALPHA INHIBITOR*[TW] OR TUMOUR NECROSIS FACTOR INHIBITOR*[TW] OR ANTI-TNF ALPHA AGENT*[TW] OR ANTI TNF ALPHA AGENT*[TW] OR ANTI TNF AGENT*[TW] OR ANTI-TNF AGENT*[TW] OR TUMOR NECROSIS FACTOR INHIBITOR*[TW] OR TUMOR NECROSIS FACTOR ALPHA INHIBITOR*[TW] OR TNF-ALPHA INHIBITOR*[TW] OR CACHECTIN INHIBITOR*[TW] OR TNF BLOCKER*[TW] OR TNF ALPHA BLOCKER*[TW] OR TUMOR NECROSIS FACTOR ALPHA BLOCKER*[TW] OR TUMOUR NECROSIS FACTOR ALPHA BLOCKER*[TW] OR TUMOR NECROSIS FACTOR BLOCKER*[TW] OR TUMOUR NECROSIS FACTOR BLOCKER*[TW]) OR ("TUMOR NECROSIS FACTORS/ANTAGONISTS AND INHIBITORS"[MESH]))))) OR ((((CELEBREX[TIAB] OR CYCLOOXYGENASE-2 INHIBITOR*[TIAB] OR COXIB*[TIAB] OR COX-2 INHIBITOR*[TIAB] OR COX 2 INHIBITOR*[TIAB] OR COX2 INHIBITOR*[TIAB] OR SC 58635[TIAB] OR SC-58635[TIAB]) OR ("CELECOXIB"[MESH] OR CELECOXIB[TIAB])) OR ((ACETYLSALICYLIC ACID[TIAB] OR ACYLPYRIN[TIAB] OR COLFARIT[TIAB] OR ECOTRIN[TIAB] OR ENDOSPRIN[TIAB] OR MAGNECYL[TIAB] OR MICRISTIN[TIAB] OR POLOPIRIN[TIAB] OR POLOPIRYNA[TIAB] OR SOLUPSAN[TIAB] OR ZORPRIN[TIAB] OR ACETYSAL[TIAB]) OR ("ASPIRIN"[MESH] OR ASPIRIN[TIAB])) OR ("DICLOFENAC"[MESH] OR DICLOFENAC[TIAB] OR DICLOPHENAC[TIAB] OR DICROFENAC[TIAB] OR DICLONATE P[TIAB] OR FELORAN[TIAB] OR VOLTAROL[TIAB] OR NOVAPIRINA[TIAB] OR ORTHOFEN[TIAB] OR ORTOFEN[TIAB] OR ORTHOPHEN[TIAB] OR SR-38[TIAB] OR SR 38[TIAB] OR SR38[TIAB] OR VOLTAREN[TIAB] OR GP45,840[TIAB] OR GP45,840[TIAB]) OR ("DIFLUNISAL"[MESH] OR DIFLUNISAL[TIAB] OR DOLOBID[TIAB] OR DOLOBIS[TIAB] OR NU DIFLUNISAL[TIAB] OR MK-647[TIAB] OR MK 647[TIAB] OR MK647[TIAB]) OR ("ETODOLAC"[MESH] OR ETODALAC[TIAB] OR ULTRADOL[TIAB] OR LODINE[TIAB] OR RAMODAR[TIAB]) OR ("FENOPROFEN"[MESH] OR FENOPROFEN[TIAB] OR NALGESIC[TIAB] OR NALFON[TIAB]) OR ("FLURBIPROFEN"[MESH] OR FLURBIPROFEN[TIAB] OR 2-FLUORO-ALPHA-METHYL- AND (1,1'-BIPHENYL) AND -4-ACETIC ACID[TIAB] OR FLUBIPROFEN[TIAB] OR BTS 18322[TIAB] OR E-7869[TIAB] OR E 7869[TIAB] OR FLUGALIN[TIAB] OR FROBEN*[TIAB] OR OCUFEN[TIAB] OR OCUFLUR[TIAB] OR STREFEN[TIAB] OR ANSAID[TIAB]) OR ((ALPHA-METHYL-4- AND (2-METHYLPROPYL) AND BENZENEACETIC ACID[TIAB] OR IBUMETIN[TIAB] OR IP 82[TIAB] OR IP82[TIAB] OR MOTRIN[TIAB] OR NUPRIN[TIAB] OR TRAUMA-DOLGIT GEL[TIAB] OR TRAUMA DOLGIT GEL[TIAB] OR BRUFEN[TIAB]) OR ("IBUPROFEN"[MESH] OR IBUPROFEN[TIAB])) OR ((INDOMETACIN[TIAB] OR AMUNO[TIAB] OR INDOCID[TIAB] OR METINDOL[TIAB] OR INDOMET 140[TIAB] OR OSMOSIN[TIAB] OR INDOCIN[TIAB]) OR ("INDOMETHACIN"[MESH] OR INDOMETHACIN[TIAB])) OR ((MECLOMEN[TIAB] OR MECLOFENAMATE[TIAB]) OR ("MECLOFENAMIC ACID"[MESH] OR MECLOFENAMIC ACID[TIAB])) OR ("MELOXICAM"[SUPPLEMENTARY CONCEPT] OR MELOXICAM[TIAB] OR MILOXICAM[TIAB] OR MOVALIS[TIAB] OR MOBIC[TIAB] OR MOBICOX[TIAB]) OR ((NABUMETON[TIAB] OR BRL 14777[TIAB] OR RELAFEN[TIAB] OR RELIF[TIAB] OR RELIFEX[TIAB] OR 4- AND (6-METHOXY-2-NAPHTHYL) AND -2-BUTANONE[TIAB]) OR ("NABUMETONE"[SUPPLEMENTARY CONCEPT] OR NABUMETONE[TIAB])) OR ((METHOXYPROPIOCIN[TIAB] OR MNPA[TIAB] OR ANAPROX[TIAB] OR NAPROSIN[TIAB] OR NAPROSYN[TIAB] OR PROXEN[TIAB] OR SYNFLEX[TIAB] OR ALEVE[TIAB]) OR ("NAPROXEN"[MESH] OR NAPROXEN[TIAB])) OR ((4,5-DIPHENYL-2-OXAZOLEPROPIONIC ACID[TIAB] OR OXAPROZIN[TIAB] OR WY-21,473[TIAB] OR DAYPRO*[TIAB]) OR ("OXAPROZIN"[SUPPLEMENTARY CONCEPT])) OR ((CP-16171[TIAB] OR CP 16171[TIAB] OR FELDENE[TIAB]) OR ("PIROXICAM"[MESH] OR PIROXICAM[TIAB])) OR (SALSALATE[TIAB]) OR ("SALICYLATES"[MESH] OR SALICYLATE*[TIAB] OR SALICYLIC ACID*[TIAB]) OR ((APO SULIN[TIAB] OR CLINORIL[TIAB] OR ARTHROCINE[TIAB] OR KLINORIL[TIAB] OR CHIBRET[TIAB] OR MK-231[TIAB] OR MK 231[TIAB] OR ACLIN[TIAB] OR COPAL[TIAB]) OR ("SULINDAC"[MESH] OR SULINDAC[TIAB])) OR ((TOLECTIN[TIAB] OR MCN-2559[TIAB] OR MCN 2559[TIAB]) OR ("TOLMETIN"[MESH] OR TOLMETIN[TIAB]))) OR ((NONSTEROIDAL ANTIINFLAMMATORY AGENT*[TIAB]

OR NONSTEROIDAL ANTI-INFLAMMATORY AGENT*[TIAB] OR NONSTEROIDAL ANTI INFLAMMATORY AGENT*[TIAB] OR NSAID*[TIAB] OR NON-STEROIDAL ANTI-INFLAMMATORY AGENT*[TIAB] OR NON STEROIDAL ANTI INFLAMMATORY AGENT*[TIAB] OR ASPIRIN-LIKE AGENT*[TIAB] OR ANTI-INFLAMMATORY ANALGESIC*[TIAB] OR NON-STEROIDAL ANTI-RHEUMATIC AGENT*[TIAB] OR NON-STEROIDAL ANTIRHEUMATIC AGENT*[TIAB]) OR ("ANTI-INFLAMMATORY AGENTS, NON-STEROIDAL"[MESH])))))) OR ((((((("SPONDYLARTHRITIS"[MESH:NOEXP] OR SPONDYLARTHRITIS[TIAB] OR SPONDYLOARTHRITIS[TIAB]) OR ("SPONDYLARTHROPATHIES"[MESH:NOEXP]) OR (SPONDYLARTHROPATH*[TIAB] OR SPONDYLOARTHROPATH*[TIAB]) OR ("SPONDYLITIS"[MESH:NOEXP] OR SPONDYLITIS[TIAB]) OR ("SPONDYLITIS, ANKYLOSING"[MESH] OR ANKYLOSING SPONDYL*[TIAB]) OR (BECHTEREW DISEASE*[TIAB] OR BECHTEREW'S DISEASE*[TIAB] OR BECHTEREW S DISEASE*[TIAB] OR MARIE STRUMPELL DISEASE*[TIAB] OR MARIE STRUMPELL DISEASE*[TIAB]) OR (AXIAL JOINT DISEASE*[TIAB] OR ENTHESITIS[TIAB]) OR ("SACROILIITIS"[MESH] OR SACROILITIS[TIAB] OR SACROILIITIS[TIAB] OR SACROILEITIS[TIAB]) OR (PERIPHERAL ARTHRITIS[TIAB]) AND (ENGLISH[LANG])) NOT ("ANIMALS"[MESH] NOT ("ANIMALS"[MESH] AND "HUMANS"[MESH]))) NOT ((((("ADOLESCENT"[MESH]) OR "CHILD"[MESH]) OR "INFANT"[MESH]) NOT ((((("ADOLESCENT"[MESH]) OR "CHILD"[MESH]) OR "INFANT"[MESH]) AND ("ADULT"[MESH]))))) NOT (EDITORIAL*[PT] OR LETTER*[PT] OR COMMENT*[PT])) AND (((SECUKINUMAB[TIAB]) OR ("SECUKINUMAB"[SUPPLEMENTARY CONCEPT] OR COSENTYX[TIAB] OR AIN 457[TIAB] OR AIN457[TIAB] OR AIN-457[TIAB])) OR (("CT-P13"[SUPPLEMENTARY CONCEPT] OR CT-P13[TIAB] OR INFLEXTRA[TIAB] OR REMSIMA[TIAB]) OR ((INFLIXIMAB[TW] OR MAB CA2[TIAB] OR MONOCLONAL ANTIBODY CA2[TIAB] OR REMICADE[TIAB] OR ETANERCEPT*[TW] OR TNF RECEPTOR TYPE II-IGG FUSION PROTEIN*[TIAB] OR TNF RECEPTOR TYPE II IGG FUSION PROTEIN*[TIAB] OR ENBREL[TIAB] OR TNFR-FC FUSION PROTEIN*[TIAB] OR TNFR FC FUSION PROTEIN*[TIAB] OR TNR-001[TIAB] OR TNR 001[TIAB] OR TNT RECEPTOR FUSION PROTEIN*[TIAB] OR ADALIMUMAB*[TW] OR D2E7 ANTIBOD*[TIAB] OR HUMIRA[TIAB] OR "CERTOLIZUMAB PEGOL"[MESH] OR CERTOLIZUMAB[TIAB] OR CIMZIA*[TIAB] OR CDP 870*[TIAB] OR "GOLIMUMAB"[SUPPLEMENTARY CONCEPT] OR GOLIMUMAB[TIAB] OR SIMPONI[TIAB]) OR ((ANTI TUMOR NECROSIS FACTOR AGENT*[TW] OR ANTI TUMOUR NECROSIS FACTOR AGENT*[TW] OR TNF ALPHA INHIBITOR*[TW] OR TNF INHIBITOR*[TW] OR TUMOUR NECROSIS FACTOR ALPHA INHIBITOR*[TW] OR TUMOUR NECROSIS FACTOR INHIBITOR*[TW] OR ANTI-TNF ALPHA AGENT*[TW] OR ANTI TNF ALPHA AGENT*[TW] OR ANTI TNF AGENT*[TW] OR ANTI-TNF AGENT*[TW] OR TUMOR NECROSIS FACTOR INHIBITOR*[TW] OR TUMOR NECROSIS FACTOR ALPHA INHIBITOR*[TW] OR TNF-ALPHA INHIBITOR*[TW] OR CACHECTIN INHIBITOR*[TW] OR TNF BLOCKER*[TW] OR TNF ALPHA BLOCKER*[TW] OR TUMOR NECROSIS FACTOR ALPHA BLOCKER*[TW] OR TUMOUR NECROSIS FACTOR ALPHA BLOCKER*[TW] OR TUMOR NECROSIS FACTOR BLOCKER*[TW] OR TUMOUR NECROSIS FACTOR BLOCKER*[TW]) OR ("TUMOR NECROSIS FACTORS/ANTAGONISTS AND INHIBITORS"[MESH])))) OR ((("USTEKINUMAB"[TW] OR STELARA[TIAB] OR CNTO 1275[TIAB] OR CNTO-1275[TIAB]) OR (ACTEMRA[TIAB] OR ATLIZUMAB[TIAB]) OR (TOCILIZUMAB[TIAB]) OR ("TOCILIZUMAB"[SUPPLEMENTARY CONCEPT]) OR (IDEC-C2B8*[TIAB] OR IDEC C2B8*[TIAB] OR GP2013[TIAB]) OR ("RITUXIMAB"[TW] OR MABTHERA[TIAB] OR RITUXAN[TIAB]) OR (ANAKINRA[TIAB]) OR (BMS-224818[TIAB] OR BMS 224818[TIAB] OR LEA29Y[TIAB] OR NULOJIX[TIAB] OR ORENCIA[TIAB] OR BMS 188667[TIAB] OR BMS-188667[TIAB] OR BMS 188667[TIAB] OR CTLA-4-LG*[TIAB] OR CTLA4-LG*[TIAB] OR CTLA4 LG*[TIAB]) OR ("ABATACEPT"[TW] OR BELATACEPT[TIAB]) OR ("SECUKINUMAB"[SUPPLEMENTARY CONCEPT] OR COSENTYX[TIAB] OR AIN 457[TIAB] OR AIN457[TIAB] OR AIN-457[TIAB])) OR (KINERET[TIAB]) OR (SECUKINUMAB[TIAB])) OR (("TIGHT CONTROL"[TIAB] OR "INTENSIVE TREATMENT"[TIAB]) OR ((TTT[TIAB] OR T2T[TIAB]) OR (TREAT-TO-TARGET*[TIAB]) OR (THERAPEUTIC TARGET*[TIAB]) OR (ASDAS[TIAB] OR SASDAS[TIAB]) OR (ANKYLOSING SPONDYLITIS DISEASE ACTIVITY SCORE*[TIAB]) OR ("TREAT TO TARGET"))) OR ((("MAGNETIC RESONANCE IMAGING"[MESH] OR NMR IMAGING*[TIAB] OR MR TOMOGRAPH*[TIAB] OR NMR TOMOGRAPH*[TIAB] OR MRI[TIAB] OR MRIS[TIAB] OR ZEUGMATOGRAPH*[TIAB] OR CHEMICAL SHIFT IMAGING*[TIAB] OR FMRI[TIAB] OR FMRIS[TIAB] OR MAGNETIC RESONANCE IMAGING*[TIAB] OR SPIN ECHO IMAGING*[TIAB]) OR (MR IMAGING*[TIAB] OR MAGNETIZATION TRANSFER*[TIAB] OR MAGNETIC RESONANCE TOMOGRAPH*[TIAB] OR NMR IMAGING*[TIAB])) AND (("SPINE"[MESH] OR SPINE*[TIAB] OR

SPINAL[TW] OR VERTEBRAL COLUMN*[TIAB] OR VERTEBRA*[TIAB]) OR ("PELVIS"[MESH] OR PELVIS[TIAB] OR PELVIC[TW])))))) NOT (HISTORICAL ARTICLE[PT])) AND (("CROSS-SECTIONAL STUDIES"[MESH] OR CORSS SECTIONAL[TW] OR CROSS-SECTIONAL[TW]) OR ("PROSPECTIVE STUDIES"[MESH] OR PROSPECTIV*[TIAB]) OR ("LONGITUDINAL STUDIES"[MESH] OR LONGITUDINAL[TIAB] OR RETROSPECTIV*[TW]) OR ("OBSERVATIONAL STUDY"[PUBLICATION TYPE] OR OBSERVATIONAL[TIAB]) OR ("FOLLOW-UP STUDIES"[MESH] OR FOLLOWUP[TIAB] OR FOLLOW-UP[TIAB] OR FOLLOW UP[TIAB]) OR (CASE CONTROL[TW] OR CASE-CONTROL[TW] OR COHORT[TW]) OR ("COHORT STUDIES"[MESH]) OR ("CASE-CONTROL STUDIES"[MESH]) OR ("EPIDEMIOLOGIC STUDIES"[MESH]) OR (RANDOMLY[TIAB] OR TRIAL[TIAB] OR GROUPS[TIAB]) OR (DRUG THERAPY[SH]) OR (PLACEBO*[TIAB]) OR (RANDOMIZED[TIAB] OR RANDOMISED[TIAB]) OR ("CONTROLLED CLINICAL TRIAL"[PUBLICATION TYPE]) OR ("RANDOMIZED CONTROLLED TRIAL"[PUBLICATION TYPE]) OR ("REVIEW LITERATURE AS TOPIC"[MESH]) OR ("REVIEW"[PUBLICATION TYPE] OR REVIEW[TI]) OR ("META-ANALYSIS"[PUBLICATION TYPE] OR META-ANALY*[TIAB] OR METAANAL*[TW]) OR ((SYSTEMATIC REVIEW[TI] OR META-ANALYSIS[PT] OR META-ANALYSIS[TI] OR SYSTEMATIC LITERATURE REVIEW[TI] OR THIS SYSTEMATIC REVIEW[TW] OR POOLING PROJECT[TW] OR (SYSTEMATIC REVIEW[TIAB] AND REVIEW[PT]) OR META SYNTHESIS[TI] OR META-ANALY*[TI] OR INTEGRATIVE REVIEW[TW] OR INTEGRATIVE RESEARCH REVIEW[TW] OR RAPID REVIEW[TW] OR UMBRELLA REVIEW[TW] OR CONSENSUS DEVELOPMENT CONFERENCE[PT] OR PRACTICE GUIDELINE[PT] OR DRUG CLASS REVIEWS[TI] OR COCHRANE DATABASE SYST REV[TA] OR ACP JOURNAL CLUB[TA] OR HEALTH TECHNOL ASSESS[TA] OR EVID REP TECHNOL ASSESS SUMM[TA] OR JBI DATABASE SYSTEM REV IMPLEMENT REP[TA]) OR (CLINICAL GUIDELINE[TW] AND MANAGEMENT[TW]) OR ((EVIDENCE BASED[TI] OR EVIDENCE-BASED MEDICINE[MH] OR BEST PRACTICE*[TI] OR EVIDENCE SYNTHESIS[TIAB]) AND (REVIEW[PT] OR DISEASES CATEGORY[MH] OR BEHAVIOR AND BEHAVIOR MECHANISMS[MH] OR THERAPEUTICS[MH] OR EVALUATION STUDIES[PT] OR VALIDATION STUDIES[PT] OR GUIDELINE[PT] OR PMCBOOK)) OR ((SYSTEMATIC[TW] OR SYSTEMATICALLY[TW] OR CRITICAL[TIAB] OR (STUDY SELECTION[TW]) OR (PREDETERMINED[TW] OR INCLUSION[TW] AND CRITERI*[TW]) OR EXCLUSION CRITERI*[TW] OR MAIN OUTCOME MEASURES[TW] OR STANDARD OF CARE[TW] OR STANDARDS OF CARE[TW]) AND (SURVEY[TIAB] OR SURVEYS[TIAB] OR OVERVIEW*[TW] OR REVIEW[TIAB] OR REVIEWS[TIAB] OR SEARCH*[TW] OR HANDSEARCH[TW] OR ANALYSIS[TI] OR CRITIQUE[TIAB] OR APPRAISAL[TW] OR (REDUCTION[TW] AND (RISK[MH] OR RISK[TW]) AND (DEATH OR RECURRENCE))) AND (LITERATURE[TIAB] OR ARTICLES[TIAB] OR PUBLICATIONS[TIAB] OR PUBLICATION[TIAB] OR BIBLIOGRAPHY[TIAB] OR BIBLIOGRAPHIES[TIAB] OR PUBLISHED[TIAB] OR POOLED DATA[TW] OR UNPUBLISHED[TW] OR CITATION[TW] OR CITATIONS[TW] OR DATABASE[TIAB] OR INTERNET[TIAB] OR TEXTBOOKS[TIAB] OR REFERENCES[TW] OR SCALES[TW] OR PAPERS[TW] OR DATASETS[TW] OR TRIALS[TIAB] OR META-ANALY*[TW] OR (CLINICAL[TIAB] AND STUDIES[TIAB]) OR TREATMENT OUTCOME[MH] OR TREATMENT OUTCOME[TW] OR PMCBOOK)) NOT (LETTER[PT] OR NEWSPAPER ARTICLE[PT])))

Filters applied: from 2018 - 2021.

Search results: 1184

EMBASE

Web link:

Syntax Guide for Embase	
/exp	Explode. Includes Embase subject headings and the narrower terms in the hierarchy.
ti,ab	Includes words in the title or abstracts
de	Includes words in Embase subject headings

Boolean Operators	
OR = retrieves results that include at least one of the search terms	AND = retrieves results that include all the search terms
NOT = excludes the retrieval of terms from the search	

No.	Query	Results
#137	#136 AND (**2018**:py OR **2019**:py OR **2020**:py OR **2021**:py)	57,128
#136	#116 AND #135	12,392,170
#135	#117 OR #118 OR #119 OR #120 OR #121 OR #122 OR #123 OR #124 OR #125 OR #126 OR #127 OR #128 OR #129 OR #130 OR #131 OR #132 OR #133 OR #134	611,458
#134	**'cross-sectional study'**/exp OR **'cross-sectional'**:ti,ab OR **'cross sectional'**:ti,ab	1,268,173
#133	**'prospective study'**/exp OR **prospectiv***:ti,ab	1,559,894
#132	**'retrospective study'**/exp OR **retrospectiv***:ti,ab	394,949
#131	**'longitudinal study'**/exp OR **longitudinal**:ti,ab	373,528
#130	**'observational study'**/exp OR **observational**:ti,ab	2,134,983
#129	**'follow up'**/exp OR **followup**:ti,ab OR **'follow-up'**:ti,ab	1,172,979
#128	**'cohort analysis'**/exp OR **cohort**:ti,ab	245,200
#127	**'case control study'**/exp OR **'case control'**:ti,ab	8,022
#126	**'epidemological study'**:ti,ab OR **'epidemiologic study'**:ti,ab	644,278
#125	**'control group'**/exp OR **'control group'**:ti,ab	3,841,307

#124
randomly:ab OR **trial**:ab OR **groups**:ab
859,156
#123
'drug therapy':ti,ab,de
313,938
#122
placebo:ab
893,156
#121
randomized:ab OR **randomised**:ab
1,745,262
#120
'randomized controlled trial'/exp OR **'controlled clinical trial'**/exp OR **'clinical trial'**:ti,ab,de OR **rct**:ti,ab OR **'controlled clinical drug trial'**:ti,ab OR **'controlled clinical comparison'**:ti,ab OR **'controlled clinical experiment'**:ti,ab OR **'controlled clinical study'**:ti,ab OR **'controlled clinical test'**:ti,ab
3,935,935
#119
'review'/exp OR **review**:ti,ab
368,529
#118
'systematic review'/exp OR **'systematic review'**:ti,ab,de OR **'systematic overview'**:ti,ab,de
315,122
#117
'meta analysis'/exp OR **'meta-analysis'**:ti,ab,de OR **'meta analysis'**:ti,ab,de OR **metaanaly***:ti,ab,de
90,208
#116
#52 OR **#115**
89,962
#115
#110 OR **#111** OR **#112** OR **#113** OR **#114**
5,649
#114
#70 AND **#109**
5,645
#113
#70 AND **#97**
9,284
#112
#70 AND **#92**
76,172
#111
#70 AND **#84**
303
#110
#70 AND **#75**
152,508
#109
#104 AND **#108**
994,218

#108
#105 OR **#106** OR **#107**
253,263
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#106
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604,746
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1,540,444
#104
#102 OR **#103**
53,377
#103
'mr imaging':ti,ab
1,538,656
#102
#100 OR **#101**
60,152
#101
fmri:ti,ab
1,536,886
#100
#98 OR **#99**
363,663
#99
'magnetic resonance':ti,ab AND **imaging***:ti,ab,de
1,517,878
#98
'nuclear magnetic resonance imaging'/exp OR **nmri**:ti,ab OR **mri**:ti,ab OR **mris**:ti,ab OR **tomograph***:ti,ab
113,834
#97
#93 OR **#94** OR **#95** OR **#96**
2,249
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42
#93
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#92

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#90
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#89
'abatacept'/exp
9,422
#88
'anakinra'/exp
85,394
#87
'rituximab'/exp
16,232
#86
'tocilizumab'/exp
8,286
#85
'ustekinumab'/exp
864,297
#84
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17,756
#83
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2,435
#82
'apremilast'/exp
831,590
#81
'antirheumatic agent'/exp
12,489
#80
'leflunomide'/exp
29,225
#79
'thalidomide'/exp
98,187
#78
'azathioprine'/exp
6,436
#77
'tofacitinib'/exp OR **'oral small molecule'**:ti,ab
26,021
#76
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4,505
#75

#71 OR **#72** OR **#73** OR **#74**

67

#74

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5

#73

'ain 457':ti,ab

36

#72

cosentyx:ti,ab

4,499

#71

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1,644,488

#70

#68 NOT **#69**

4,243,532

#69

'letter'/exp OR **'editorial'**/exp OR **'case report'**/exp

1,777,800

#68

#66 NOT **#67**

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#67

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1,894,655

#66

64 NOT **#65**

5,600,082

#65

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4,377

#64

#63 AND [embase]/lim NOT [medline]/lim AND (**'article'**/it OR **'article in press'**/it OR **'review'**/it) AND [english]/lim

58,290

#63

#53 OR **#54** OR **#55** OR **#56** OR **#57** OR **#58** OR **#59** OR **#60** OR **#61** OR **#62**

1,869

#62

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6,905

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#60

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#59

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5,758

#58
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24,235
#57
'ankylosing spondylitis':ti,ab
9,480
#56
spondyloarthritis:ti,ab
1,474
#55
spondylarthritis:ti,ab
7,344
#54
'spondyloarthropathy'/de OR **spondyloarthropath***:ti,ab OR **spondylarthropath***:ti,ab
47,232
#53
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269
#52
#50 OR **#51**
51
#51
#18 AND **#37** AND **#49**
267
#50
#18 AND (**#19** OR **#20** OR **#29**)
3,610,662
#49
38 OR **#39** OR **#40** OR **#41** OR **#42** OR **#43** OR **#44** OR **#45** OR **#46** OR **#47** OR **#48**
288
#48
'regional ileitis':ti,ab
647
#47
'terminal ileitis':ti,ab
686
#46
ileocolitis:ti,ab,de
63,017
#45
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'bowel inflammation':ti,ab
64,172
#43
'enteritis':ti,ab,de
30,344
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#41
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182,202
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'antirheumatic agent'/exp
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#25
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29,225

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'thalidomide'/exp
98,187
#23
'azathioprine'/exp
6,436
#22
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#21
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#20
'tumor necrosis factor inhibitor'/exp
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#19
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#18
#16 NOT **#17** AND [9-7-2014]/sd NOT [9-9-2017]/sd
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#15
'juvenile'/exp NOT (**'juvenile'**/exp AND **'adult'**/exp)
4,297
#14
#12 NOT **#13**
5,600,082
#13
'animal'/exp NOT (**'animal'**/exp AND **'human'**/exp)
4,377
#12
#11 AND [embase]/lim NOT [medline]/lim AND (**'article'**/it OR **'article in press'**/it OR **'review'**/it) AND [english]/lim
58,290
#11
#1 OR **#2** OR **#3** OR **#4** OR **#5** OR **#6** OR **#7** OR **#8** OR **#9** OR **#10**
1,869
#10
'peripheral arthritis'/exp OR **'peripheral arthritis'**:ti,ab
6,905
#9
'enthesopathy'/exp OR **enthesopath***:ti,ab OR **enthesitis**:ti,ab
10
#8
'axial joint disease':ti,ab

3
#7
'marie-struempell disease':ti,ab OR **'marie struempell disease'**:ti,ab
5,758
#6
'sacroiliitis'/exp OR **sacroiliitis**:ti,ab OR **sacroilitis**:ti,ab OR **sacroileitis**:ti,ab
24,235
#5
'ankylosing spondylitis':ti,ab
9,480
#4
spondyloarthritis:ti,ab
1,474
#3
spondylarthritis:ti,ab
7,344
#2
'spondyloarthropathy'/de OR **spondyloarthropath***:ti,ab OR **spondylarthropath***:ti,ab
47,232
#1
'spondylitis'/de OR **'ankylosing spondylitis'**/exp OR **'spondylarthritis'**/exp OR **spondylitis**:ti,ab

Resultados: 12,247

Cochrane Library (Including Cochrane Database of Systematic Reviews)

Web link: https://www.cochranelibrary.com/

Syntax Guide for Cochrane (Wiley)	
MeSH descriptor = Medical Subject Heading	ti,ab,kw = Word appears in title, abstract or keyword field of record
near/2 = Terms must be within two words of each other	Next = terms must be adjacent, e.g. bone next density means that the term beginning with bone must be adjacent to the term beginning with density
* = truncation symbol	
Boolean Operators	
OR = retrieves results that include at least one of the search terms	AND = retrieves results that include all the search terms
NOT = excludes the retrieval of terms from the search	

#	Consulta	Resultados 20 Abr 2021
1	Spondylarthritis.sh.	201
2	(spondylarthritis or SPONDYLOARTHRITIS).af.	1,138
3	Spondylarthropathies.sh.	39
4	(SPONDYLARTHROPATH* or SPONDYLOARTHROPATH*).af.	241

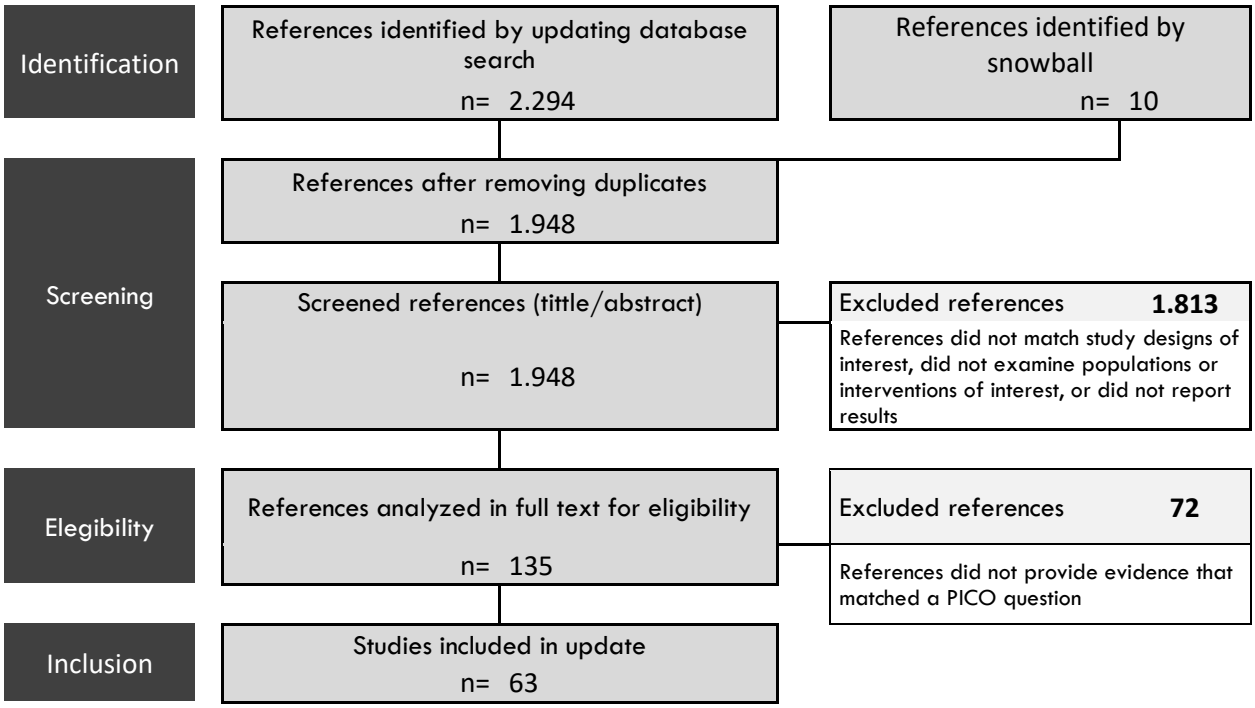
5	Spondylitis.sh.	189
6	SPONDYLITIS.af.	2,564
7	Spondylitis, Ankylosing.sh.	698
8	ANKYLOSING SPONDYLITIS.af.	2,323
9	(BECHTEREW DISEASE or BECHTEREW'S DISEASE or BECHTEREWS DISEASE).af.	8
10	(MARIE-STRUEMPELL DISEASE or MARIE STRUEMPELL DISEASE).af.	0
11	AXIAL JOINT DISEASE.af.	0
12	ENTHESITIS.af.	613
13	Sacroiliitis.sh.	16
14	(SACROILIITIS or SACROILETIS or SACROILEITIS).af.	240
15	PERIPHERAL ARTHRITIS.af.	129
16	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15	3,478
17	Anti-Inflammatory Agents, Non-Steroidal.sh.	6,471
18	nsaid*.af.	7,038
19	celebrex.af.	186
20	Celecoxib.sh.	958
21	(CELECOXIB or ASPIRIN or DICLOFENAC or DIFLUNISAL or ETODALAC or FENOPROFEN or FLURBIPROFEN or IBUPROFEN or INDOMETHACIN or MECLOFENAMIC or MELOXICAM or NABUMETONE or NAPROEN or OXAPROZIN or PIROXICAM or SALICYLATE* or SULINDAC or TOLMETIN).af.	32,641
22	Aspirin.sh.	5,951
23	Diclofenac.sh.	1,931
24	Diflunisal.sh.	100
25	Etodolac.sh.	109
26	Fenoprofen.sh.	36
27	Flurbiprofen.sh.	453
28	Ibuprofen.sh.	2,002
29	Indomethacin.sh.	1,544
30	Meclofenamic Acid.sh.	48
31	Naproxen.sh.	1,146
32	Piroxicam.sh.	657
33	Salicylates.sh.	723
34	Sulindac.sh.	167
35	Tolmetin.sh.	362
36	17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35	39,955
37	(((((((CYCLOOXYGENASE-2 INHIBITOR* or COXIB* or COX-2 INHIBITOR* or COX 2 INHIBITOR* or COX2 INHIBITOR* or SC 58635 or SC-58635 or ACETYLSALICYLIC ACID or ACYLPYRIN or COLFARIT or ECOTRIN or ENDOSPRIN or MAGNECYL or MICRISTIN or POLOPIRIN or POLOPIRYNA or SOLUPSAN or ZORPRIN or ACETYSAL or DICLOPHENAC or DICROFENAC or DICLONATE P or FELORAN or VOLTAROL or NOVAPIRINA or ORTHOFEN or ORTOFEN or ORTHOPHEN or SR-38 or SR 38 or SR38 or VOLTAREN or GP45,840 or GP45,840 or DOLOBID or DOLOBIS or NU DIFLUNISAL or MK-647 or MK 647 or MK647 or ULTRADOL or LODINE or RAMODAR or NALGESIC or NALFON or 2-FLUORO-ALPHA-METHYL-) and 1,1'-BIPHENYL and -4-ACETIC ACID)	9,160

	or FLUBIPROFEN or BTS 18322 or E-7869 or E 7869 or FLUGALIN or FROBEN* or OCUFEN or OCUFLUR or STREFEN or ANSAID or ALPHA-METHYL-4-) and 2-METHYLPROPYL and BENZENEACETIC ACID) or IBUMETIN or IP 82 or IP82 or MOTRIN or NUPRIN or TRAUMA-DOLGIT GEL or TRAUMA DOLGIT GEL or BRUFEN or INDOMETACIN or AMUNO or INDOCID or METINDOL or INDOMET 140 or OSMOSIN or INDOCIN or MECLOMEN or MECLOFENAMATE or "MELOXICAM" or MELOXICAM or MILOXICAM or MOVALIS or MOBIC or MOBICOX or NABUMETON or BRL 14777 or RELAFEN or RELIF or RELIFEX or 4-) and 6-METHOXY-2-NAPHTHYL and -2-BUTANONE) or "NABUMETONE" or NABUMETONE or METHOXYPROPIOCIN or MNPA or ANAPROX or NAPROSIN or NAPROSYN or PROXEN or SYNFLEX or ALEVE or 4,5-DIPHENYL-2-OXAZOLEPROPIONIC ACID or OXAPROZIN or WY-21,473 or DAYPRO* or "OXAPROZIN" or CP-16171 or CP 16171 or FELDENE or SALSALATE or SALICYLIC ACID* or APO SULIN or CLINORIL or ARTHROCINE or KLINORIL or CHIBRET or MK-231 or MK 231 or ACLIN or COPAL or TOLECTIN or MCN-2559 or MCN 2559 or NONSTEROIDAL ANTIINFLAMMATORY AGENT* or NONSTEROIDAL ANTI-INFLAMMATORY AGENT* or NONSTEROIDAL ANTI INFLAMMATORY AGENT* or NSAID* or NON-STEROIDAL ANTI-INFLAMMATORY AGENT* or NON STEROIDAL ANTI INFLAMMATORY AGENT* or ASPIRIN-LIKE AGENT* or ANTI-INFLAMMATORY ANALGESIC* or NON-STEROIDAL ANTI-RHEUMATIC AGENT* or NON-STEROIDAL ANTIRHEUMATIC AGENT*).af.	
38	36 or 37	40,996
39	Tumor Necrosis Factor-alpha.sh.	3,141
40	Adalimumab.sh.	769
41	adalimumab.af.	3,563
42	Certolizumab Pegol.sh.	171
43	certolizumab.af.	729
44	golimumab.af.	799
45	Etanercept.sh.	768
46	etanercept.af.	2,471
47	CT-P13.af.	141
48	(INFLEXTRA or REMSIMA or INFLIXIMAB or MAB CA2 or MONOCLONAL ANTIBODY CA2 or REMICADE or TNF RECEPTOR TYPE II-IGG FUSION PROTEIN* or TNF RECEPTOR TYPE II IGG FUSION PROTEIN* or ENBREL or TNFR-FC FUSION PROTEIN* or TNFR FC FUSION PROTEIN* or TNR-001 or "TNR 001" or TNT RECEPTOR FUSION PROTEIN* or D2E7 ANTIBOD* or HUMIRA or CIMZIA* or CDP 870* or SIMPONI or ANTI TUMOR NECROSIS FACTOR AGENT* or ANTI TUMOUR NECROSIS FACTOR AGENT* or TNF ALPHA INHIBITOR* or TNF INHIBITOR* or TUMOUR NECROSIS FACTOR ALPHA INHIBITOR* or TUMOUR NECROSIS FACTOR INHIBITOR* or ANTI-TNF ALPHA AGENT* or ANTI TNF ALPHA AGENT* or ANTI TNF AGENT* or ANTI-TNF AGENT* or TUMOR NECROSIS FACTOR INHIBITOR* or TUMOR NECROSIS FACTOR ALPHA INHIBITOR* or TNF-ALPHA INHIBITOR* or CACHECTIN INHIBITOR* or TNF BLOCKER* or TNF ALPHA BLOCKER* or TUMOR NECROSIS FACTOR ALPHA BLOCKER* or TUMOUR NECROSIS FACTOR ALPHA BLOCKER* or TUMOR NECROSIS FACTOR BLOCKER* or TUMOUR NECROSIS FACTOR BLOCKER*).af.	5,090
49	39 or 40 or 41 or 42 or 43 or 44 or 45 or 46 or 47 or 48	12,048
50	TOFACITINIB.af.	872
51	Azathioprine.sh.	1,203
52	AZATHIOPRINE.af.	3,503

53	Thalidomide.sh.	871
54	THALIDOMIDE.af.	1,993
55	LEFLUNOMIDE.af.	707
56	Antirheumatic Agents.sh.	2,234
57	ANTIRHEUMATIC AGENT*.af.	2,437
58	APREMILAST.af.	472
59	Janus Kinases.sh.	33
60	(IMUREL or IMURAN or IMMURAN or HWA 486 or HWA-486 or SU101 or ARAVA or ANTIRHEUMATIC DRUG* or ANTI-RHEUMATIC AGENT* or ANTI RHEUMATIC AGENT* or ANTI-RHEUMATIC DRUG* or ANTI RHEUMATIC DRUG* or DMARD* or ANTIRHEUMATIC DISEASE-MODIFYING SECOND-LINE DRUG* or ANTIRHEUMATIC DISEASE MODIFYING SECOND LINE DRUG* or DISEASE-MODIFYING ANTIRHEUMATIC DRUG* or DISEASE MODIFYING ANTIRHEUMATIC DRUG* or OTEZLA or CC 10004 or CC-10004 or ORAL SMALL MOLECULE* or TASOCITINIB or XELJANZ or CP 690,550 or CP690550 or CP-690550 or CP 690550 or CP-690,550 or JAK INHIBITOR* or JANUS TYROSINE KINASE INHIBITOR* or JANUS KINASE ANTAGONIST or JANUS KINASE INHIBITOR* or JANUS KINASE BLOCKER* or ANTI-JANUS KINASE*).af.	5,291
61	50 or 51 or 52 or 53 or 54 or 55 or 56 or 57 or 58 or 59 or 60	12,898
62	38 or 49 or 61	61,664
63	16 and 62	2,098
64	limit 63 to yr="2018 -Current"	539

D. LITERATURE SEARCH FLOW CHART

Supplementary Figure 3: Literature Search Flow Chart



E. CONVERSATIONS WITH PATIENTS

GRADE Methodologist Group
Linda Margarita Ibatá Bernal
Susan Paola Martínez Rojas

Coordination
Dr. Ma. Lorena Brance. Rheumatologist from Argentina - PANLAR Research Unit
Dr. Daniel Fernández. Rheumatologist from Colombia - PANLAR Research Unit
Dr. Wilson Bautista Molano. Colombian rheumatologist. PANLAR Spondyloarthritis Study Group

Patient representatives
Patient 1: María Daniela Martinez Mendoza (México)
Patient 2: Mariellis Portolero (Venezuela)
Patient 3: Juliet Buitrago (Colombia)

Contents

Presentation of attendees

Patient context

Patient 1, Daniela, Mexico, age 33 years old, diagnosed with ankylosing spondylitis (AS) 8 years ago. She does not belong to a patient association.

Patient 2, Mariellis, Venezuela, 36 years old, approximately ten years with the disease. They have a national group for rheumatic patients. She helps patients from the town of Valencia-State of Carabobo.

Patient 3, Juliet, Colombia, 34 years old, spondylitis diagnosed 12 years ago. Director of the Ankylosed Spondylitis Foundation in Colombia.

Introduction to the Clinical Practice Guideline

The objective, scope and development of the CPG are presented. Each topic addressed in the guide is introduced with guiding questions for free conversation in front of patients' perspectives.
Context
Framework of the Clinical Practice Guideline for Axial Spondylarthritis carried out by the Pan American League of Rheumatology Associations (PANLAR).

Objective
Know the perspective of patients, beliefs, expectations, and preferences regarding the medical management of psoriatic arthritis, the impact of interventions and their relationship with health and life goals.

The patient's view

Therapeutic objectives

What objectives would you like to achieve in treatment? What should the doctor consider as criteria when formulating or thinking about a therapy in Axial Spondylarthritis*?*

Patient 1, states that the first thing should be empathy with the patient, who should be involved in a non-superficial way, understanding the feeling "that they understand how we feel so that they can give us a treatment, then the most appropriate". Wait for the doctor's guidance in the treatment according to the progress of the disease, the type of exercises to perform, lead "as normal life as possible".

Patient 2 reaffirms the importance of feedback and the relationship with the doctor. Holistic work of therapies and treatment team. Personalized therapy for each patient "to seek a better quality of life to control the disease".

Patient 3 indicates the need to improve the quality of life, the patient's treatments must be safe, the importance of teamwork, balance of medications, meals and non-therapeutic arrangements.

First line pharmacological management in Axial Spondylarthritis
Have they been formulated with anti-inflammatories, or with glucocorticoids? Have you used these medications? What information would be important for clinicians to share with patients prior to formulating? What do you think of these therapies?

Patient 2, manifests receiving biological therapy and having the disease in good control. However expresses difficulty of access to biologicals because high costs; which made her return to treatment with "sulfasalazine and methotrexate that I didn't like very much and not only that, but they couldn't control the disease". The patient indicates that in her case she currently has private insurance, but she must make collections to be able to pay for it and have access to the drug etanercept. She seeks the other medicines through donation and in turn to help other patients.
She expresses that she has used all the medication (NSAIDs and cDMARD) previously.

Participant 3 was medicated with NSAIDs while doctors studying and confirming the diagnosis of spondylitis. Sulfasalazine was one of her drugs for a few months because "it did not generate any effect, and the pain really progressed". Respect the use of corticosteroids was for a short time, and nowadays they were used in flareups and due to therapeutic failure of the biological medicine. In addition, she highlights the importance of the explanation of side effects by the treating physician.

Patient 1 has not access to social security, and her care has always been with private medicine. She refers to the disadvantage of not being able to pay for biological therapy independently and therefore the lack of knowledge of it "with what I have dealt with the disease has been with sulfasalazine". However she has not seen much improvement. At the beginning she felt that the symptoms were enhanced. Other referred treatments have been with celecoxib and indomethacin, and tramadol for pain. In addition, she refers several periods of flareups without being able to walk and limiting activities of daily living.

Biological drugs

What should doctors take into account before prescribing these drugs? Do you have any preference for the route of administration of these medications? What impact do access barriers have on the disease?

Patient 2 mentions that the first 2 years used adalimumab. Due to continuous pain and inflammation was switched to etanercept (access was facilitated at that time, social security Venezuela). She refers to feeling an important change in relation to stopping the progression of the disease. She did not like the biosimilar from India, so she continues to use etanercept every week and other drugs such as pregabalin and tramadol.

Participant 3 was with adalimumab for 10 years. She highlights the learning "to do a biological therapy, they have to formally do the tuberculosis test, and additionally, do the same as the whole disease filter". After a crisis she has been with infliximab for two years. The change for a biosimilar by the provider generated a new crisis, which forced her to return to the innovative infliximab: "I think it is very good that its application is every eight weeks". She also mentions learning with a pain clinic to manage her treatment and has been starting to into the topic of medical cannabis.

Non-pharmacological complementary therapies

Have they had the possibility of accessing non-pharmacological complementary therapies or what do they know about them?

Participant 1, resorted to physiotherapy when having a crisis and not being able to walk, manifesting the benefits of it. She indicates the understanding of "ankylosing spondylitis as a whole" by having to involve multidisciplinary work and therapies to improve inflammation and pain".

Participant 2, refers to go to rehabilitation, points out the importance of thermal waters, the beach, and massages. In addition, to improve mobility and she also uses TENS. She mentions the fatigue that physical therapy produces every day due to the administrative wear and session authorization, for which the patients prefer to do it at home.

Medical follow-up in Axial Spondylarthritis
What do you consider important regarding the monitoring of the disease? What do you expect from the care you receive in this regard?

Participant 3 attends the rheumatologist every 4 or 5 months for ASDAS and BASDAI monitoring, and highlights the importance of determining the patient's progress or regression and the therapeutic plan. She highlights the importance of tests such as PCR or ESR, to determine "how the body is with respect to the medications we are receiving." She emphasizes that the adverse or secondary effects generated by the treatment must be evaluated.

Other relevant aspects
Are there any limitations to access to MRI or laboratory tests for diagnosis?

Patient 2 expresses the difficulty of access to the rheumatologist. The patients of the group carry out collections to acquire the medicines. He refers to resonance as "unmentionable that is very expensive".

Log out

The session coordinators and rheumatologists express their gratitude to the participating patients for their invaluable life experiences.

F. SUMMARY OF FINDINGS, GRADE.

Strategy to achieve treatment goals in axial spondyloarthritis

A PICO was raised on this topic:

PICO 1.1. In adults with axial spondyloarthritis, is a treat-to-target strategy with a target ASDAS <1.3 (or <2.1) more effective than a symptom-based treatment strategy in improving outcomes?

Summary

This PICO was directly addressed by the TRICOPSA study, a pragmatic, cluster-randomized, open-label, controlled trial comparing a strict control/treat-to-target strategy (visits every 4 weeks and a prespecified strategy based on intensification of treatment until reaching the ASDAS goal <2.1) versus standard care (visits every 12 weeks and treatment at the discretion of the rheumatologist)[3]. At one-year follow-up, there was no significant difference in most efficacy outcomes between the compared groups, including the proportion of patients who achieved ≥30% improvement in ASAS-HI, although response rates between the two groups of treatment differed by 11% in favor of treat-to-target (see evidence summary tables).

An additional clinical trial focused on evaluating the treat-to-target strategy compared to standard of care in axial spondyloarthritis. The STRIKE2 study included 22 subjects at 9 centers in Germany. At week 32, 80% of 5 treat-to-target subjects achieved ASDAS disease inactivity, and the only patient remaining in standard of care did not achieve this primary endpoint[4].

As indirect evidence, an RCT (Breban et al.)[5] compared continuous treatment with infliximab with treatment on demand (when symptoms recur) for patients with spondyloarthritis. For most primary outcomes, the efficacy of continuous infliximab treatment was superior to on-demand treatment. However, we rated the certainty of evidence for all outcomes as 'low', mainly due to limited data from a single study of moderate size (imprecision).

Evidence Profiles

Treat-to-target strategy with strict control compared with usual management, for patients with active spondyloarthritis, 48 weeks (direct evidence1)

Certainty assessment							№ of patients		Effect		Certainly
№ of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Treat-to-target*	Usual management*	Relative (95% CI)	Absolute (95% CI)	
Performance status (follow-up: median 48 weeks; assessed by: Percentage of patients achieving ≥30% improvement on ASAS-HI)											
1	Randomized clinical trial [a]	Serious [a,b]	Not serious	Not serious	Serious[c]	None	34/72 (47.2%)	26/72 (36.1%)	RR 1.3080 (0.8832 - 1.9360)	111 per 1000 (- 42, 338)	⨁⨁◯◯ Low

Disease activity (follow-up: median 48 weeks; assessed by: Percentage of patients achieving low ASDAS disease activity)											
1	Randomized clinical trial [a]	Serious [a,b]	Not serious	Not serious	Serious [c]	None	55/72 (76.4%)	43/72 (59.7%)	RR 1.279 (1.017 - 1.608)	167 per 1000 (10,363)	⊕⊕◯◯ Low
Disease activity (follow-up: median 48 weeks; assessed by: Percentage of patients achieving ASDAS-inactive disease)											
1	Randomized clinical trial [a]	Serious [a,b]	Not serious	Not serious	Serious [c,d]	None	18/72 (25.0%)	13/72 (18.1%)	RR 1.3850 (0.7344-2.6110)	70 per 1000 (48, 291)	⊕⊕◯◯ Low
Disease response (follow-up: median 48 weeks; assessed by: Proportion of patients achieving ASAS20)											
1	Randomized clinical trial [a]	Serious [a,b]	Not serious	Not serious	Serious [c,d]	None	66/72 (91.7%)	61/72 (84.7%)	RR 1.0820 (0.9593 - 1.2200)	69 per 1000 (34,186)	⊕⊕◯◯ Low
Disease response (follow-up: median 48 weeks; assessed by: Proportion of patients achieving ASAS40)											
1	Randomized clinical trial [a]	Serious [a,b]	Not serious	Not serious	Serious [c,d]	None	30/72 (41.7%)	20/72 (27.8%)	RR 0.6667 (0.4200 - 1.0580)	93 less per 1000 (- 161, 16)	⊕⊕◯◯ Low
Disease activity (follow-up: median 48 weeks; assessed by: Percentage of patients improving ≥30% on BASDAI)											
1	Randomized clinical trial [a]	Serious [a,b]	Not serious	Not serious		None	57/72 (79.2%)	31/72 (43.1%)	RR 1.839 (1.375 -2.459)	361 per 1000 (161,628)	⊕⊕◯◯ Low

CI: confidence interval; RR: Risk ratio.

*The Treat-to-target strategy was carried out with strict follow-up, visits were scheduled every 4 weeks and the strategy was pre-specified, according to the current recommendations for the management of axial SpA, with an ASDAS target <2.1. In the usual management group, visits to assess study results were scheduled every 12 weeks, and all treatment decisions, including frequency of follow-up, were left to the discretion of the investigator.

explanations

a. Pragmatic, open-label, cluster-randomized study

b. The control group was a standard of care approach according to the treating rheumatologist

c. Unique studio

d. The confidence interval includes the possibility of no difference

On-demand infliximab treatment compared with continuous treatment, for patients with active spondyloarthritis, 58 weeks (indirect evidence[3])

Certainty assessment						№ of patients		Effect		Certainly
№ of studies-Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	With continuos treatment	On demand	Relative (95% CI)	Absolute (95% CI) Risk difference with on-demand treatment	
ASAS20, week 58										
1RCT	Not serious	Not serious [a]	Serious b	Serious [c]	None	93/124 (75.0%)	56/123 (45.5%)	OR 0.28 (0.16 - 0.48)	293 less per 1000 (-426, - 160)	⊕⊕◯◯ Low
ASAS40, week 58										

1RCT	Not serious	Not serious [a]	Serious [b]	Serious [c]	None	63/124 (50.8%)	37/123 (30.1%)	OR 0.42 (0.25 - 0.70)	206 less per 1000 (-303, -88)	⊕⊕◯◯ Low
Partial remission, 58 weeks										
1RCT	Not serious	Not serious [a]	Serious [b]	Serious [c]	None	34/124 (27.4%)	9/123 (7.3%)	OR 0.21 (0.10 - 0.46)	201 less per 1000 (-238 ,-126)	⊕⊕◯◯ Low
Pain (assessment on a 0-10 scale), 58 weeks										
1RCT	Not serious	Not serious [a]	Serious [b]	Serious [c]	None	124	123	-	DM 1.7 (1.03 ,2.37)	⊕⊕◯◯ Low
Change in PGA patient global assessment (0-10 scale), 58 weeks										
1RCT	Not serious	Not serious [a]	Serious [b]	Serious [c]	None	124	123	-	DM 1.3 (0.64 ,1.96)	⊕⊕◯◯ Low
BASDAI (change), 58 weeks										
1RCT	Not serious	Not serious [a]	Serious [b]	Serious [c]	None	124	123	-	DM 1.2 (0.65 ,1.75)	⊕⊕◯◯ Low
BASFI (change), 58 weeks										
1RCT	Not serious	Not serious [a]	Serious [b]	Serious [c]	None	124	123	-	DM 1.2 (0.66 ,1.74)	⊕⊕◯◯ Low
Death, 58 weeks										
1RCT	Not serious	Not serious [a]	Serious [b]	Serious [e]	None	0/124 (0.0%)	1/123 (0.8%)	OR 3.05 (0.12 - 75.57)	0 per 1000 (0 ,0)	⊕⊕◯◯ Low
Cancer										
1RCT	Not serious	Not serious [a]	Serious [b]	Serious d	None	1/124 (0.8%)	1/123 (0.8%)	OR 1.01 (0.06 - 16.30)	0 per 1000 (-0, 109)	⊕⊕◯◯ Low
Severe infection, 58 weeks										
1RCT	Not serious	Not serious [a]	Serious [b]	Serious [e]	None	3/124 (2.4%)	4/123 (3.3%)	OR 1.36 (0.30 - 6.19)	8 more per 1000 (-17, 109)	⊕⊕◯◯ Low

CI: confidence interval; OR: odds ratio; MD: mean difference
Explanations
a. Does not apply; unique studio.
b. Indirect comparison.
c. Unique study.
d. Unique study. The 95% CI overlaps the line with no difference and single study; very low occurrence rate. 95% CI very wide and overlaps the line with no difference.

Non-steroidal anti-inflammatory drugs - NSAIDs (including COX2) in axial spondyloarthritis

Three PICO questions were asked in this topic:

In adults with axial spondyloarthritis, what is the efficacy and safety of NSAIDs compared to placebo?
In adults with axial spondyloarthritis, are some NSAIDs more effective and safer than other NSAIDs?
In adults with axial spondyloarthritis, is continuous NSAID treatment more effective than on-demand treatment?

PICO 2.1 In adults with axial spondyloarthritis, what is the efficacy and safety of NSAIDs compared to placebo?

Summary

This PICO question was directly addressed by 6 RCTs[6-11]. Regarding the literature review of the source guideline (ACR, 2019), a new RCT was included (Fattahi et al., 2018)[10]. Although all included patients had a diagnosis of axial spondyloarthritis, there were some differences in pain score, PGA, and BASFI at baseline. Treatment duration ranged from 6 to 12 weeks. BRCT use outcomes were variably reported across studies, we did not include more than 2-3 studies for some outcomes. There is sufficient evidence that NSAIDs improve symptoms of axial spondyloarthritis (defined by pain, stiffness, or BASDAI)[7-11]. All efficacy outcomes reported below favored the intervention.

Additionally, a meta-analysis of indirect comparisons (Fan et al., 2020)[12] was identified that concluded, regarding the indirect comparison of each of the NSAIDs with placebo, that all NSAIDs are significantly more effective in reducing the severity of pain in patients with axial spondyloarthritis.

Evidence Profiles

NSAIDs versus placebo

Certainty assessment							Nº of patients		Effect		Certainly
Nº of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	NSAID	Placebo	Relative (95% CI)	Absolute	
Pain (follow-up: 6-12 weeks; assessed by: VAS; 0-100; Lower values are considered better)											
3[6-8]	Randomized clinical trial	Serious[a]	Not serious	Not serious	Serious[b]	None	1106	410	-	MD 17.06 lower (20.76, 13.37)	⊕⊕◯◯ Low

Patients global assessment - PGA (follow-up 6-12 weeks; measured by: VAS 0-100 mm; range of scale: 0-100; Lower values are considered better)											
5[6-10]	Randomized clinical trial	Serious[a]	Serious[f]	Serious[c,d]	Serious[b]	None	1324	530	-	MD 19.5 lower (-23.0, 15.9)	⊕◯◯◯ Very low
BASDAI (follow-up 6-12 weeks; range of score: 0-100; Lower values are considered better)											
3[8-10]	Randomized clinical trial	Serious[a]	Serious	Serious[d]	Not serious	None	802	333	-	MD 19.5 lower (-22.9, 15.9)	⊕⊕◯◯ Low
Performance status: BASFI (follow-up 6-12 weeks; range of score: 0-100; Lower values are considered better)											
4[7-10]	Randomized clinical trial	Serious[a]	Not serious	Serious[d]	Not serious	None	972	409	-	MD 15.04 lower (-16.31, 13.8)	⊕⊕◯◯ Low
Serious adverse event: gastrointestinal bleeding (follow-up 6-52 weeks)											
2	Randomized clinical trial	Serious[g]	Not serious	Not serious	Not serious	None	8/807 (0.99%)	0/277 (0%)	RR 2.86 (0.36, 22.94)	-	⊕⊕⊕◯ Moderate
Serious adverse event: all combined (follow-up 6-52 weeks)											
2	Randomized clinical trial	Not serious	Not serious	Not serious	Not serious	None	5/554 (0.9%)	2/249 (0.8%)	RR 0.86 (0.17, 4.37)	1 less per 1000 (-7, 27)	⊕⊕⊕⊕ High

Explanations
a Benhamou 2010[8] is a post hoc analysis of 2 studies (1 of which was not otherwise included in this PICO due to lack of SD/SE)[1].
b Dougados 1999 and Dougados 2001[6,7] required splitting of the placebo group to assess effect.
c Patient global disease activity is defined differently across studies.
d The main intervention comparison was etoricoxib, but only one arm was compared with naproxen and also with placebo. Therefore, indirect comparison of naproxen vs placebo.
e Required to split the placebo group to assess the effect.
f Measurement methodology not necessarily consistent across studies.
g No prospective endoscopy.

PICO 2.2 In adults with axial spondyloarthritis, are some NSAIDs more effective and safer than other NSAIDs?

Summary

This PICO question was directly addressed by 26 RCTs[6,7,11,13-34]. Regarding the literature review of the ACR guideline, 6 RCTs were identified that included direct comparisons between NSAIDs[6,9,11,32-34]. No new studies of indomethacin were identified. The new studies identified include three of celecoxib compared to naproxen and diclofenac, one of piroxicam versus meloxicam, and two of etoricoxib compared to naproxen that demonstrated the non-inferiority of etoricoxib. The evidence profiles for indomethacin (without changes compared to that presented in the 2019 ACR guideline) and celecoxib (updated with the new studies identified) are shown below. There is no evidence to suggest that indomethacin has different effects on pain or stiffness compared to other NSAIDs, or differences in efficacy between celecoxib, diclofenac, or ketoprofen.

Additionally, a meta-analysis of indirect comparisons was identified (Fan et al., 2020)[12] whose objective was to evaluate the efficacy and safety of NSAIDs in patients with axial spondyloarthritis. A total of 9 randomized controlled trials focused on 6 NSAIDs, including etoricoxib, celecoxib, meloxicam, diclofenac, naproxen, and beta-D-mannuronic acid (M2000), were analyzed in this meta-analysis. The analysis revealed that all NSAIDs were significantly more effective in reducing pain severity than placebo (MD between 17.49 and 25.99). Similarly, significant improvements in PGA, BASFI, and ASAS20 were found in patients receiving NSAIDs. Furthermore, etoricoxib was ranked as the most effective treatment for patients with axial spondyloarthritis. Regarding safety, there were no significant differences between NSAIDs and placebo in terms of total adverse events, withdrawals due to adverse events, or serious adverse events. However, patients treated with diclofenac and naproxen had a higher risk of gastrointestinal events than those taking placebo. In conclusion, NSAIDs were all highly effective and well tolerated in the treatment of axial spondyloarthritis.

Evidence Profiles

Indomethacin versus others NSAIDs

Certainty assessment							Nº of patients		Effect		Certainly
Nº of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Indo methacin	Other NSAID	Relative (95% CI)	Absolute	
Pain (follow-up median, 6 weeks; assessed by: VAS or other; Lower values are considered better)											
8	Randomized clinical trial	Serious[a]	Serious	Not serious	Not serious	None	444	434	-	MD 0.36 lower (-1.06, 0.34)	⊕⊕◯◯ Low
Stiffness (follow-up median, 6 weeks; assessed by: Stiffness duration; Lower values are considered better)											
8	Randomized clinical trial	Serious[a]	Not serious	Not serious	Not serious	None	444	434	-	MD 0.16 lower (-0.56, 0.23)	⊕⊕⊕◯ Moderate
Serious adverse event: all combined (follow-up median, 6 weeks, assessed by: medical report)											
2	Randomized clinical trial	Not serious	Not serious	Not serious	Serious[b]	None	4/121 (3.3%)	7/121 (5.8%)	RR 0.65 (0.14, 3.16)	23 less per 1000 (-47, 48)	⊕⊕⊕◯ Moderate
Any secondary gastrointestinal effect (follow-up median, 6 weeks, assessed by: medical report)											
10	Randomized clinical trial	Not serious	Not serious	Not serious	Serious[b]	None	129/477 (27%)	90/357 (25.2%)	RR 0.95 (0.74, 1.23)	25 less per 1000 (-79, 41)	⊕⊕⊕◯ Moderate

Explanations

[a] Randomization not fully described.

[b] Wide confidence intervals.

Celecoxib versus others NSAIDs

Certainty assessment							Nº of patients		Effect		Certainly
Nº of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Celecoxib	Other NSAID	Relative (95% CI)	Absolute	
BASDAI (follow-up median, 12 weeks; Lower values are considered better)											
3	Randomized clinical trial	Serious[a]	Serious	Not serious	Not serious	None	635	389	-	MD 1.65 higher (-0.54, 3.89)	⊕⊕◯◯ Low
Pain (follow-up median, 12 weeks; assessed by VAS; Lower values are considered better)											
4	Randomized clinical trial	Serious[a]	Serious	Not serious	Not serious	None	715	427	-	MD 0.46 higher (-2.82, 3.74)	⊕⊕◯◯ Low
Performance status: BASFI (follow-up median, 12 weeks; Lower values are considered better)											
4	Randomized clinical trial	Serious[a]	Serious	Not serious	Not serious	None	715	427	-	MD 0.74 higher (-1.5, 3.05)	⊕⊕◯◯ Low
Serious adverse event: myocardial infarction (follow-up median, 12 weeks; assessed by: medical report)											
1	Randomized clinical trial	Not serious	Not serious	Not serious	Serious[b]	None	0/303 (0%)	2/310 (0.6%)	RR 0.34 (0.04, 3.26)	4 less per 1000 (-6, 14)	⊕⊕⊕◯ Moderate
Serious adverse event: all combined (follow-up median, 12 weeks; assessed by: medical report)											
1	Randomized clinical trial	Not serious	Not serious	Not serious	Serious[b]	None	5/303 (1.7%)	4/310 (1.3%)	RR 1.28 (0.34, 4.74)	4 more per 1000 (-8, 46)	⊕⊕⊕◯ Moderate

Any secondary gastrointestinal effect (follow-up median, 12 weeks; assessed by: medical report)											
2	Randomized clinical trial	Not serious	Serious	Not serious	Not serious	None	48/383 (12.5%)	85/400 (21.3%)	RR 0.56 (0.26, 1.18)	87 less per 1000 (-124, -37)	⊕⊕⊕◯ Moderate

Explanations

[a] Randomization was not described.

[b] Wide confidence intervals.

PICO 2.3 In adults with axial spondyloarthritis, is continuous NSAID treatment more effective than on-demand treatment?

Summary

No evidence additional to that reported by the 2019 ACR guideline was identified. This PICO question was directly addressed by 2 RCTs. The first (Wanders, 2015)[35] is an open-label study with a 2-year follow-up that included patients who started celecoxib (100 mg twice daily), and were able to increase the dose to 200 mg twice daily or switch to another NSAIDs while maintaining the same treatment strategy. No significant differences were observed between groups in patient-reported outcomes, with wide confidence intervals and high risk of bias. The change in mSASSS (read by a radiologist in a blinded manner) was less in the continuous treatment group. Hypertension and depression were more common in the continuous treatment group.

The other study is the multicenter randomized trial (ENRADAS) (Sieper, 2016)[36] that compared on-demand treatment with continuous treatment with diclofenac. Continuous treatment consisted of a maximum of 150 mg/day, with at least 50% of this maximum recommended dose taken daily. Switching to a different NSAID for intolerance or inefficacy was allowed, but treatment with TNFi was prohibited. The change in mSASSS from baseline was numerically greater for the continuous group, but not significantly different from the on-demand group. The incidence of adverse events (inflammatory bowel disease, cardiovascular disorders, and significant adverse events overall) was not significantly different between groups.

Evidence Profiles

Treatment with NSAIDs, continuous vs on-demand

Certainty assessment							Conclusions summary				
							Event rates (%)			Expected absolute effects	
Nº of patients (studies)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Overall certainty of evidence	On demand NSAID	Continuous NSAID	Relative effect (95% CI)	Risk with on demand NSAID	Risk difference with continuous NSAID
mSASS (change) ITT, 2 years											
167 (1 RCT) (Sieper)[36]	Not serious	Not serious [a]	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	82	85	-	-	MD 0.58 higher (-0.28, 1.44)
mSASS (change) 2 years (patients with all radiographs)											

272 (2 RCT) (Wanders & Sieper)[35,36]	Not serious	Serious [c]	Not serious	Serious [d]	None	⊕⊕◯◯ Low	134	138	-	-	MD 0.32 lower (-1.88, 1.24)
SAE: Cardiovascular disorders, 2 years											
122 (1 RCT) (Sieper)[36]	Not serious	Not serious	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	2/60 (3.3%)	3/62 (4.8%)	OR 1.47 (0.24, 9.15)	33 per 1000	15 more per 1000 (-25, 207)
SAE: IBD (colitis or Crohn disease), 2 years											
122 (1 RCT) (Sieper)[36]	Not serious	Not serious	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	3/60 (5.0%)	1/62 (1.6%)	OR 0.31 (0.03, 3.08)	50 per 1000	34 less per 1000 (-48, 89)
SAE (total), 2 years											
122 (1 RCT) (Sieper)[36]	Not serious	Not serious	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	21/60 (35.0%)	19/62 (30.6%)	OR 0.82 (0.38, 1.75)	350 per 1000	44 less per 1000 (-180, 135)
BASDAI											
150 (1 RCT)[35]	Serious [e]	Not serious	Not serious	Serious [f]	None	⊕⊕◯◯ Low	74	76	-	-	MD 6 lower (-11.95, -0.05 lower)
Pain											
150 (1 RCT)[35]	Serious [e]	Not serious	Not serious	Serious [b]	None	⊕⊕◯◯ Low	74	76	-	-	MD 6 lower (-12.59, 0.59)
BASFI											
150 (1 RCT)[35]	Serious [e]	Not serious	Not serious	Serious [b]	None	⊕⊕◯◯ Low	74	76	-	-	MD 3 lower (-9.76, 3.76)
Hypertension											
214 (1 RCT)[35]	Not serious	Not serious	Not serious	Serious [g]	None	⊕⊕⊕◯ Moderate	3/103 (2.9%)	10/111 (9.0%)	OR 3.30 (0.88, 12.35)	29 per 1000	61 more per 1000 (-3, 241)
Dyspepsia											
214 (1 RCT)[35]	Not serious	Not serious	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	39/103 (37.9%)	46/111 (41.4%)	OR 1.16 (0.67, 2.01)	379 per 1000	35 more per 1000 (-89, 172 more)
Depression											
214 (1 RCT)[35]	Serious [e]	Not serious	Not serious	Serious [f]	None	⊕⊕◯◯ Low	4/103 (3.9%)	15/111 (13.5%)	OR 3.87 (1.24, 12.07)	39 per 1000	96 more per 1000 (9, 289)

CI: Confidence interval; MD: Mean differences; OR: Odds ratio; RCT: Randomized clinical trial.

Explanations

a. Does not apply; single study.
b. Single study; CI 95% overlaps the line of no difference.
c. 2 studies report different findings for the outcome measure.
d. CI 95% crosses the line of no difference.
e. Unblinded study (patients).
f. Single study; wide CI95%.
g. Single study; low incidence of events. Wide CI 95% overlaps the line of no difference.

Glucocorticoids in axial spondyloarthritis

Two PICO questions were raised in this topic:

In adults with axial spondyloarthritis, what is the efficacy and safety of systemic glucocorticoids compared to placebo?
In adults with axial spondyloarthritis and isolated sacroiliitis despite NSAID treatment, what is the efficacy of treatment with locally administered glucocorticoids?

PICO 3.1 In adults with axial spondyloarthritis, what is the efficacy and safety of systemic glucocorticoids compared to placebo?

Summary

An RSL (Dhir et al., 2021)[37] evaluating the efficacy and safety of systemic glucocorticoids in patients with axial spondyloarthritis was identified that included 14 studies on the use of systemic glucocorticoids in axial spondyloarthritis (364 patients): 9 on glucocorticoid pulses and 5 on continuous treatment with high or low doses of oral glucocorticoids. Regarding glucocorticoid pulses, two RCTs and 7 observational studies were identified[38-46]. In general, adequate responses have been documented with pulses of methylprednisolone lasting from a few weeks to several months.

Regarding studies with continuous treatment with high and low doses of oral glucocorticoids, two RCTs (Haibel 2014, Mishra 2020)[47,48] and two observational studies (Bandinelli 2016, Haroon 2018)[49,50] were identified. The two RCTs compared oral prednisolone with placebo with follow-up from 2 to 24 weeks. A quantitative summary of the efficacy reported in these RCTs was performed and found that BASDAI 50 was achieved in 20–40% of patients and ASAS 20 in 40–60% of patients treated with oral glucocorticoids. Pooling data from the two RCTs comparing high-dose oral prednisolone with placebo in the short term (<6 months) in patients with axial spondyloarthritis, BASDAI 50 was 4.2 times more likely (95% CI 1.5 to 11.5) and ASAS 20 was twice as likely (95% CI 1.1 to 3.64) in patients treated with prednisolone versus placebo. Observational studies reported improvements in axial and peripheral pain at 12 weeks.

In all studies of low- to high-dose oral glucocorticoids, only minor side effects such as fluid retention, cushingoid facies, weight gain, or hyperglycemia were reported. Not serious adverse events were reported.

Evidence Profiles

Oral glucocorticoids versus placebo

Certainty assessment							Conclusions summary			
Nº of patients (studies)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Overall certainty of evidence	Event rates (%)		Relative effect (95% CI)	Expected absolute effects	
							With Placebo	With Glucocorticoids		Risk with Placebo	Risk differences with glucocorticoids

Efficacy; follow-up: mean ≤24 weeks; assessed by: Bath Ankylosing Spondylitis Disease Activity Index (BASDAI 50)											
90 (2 RCT)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕t Moderate	4/46 (8.7%)	16/44 (36.4%)	RR 4.18 (1.51, 11.52)	87 per 1000	277 more per 1000 (44, 915)
Efficacy; follow-up: mean ≤24 weeks; assessed by: ASAS 20											
90 (2 RCT)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ Moderate	11/46 (23.9%)	21/44 (47.7%)	RR 2.00 (1.10, 3.64)	239 per 1000	239 more per 1000 (-24, 631)
Efficacy; follow-up: mean ≤24 weeks; assessed by: ASAS 40											
90 (2 RCT)	Not serious	Not serious	Not serious	Serious[a]	None	⊕⊕⊕◯ Moderate	7/46 (15.2%)	16/44 (36.4%)	RR 2.38 (1.08, 5.24)	152 per 1000	210 more per 1000 (12, 645)
Pain (Follow-up mean 4,5 months; range of scale: 0-100; Lower values are considered better)											
15 (2 observational studies)	Very serious[c]	Not serious	Not serious	Very serious[c]	None	⊕◯◯◯ Very low					MD 34 lower (unable a calculate CI)
Adverse events; follow up: mean ≤24 weeks											
90 (2 RCT)	Serious[a]	Not serious	Not serious	Not serious		⊕⊕⊕⊕ High	Minor secondary adverse events were reported: fluid retention, cushingoid facies, weight gain or hyperglycemia. There were not serious adverse effects.				

CI: Confidence interval; MD: Mean differences; RR: Risk rate; RCT: Randomized clinical trial.

Explanations

a. Wide confidence intervals.

b. Study was not randomized and data collection was retrospective.

c. Case series.

PICO 3.2 In adults with axial spondyloarthritis and isolated sacroiliitis despite NSAID treatment, what is the efficacy of treatment with locally administered glucocorticoids?

Summary

Regarding the application of glucocorticoids in the sacroiliac joint, this PICO was directly addressed by two RCTs (Maugars 1996, Luukkainen 1999)[51,52] with low sample size, poor quality, non-standardised, one unblinded and 2 observational pre/post studies (Gunaydin 2006, Migliore 2009)[53,54] (n = 34 total) with 18 month follow up consistently showing an improvement of approximately 40 mm on a 0-100 mm pain scale with 9 month duration of response. No new RCTs or comparative observational studies were identified. A pre/post observational study was identified (Nam 2020)[55] that included 96 patients with a three-month follow-up, which showed that after the application of glucocorticoids in the sacroiliac joint, a decrease in pain and in the BASDAI index was observed, and an improvement in the ASDAS indices and BASFI.

Additionally, an SR was identified (Dhir 2021)[37] that evaluated the efficacy and safety of intra-articular or local application of glucocorticoids in patients with axial spondyloarthritis that included 7 studies, 2 of intra-articular application (2 RCTs) and 5 of local injections for enthesitis (all observational). Regarding the intra-articular application of glucocorticoids, the two RCTs reported a sustained response for 6 months in 51.5% to 90% of the patients. No major adverse events were

reported, except for some local ones such as skin hypopigmentation. Regarding local steroid injection for enthesitis, tenosynovitis and dactylitis, of the five studies, two were performed in a small number of patients with enthesitis (and bursitis), one in patients with tendinitis and one in patients with tendon inflammation. Achilles. All reported a good response, improvement in pain, sensitivity, and Doppler signal strength at 2 to 6 weeks. One study compared guided GC injections with blind injections and found guided injections to be more effective and less painful.

Evidence Profiles

Sacroiliac joint glucocorticoid injection

Certainty assessment							Nº of patients		Effect		Certainly
Nº of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Local GC for sacroiliits	Control	Relative (95% CI)	Absolute	
Pain (follow-up mean, 1,5 months; range of scale: 0-100; Lower values are considered better)											
2	Randomized clinical trial.	Serious[a]	Not serious	Serious[b]	Serious[c]	None	11	13	-	MD 20 lower (unable a calculate CI)	⊕◯◯◯ Very low
Pain at 9 months (follow-up mean, 18 months; range of scale: 0-100; Lower values are considered better)											
2	Observational studies	Very serious[a]	Not serious	Not serious	Not serious	None	85	-	-	Mean 45 lower (unable a calculate CI)	⊕◯◯◯ Very low

GC= Glucocorticoides; CI: confidence interval.
Explanations.
[a] Small samples; unblinded.
[b] The patients have axial spondyloarthritis, but it is unclear if they meet with mNYCC. Patients with OSAHS were excluded.
[c] The outcome measure is not standardized.

Conventional DMARDs in axial spondyloarthritis

A PICO question was raised on this topic:

PICO 4.1 In adults with axial spondyloarthritis, what is the efficacy and safety of conventional DMARDs compared to placebo?

Summary

This PICO was directly addressed by 13 RCTs, selected from the ACR source guide. The intervention drugs considered for this PICO were: sulfasalazine in 9 trials, methotrexate in 3 trials, leflunomide in 1 trial. Recent evidence selection included a quasi-experimental trial of sulfasalazine and a cohort of combination methotrexate and sulfasalazine.
Eight of the nine trials examining the effect of sulfasalazine (see Evidence Summary Tables[56-65]) were conducted before 1996 and thus before the development of the current composite scores. Outcome measures were diverse, which in many cases precluded data pooling for meta-analysis. In Khanna-Sharma et al[56] the efficacy of sulfasalazine was evaluated in 67 adult patients with spondyloarthritis versus placebo for six months. Sulfasalazine produced a clinically significant improvement in axial symptoms (ASDAS change > 1.1) in 67.7% (mean 1.33 ± 0.38, range: 0.9 to 2.3) and in 15.1% placebo group (mean 0.75 ?0.23, range: 0.4 to 1.3) (p=0.001). Changes in BASDAI and BASMI were also significantly greater for the treatment group. The data also showed that sulfasalazine had a weak beneficial effect on spinal pain, but not on other critical outcomes apart from "ill-defined episodes of joint symptoms (arthritis or periarthritis)" and ad-hoc "composite scores of peripheral joints" (Kirwan 1993; Clegg 1996)[57-58]. The quasi-experimental trial (Venkatesh 2015)[65] included as recent evidence, compared sulfasalazine with combined DMARDs in patients with inflammatory back pain associated with spondyloarthritis, showing no significant differences in ASAS 20 (achieved in 68.4% of study therapy and 50% in the control group, p 0.47), BASDAI (significant decrease in both groups), BASFI (MD 0.30; 1.0-1.6) and VAS (MD 3.80; -9.85 to 17.45).
All three studies comparing methotrexate (see Evidence Summary Tables[66-70]) with placebo used weekly doses of 10 mg or less. There was no benefit over placebo for critical outcomes. A cohort study (Haibel 2007)[66] looked at the efficacy of 20mg weekly in spondyloarthritis and also found no significant benefit, except in peripheral disease. Recently, a cohort study (Ganapati 2021)[70] evaluated the response to combination therapy of conventional synthetic DMARDs with methotrexate and sulfasalazine in patients with active axial spondyloarthritis without peripheral arthritis versus those with peripheral arthritis. No significant differences were found in ASAS20 and BASDAI at 3 months and 6 months (p 0.6).
There was no benefit of leflunomide on any outcome in one study (van Denderen 2005) (see Evidence Summary Tables)[71].
Overall, there is weak evidence for the use of sulfasalazine, and evidence that the other treatments evaluated improve outcomes in spondyloarthritis is lacking. It should also be considered that the number of trials is small, as well as the number of patients included in these studies. In addition, methotrexate was used at a dose considered subtherapeutic for the treatment of rheumatoid arthritis.

Quality of evidence: Low to moderate

Evidence Profiles

Data for sulfasalazine[56-65].

Certainty assessment							Nº of patients		Effect		Certainly
Nº of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Sulfasalazine	Control	Relative (95% CI)	Absolute	
ASDAS (mean change, 6 months)											
1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[3]	None	31	33	-	MD 0.58 higher (0.42, 0.74)	⊕⊕⊕◯ Moderate
BASDAI (mean change, 6 months)											
1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[3]	None	31	33	-	MD 1.82 higher (1.34, 2.3)	⊕⊕⊕◯ Moderate
Axial Pain (follow-up median, 31 weeks; assessed by: VAS; Lower values are considered better)											
6	Randomized clinical trials	Serious[1]	Not serious (1%)	Not serious	Not serious	None	264	262	-	MD 1.84 lower (-3.44, -0.24)	⊕⊕⊕◯ Moderate
Performance status: DFI (follow-up median, 30 weeks; Lower values are considered better)											
2	Randomized clinical trials	Serious[2]	Not serious (0%)	Not serious	Not serious	None	154	157	-	MD 0.21 lower (-1.21, 0.8)	⊕⊕⊕◯ Moderate
Percent of responders, physician assessment (follow-up median, 26 weeks; assessed by: five points scale)											
1	Randomized clinical trial	Serious[2]	Not serious	Not serious	Not serious	None	70/131 (53.4%)	74/133 (55.6%)	OR 0.91 (0.56, 1.49)	23 less per 1000 (-144, 95)	⊕⊕⊕◯ Moderate
Percent of responders, patient assessment (follow-up median, 26 weeks; assessed by: five points scale)											
1	Randomized clinical trials	Serious[2]	Not serious	Not serious	Not serious	None	53/131 (40.5%)	56/133 (42.1%)	OR 0.93 (0.57, 1.53)	18 less per 1000 (-128, 106)	⊕⊕⊕◯ Moderate
Joint paint (follow-up median, 48 weeks; assessed by: VAS; Lower values are considered better)											
1	Randomized clinical trials	Serious[2]	Not serious	Not serious	Not serious	None	32	30	-	MD 0 higher (unable a calculate CI)	⊕⊕⊕◯ Moderate
Dactylitis score (follow-up median, 48 weeks; Lower values are considered better)											
1	Randomized clinical trials	Serious[2]	Not serious	Not serious	Not serious	None	131	133	-	MD 0.1 higher (-0.04, 0.24)	⊕⊕⊕◯ Moderate
Enthesitis score (follow-up median, 48 weeks; Lower values are considered better)											
1	Randomized clinical trials	Serious[2]	Not serious	Not serious	Not serious	None	131	133	-	MD 0.3 higher (-0.94, 1.54)	⊕⊕⊕◯ Moderate

Serious adverse events: all combined (withdrawal from the study) (follow-up median, 36 weeks)											
7	Randomized clinical trials	Serious[1]	Not serious	Not serious	Not serious	None	42/306 (13.7%)	30/309 (9.7%)	OR 1.52 (0.91, 2.55)	43 more per 1000 (-8, 118)	⊕⊕⊕◯ Moderate
Gastrointestinal adverse events (follow-up median, 36 weeks)											
7	Randomized clinical trials	Serious[1]	Serious	Not serious	Not serious	None	18/306 (5.9%)	16/309 (5.2%)	OR 1.52 (0.91, 2.55)	25 more per 1000 (-4, 70)	⊕⊕◯◯ Low

ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; DFI, Dougados functional index; MD, Mean differences.

Explanations

[1] Randomization and blinding are poorly described in several studies.

[2] Randomization poorly described.

[3] Data of single study with small sample size.

[4] Study was not randomized.

Data for methotrexate[66-70]

Certainty assessment							Nº of patients		Effect		Certainly
Nº of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Methotrexate	Control	Relative (95% CI)	Absolute	
BASDAI (follow up median, 24 weeks; Lower values are considered better)											
2	Randomized clinical trials	Not Serious	Serious	Serious[1]	Not Serious	None	29	34	-	MD 0.39 higher (-0.69, 1.47)	⊕⊕◯◯ Low
Pain (follow-up median, 38 weeks; assessed by: VAS; Lower values are considered better)											
2	Randomized clinical trials	Serious[2]	Not Serious	Serious[1]	Not Serious	None	43	43	-	MD 0.76 lower (-2.02, 0.49)	⊕⊕◯◯ Low
Performance status: BASFI (follow-up median, 24 weeks; Lower values are considered better)											
1	Randomized clinical trials	Not Serious	Not Serious	Serious[1]	Not Serious	None	17	18	-	MD 0.3 higher (-1.03, 1.63)	⊕⊕⊕◯ Moderate
HAQ-S (follow-up median, 24 weeks; Lower values are considered better)											
1	Randomized clinical trials	Not Serious	Not Serious	Serious[1]	Not Serious	None	17	18	-	MD 0 higher (-0.3, 0.3)	⊕⊕⊕◯ Moderate
Performance status: DFI (follow-up median, 52 weeks; Lower values are considered better)											
1	Randomized clinical trials	Serious[3,4]	Not Serious	Serious[1]	Not Serious	None	26	25	-	MD 4.41 higher (-0.27, 9.09)	⊕⊕◯◯ Low
Patient global assessment (follow-up median, 38 weeks; assessed by: VAS or five points scale; Lower values are considered better)											
2	Randomized clinical trials	Serious[2]	Not Serious (0%)	Serious[1]	Not Serious	None	43	43	-	MD 0.31 higher (-0.41, 1.02)	⊕⊕◯◯ Low

Physician global assessment (follow-up median, 38 weeks; assessed by: VAS or five points scale; Lower values are considered better)											
2	Randomized clinical trials	Serious[2]	Serious (70%)	Serious[1]	Not Serious	None	43	43	-	MD 4.95 lower (-16.95, 6.60)	⊕◯◯◯ Very low
Enthesitis (follow-up median, 52 weeks; Lower values are considered better)											
1	Randomized clinical trials	Serious[4]	Not Serious	Serious[1]	Not Serious	None	26	25	-	MD 1.27 lower (-4.6, 2.06)	⊕⊕◯◯ Low

BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Function Index; DFI, Dougados functional index; HAQ-S, Health Assessment Questionnaire for the Spondyloarthropaties; MD, Mean differences.

Explanations

[1] Lower dose than that used in clinical practice.

[2] One of the two studies were unblinded.

[3] Randomization was not described.

[4] Study was unblinded.

[5] Study was not randomized.

Data for leflunomide[71]

Certainty assessment							Nº of patients		Effect		Certainly
Nº of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Leflunomide	Control	Relative (95% CI)	Absolute	
BASDAI (follow-up median, 24 weeks; Lower values are considered better)											
1	Randomized clinical trials	Serious[1]	Not serious	Not serious	Not serious	None	30	15	-	MD 0.8 lower (-2, 0.5)	⊕⊕⊕◯ Moderate
Pain (follow-up median, 24 weeks; assessed by: VAS; Lower values are considered better)											
1	Randomized clinical trials	Serious[1]	Not serious	Not serious	Not serious	None	30	15	-	MD 0.9 lower (-2.8, 0.9)	⊕⊕⊕◯ Moderate
Performance status: BASFI (follow-up median, 24 weeks; Lower values are considered better)											
1	Randomized clinical trials	Serious[1]	Not serious	Not serious	Not serious	None	30	15	-	MD 0.4 higher (-0.5, 1.3)	⊕⊕⊕◯ Moderate
ASAS20 (follow-up median, 24 weeks)											
1	Randomized clinical trials	Serious[1]	Not serious	Not serious	Not serious	None	8/30 (26.7%)	3/15 (20%)	OR 1.45 (0.32, 6.53)	66 more per 1000 (-126, 420)	⊕⊕⊕◯ Moderate
Physician global assessment (follow-up median, 24 weeks; assessed by: VAS; Lower values are considered better)											
1	Randomized clinical trials	Serious[1]	Not serious	Not serious	Not serious	None	30	15	-	MD 0.2 higher (-0.8, 1.1)	⊕⊕⊕◯ Moderate
Gastrointestinal adverse events											
1		Serious[1]	Not serious	Not serious	Not serious	None	17/30	5/15		234 more per 1000	⊕⊕⊕◯

	Randomized clinical trials						(56.7%)	(33.3%)	OR 2.62 (0.72, 9.54)	(-69, 493)	Moderate
Adverse events: Deep veins thrombosis (DVT)											
1	Randomized clinical trials	Serious[1]	Not serious	Not serious	Not serious	None	0/30 (0%)	1/15 (6.7%)	OR 0.16 (0.01, 4.13)	55 less per 1000 (-66, 161)	⊕⊕⊕◯ Moderate

ASAS 20, is defined as an improvement of at least 20% of ASAS criteria, BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Function Index; DFI, Dougados functional index; HAQ-S, Health Assessment Questionnaire for the Spondyloarthropaties; MD, mean differences.

Explanations

[1] Randomization was not described.

Treatment with biological agents

A PICO question was posed for this topic:

PICO 5.1 In adults with axial spondyloarthritis, are certain anti-TNFs more effective than other anti-TNFs in improving outcomes?

Summary

This PICO was directly addressed by 2 RCTs and one observational study. The first RCT reports a direct comparison of infliximab and etanercept (Giardina 2009)[72], the second the comparison between etanercept and adalimumab (Wei 2020)[73]. The observational study (Ruwaard 2017)[74] reports the effectiveness results of etanercept versus adalimumab in clinical practice.

Although direct evidence for head-to-head comparisons is scant, numerous indirect comparisons can be made using the results of more than 20 RCTs of anti-TNFi versus placebo. After the updated literature search, a systematic review of network meta-analysis was identified (Migliore 2021)[75] whose results are reported below.

Direct comparisons

The open-label RCT of infliximab versus etanercept at 2 years (Giardina 2009)[72] included 50 patients with active axial spondyloarthritis; no statistically significant differences between groups were reported at 2 years for ASAS 20/40, BASDAI, or BASFI, although patients showed significant improvements with infliximab at 12 weeks over baseline for these outcomes. The second RCT providing direct evidence to this PICO question is an open RCT (Wei 2020)[73] comparing adalimumab versus etanercept and included 19 patients. At week 8, no significant differences were observed in ASDAS or ASAS 20/40. Both treatments were well tolerated, with Not seriousus adverse events.

The observational study (Ruwaard 2017)[74] compared drug survival and clinical response of etanercept versus adalimumab with a 2-year follow-up. 245 patients were included (163 with etanercept and 82 with adalimumab), 32.9% treated with adalimumab and 18.4% with etanercept discontinued treatment (HR 2.1; 95% CI 1.3–4.5, p = 0.005); however, selection bias cannot be excluded. No significant differences were observed at 2-year follow-up between patients treated with adalimumab and etanercept in mean ASDAScrp.

Indirect comparisons

Multiple network meta-analyses have been performed to compare the efficacy of different anti-TNFs in axial spondyloarthritis. A systematic review of the network meta-analysis literature (Migliore 2021)[75] that identified seven studies reports that infliximab is the drug most likely to achieve clinical efficacy by ASAS20 at 12 and 24 weeks. Considering only subcutaneous biologics, golimumab achieved the highest probability of achieving the ASAS20 response at 12 weeks. However, this evidence is insufficient, especially when other outcomes and long-term treatment are not taken into account. Therefore, a more exhaustive analysis and more complex evaluation systems are needed. A summary table of all the meta-analyses included in this literature review is attached below.

Evidence Profiles

Direct comparison between infliximab and etanercept

Certainty assessment							Nº of patients		Effect		Certainly
Nº of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Infliximab	Etanercept	Relative (95% CI)	Absolute	
BASDAI (follow-up mean, 104 weeks, Lower values are considered better)											
1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[a,b]	None	25	25	-	Mean o higher (unable a calculate CI) [a]	⊕⊕⊕◯ Moderate
Performance status: BASFI (follow-up mean, 104 weeks, Lower values are considered better)											
1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[b]	None	25	25	-	MD o higher (unable a calculate CI) [a]	⊕⊕⊕◯ Moderate

[a] Intervals does not report confidence.
[b] Small sample size.

Direct comparison between adalimumab and etanercept

Certainty assessment							Nº of patients		Effect		Certainly
Nº of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Etanercept	Adalimumab	Relative (95% CI)	Absolute (95% CI)	
Performance status (follow-up mean, 8 weeks, assessed by: Bath AS activity index (BASDAI))											
1	Randomized clinical trials	Very serious [a]	Not serious	Not serious	Not serious	None	9	9	-	MD 1.59 lower (unable a calculate CI) [b]	⊕⊕◯◯ Low
Disease activity (follow-up, mean 8 weeks, assessed by: ASDAScrp (AS disease activity score)											
1	Randomized clinical trials	Very serious [a]	Not serious	Not serious	Not serious	None	9	9	-	MD 1.08 lower (unable a calculate CI) [b]	⊕⊕◯◯ Low
Disease activity (follow-up, mean 8 weeks, assessed by: ASDASesr (AS disease activity score)											
1	Randomized clinical trials	Very serious [a]	Not serious	Not serious	Not serious	None	9	9	-	MD 0.67 lower (unable a calculate CI) [b]	⊕⊕◯◯ Low
Disease response (follow-up, mean, 8 weeks, assessed by: ASAS 20)											
1	Randomized clinical trials	Very serious [a]	Not serious	Not serious	Not serious	None	3/9 (33.3%)	4/9 (44.4%)	RR 0.75 (0.23, 2.43)	111 less per 1000 (-342, 636 more)	⊕⊕◯◯ Low
Disease response (follow-up, mean, 8 weeks, assessed by: ASAS 40)											
1	Randomized clinical trials	Very serious [a]	Not serious	Not serious	Not serious	None	2/9 (22.2%)	2/9 (22.2%)	RR 1.00 (0.17, 5.63)	0 less per 1000 (-184, 1000)	⊕⊕◯◯ Low

CI: Confidence interval; MD: mean differences; RR: Risk ratio.
Explanations
[a] Study was unblinded.
[b] Intervals do not report confidence.

Indirect Comparisons. Results on ASAS responses in the red metaanálisis included in Migliore, 2021[75]

Author/ year	Primary Outcome	bDMARDs	Bias, consistency and homogeneity reporting	Ranking	Results
Migliore *et al* 2012[76]	ASAS20	INF, ETA, ADA	No test for consistency or homogeneity was performed	INF: 1ª (75%*) ETA: 2ª (15%*) ADA: 3ª (13%*)	All anti-TNF agents reported to be more effective than placebo. INF has a 72% chance of being the best treatment, while ADA and ETA have a 13% and 15% chance, respectively. There are no differences when directly comparing one anti-TNFα agent with another.
Shu *et al* 2013[77]	ASAS20	INF, GOL,ETA, ADA	No test for consistency or homogeneity was performed	INF: 1ª (6.53#) GOL 100: 2ª (6.09#)	All treatments reported to be more effective than placebo. Ranking analysis suggested that INF 5 mg/kg at 0, 2, 6 weeks may be the most effective therapy compared to placebo followed by GOL

				ETA 50: 3ª (5.98#) GOL 50: 4ª (5.94#) ADA: 5ª (5.92#) ETA 25: 7 (5.05#)	100, ETA 50, GOL 50, ADA, and ETA 25. All these comparisons between treatments were not statistically significant.
Baji *et al* 2014[78]	ASAS20	INF, INF biosimilar, GOL, ADA, ETA	No test for consistency or homogeneity was performed	INF: 1ª (6.74#) INF bio: 2ª (6.39#) GOL: 3ª (5.7#); ADA: 4ª (4.81#) ETA: 5ª (4.35#)	At week 12, regarding the ASAS20 response, all biologics were found to be significantly superior to placebo. Compared to placebo, INF showed the highest OR 6.74, followed by INF biosimilar OR 6.39, GOL OR 5.7, ADA OR 4.81, ETA OR 4.35.
Baji *et al* 2014[78]	ASAS20	INF, INF biosimilar, GOL, ADA, ETA	No test for consistency or homogeneity was performed	INF: 1ª (7.2#); INF bio: 2ª (6.25#) ADA: 3ª (4.81#) ETA: 4ª (4.76#) GOL: 5ª (4.53#)	At week 24, all biologics were found to be significantly superior to placebo. INF showed the highest OR compared to placebo, OR 7.2, followed by INF biosimilar OR 6.25, ADA OR 4.81, ETA OR 4.76, and GOL OR 4.53.
Migliore *et al* 2015[79]	ASAS20	GOL, ADA, ETA, CTZ	No test for consistency or homogeneity was performed	GOL: 1ª (41.28%*) ADA: 2ª (29.91%*) ETA: 3ª (28.74%*) CTZ: 4ª (0.07%*)	All subcutaneous anti-TNFα agents are more effective in achieving ASAS20 response than placebo. At 12 weeks, GOL was the drug that most likely represents the best option (41.28%), followed by ADA 29.91%, ETA 28.74% and CTZ 0.07%. No differences were observed when directly comparing one anti-TNFα agent with another.
Betts *et al* 2016[80]	ASAS20/ ASAS40	INF, ADA, ETA, GOL, SEC, CTZ	No test for consistency or homogeneity was performed	INF: 1ª (2.3°; 71,7%*) ADA: 2ª (2.8°; 63.6%*) ETA: 3ª (2.9°; 62%*) GOL: 4ª (3.1°; 60.3%*) SEC: 4ª (3.1°; 60.2%*) CTZ: 5ª (4.4°; 50.5%*)	At 12 weeks, INF had the lowest NNT 2.3, followed by ADA 2.8, ETA 2.9, GOL and SEC 3.1, and CTZ 4.4. In terms of percentage to be the best treatment, the classification is the same: INF 71.7%, ADA 63.6%, ETA 62%, GOL 60.3%, SEC 60.2%, CTZ 50.5%. For ASAS 40, INF had the highest probability of being the best treatment with NNT of 2.6 and percentage of 51.5%, followed by ADA 2.8/49.2%, SEC 3.5/42.4%, ETA 3.6/41.4%, GOL 4.0 / 38.6% and CTZ 4.7 / 34.8%.
Chen *et al* 2016[81]	ASAS20/ ASAS 40/ ASAS5/6/ ASAS partial remission / BASDAI50	INF, ETA, SEC, GOL, ADA	Inconsistency in each comparison would be identified if they yielded a 95% confidence interval excluding 0. Second, they assessed whether the direct and indirect evidence was in agreement. A large p-value indicates that no significant inconsistency was found.	ASAS20 INF: 1ª (3.23^) SEC: 2ª (2.35^) ADA: (2.80^) GOL50: (2.73^) GOL100: (2.75^) ETA50: (1.99^) ETA25: (2.09^)	Regarding ASAS20, ADA, ETA 25 mg every 2 weeks or 50 mg weekly, GOL 100 mg or 50 mg, and INF were associated with a better therapeutic effect compared to placebo. INF had the highest probability of being the best to achieve ASAS20, followed by SEC. INF was most likely to be ranked best for the secondary outcomes, ASAS40 and ASAS5/6.
Wang *et al* 2018[82]	BASFI BASDAI CRP	INF, INF biosimilar, ETA, GOL, ADA, CTZ	Due to the small number of comparative trials, the authors assumed consistency in the analysis, which reduces confidence in the estimate.	BASDAI INF bio: 1ª -2.67§ (-1.94¢); INF: 2ª -2.66§ (-1.95¢) ADA: 3ª -1.55§ (-1,54¢) GOL: 3ª -1.55§ (-1.47¢) ETA: 4ª -1.51§ (-1.76¢) CTZ: 5ª -1.45§ (-1.45¢) BASFI INF: 1ª -1.99§ (-1.53¢) INF bio: 2ª -1.81§ (-1.34¢) GOL: 3ª -1.57§ (-1.57¢); ADA: 4ª -1.44§ (-1.46¢) ETA: 5ª -1.43§ (-1.54¢)	All anti-TNFs were significantly more effective than placebo in reducing BASDAI and BASFI scores. All anti-TNF except CTZ and INF-bio were superior to placebo in reducing CRP. At 12 weeks in the analysis that added the open label, INF was significantly more effective in reducing BASDAI than ADA, CTZ, ETA, and GOL. INF was also significantly better at reducing BASFI than CTZ, with no significant difference between anti-TNF comparing changes in CRP. In the analysis excluding the open-label trial, INF was no more effective than other anti-TNFs in lowering BASDAI, but when adjusted for baseline BASDAI and baseline CRP, INF remained superior to CTZ, ADA, and ETN in reducing BASDAI. When adjusted for baseline BASFI and baseline CRP, INF was superior to CTZ and ETN in reducing BASFI. At 24 weeks, there was no statistically significant difference in the reduction of BASDAI, BASFI, or CRP. However, INF-bio had a numerically greater reduction in BASDAI and BASFI compared to other anti-TNFs, and ADA had a numerically greater reduction in CRP compared to other anti-TNFs.

				CTZ: 6ª -1.05§ (-1.05¢)	

ASAS, Ankylosing Spondylitis Assessment Study; BASDAI, Bath Ankylosing Spondylitis Activity Index; BASFI, Bath Ankylosing Spondylitis Function Index; CRP, C-reactive protein; ADA, Adalimumab; CTZ, Certolizumab pegol; ETA, Etanercept; GOL, Golimumab; INF, Infliximab; SEC, Secukinumab; NNT; Number needed to treat; OR; Odds ratio; TNF; Tumor necrosis factor.
* Probability of being the best treatment expressed as a percentage from 0-100.
# Probability of being the best treatment expressed as Odds ratio.
° Probability of being the best treatment expressed as Number needed to treat.
^ Forest plot subtotal.
§ Probability of being the best treatment expressed as effect size in the analysis with the open-label trial.
¢ Probability of being the best treatment expressed as effect size in the analysis without the open-label trial.

PICO 5.2. In adults with axial spondyloarthritis despite NSAID treatment, is anti-IL17 treatment more effective than anti-TNF treatment in improving outcomes?

Summary

This PICO question was directly addressed by a phase 3 RCT of Ixekizumab (COAST-V)[83,84] in patients with active radiographic axial spondyloarthritis. A subgroup of treatment-naïve patients included ixekizumab (every 2 or every 4 weeks) and adalimumab active comparator treatment arms. At week 16, both doses of ixekizumab resulted in greater improvement in SF-36, ASAS HI, and EQ-5D-5L compared to placebo. Likewise, patients treated with adalimumab showed a significant improvement in the physical components score, in all domains of the SF-36, mean ASAS HI from baseline, and a greater proportion of patients who achieved ASAS HI ≥ 3 and improvements in EQ-5D-5L, compared to placebo. Comparison of treatment arms shows better responses for ixekizumab (both dosing regimens) in terms of patients achieving ASAS20 or ASAS40 (see Evidence Summary Tables). Patients initially treated with adalimumab demonstrated additional numerical improvements after switching to ixekizumab. The safety results were consistent with the known drug profiles.

Indirect evidence for other comparisons of anti-TNF with anti-IL17 may be derived from meta-analyses or by qualitatively comparing clinical responses between patients receiving anti-TNF versus placebo with those receiving anti-IL17 versus placebo. Systematic reviews with meta-analyses indirectly compared secukinumab and anti-TNF, without identifying differences in the ASAS20 response between secukinumab and anti-TNF (adalimumab, infliximab, etanercept, golimumab and certolizumab pegol) (Chen 2016, Ungprasert 2017)[81,85]. However, both analyzes do not include several published RCTs (Baeten, Pavelka)[86,87]. A more recent meta-analysis (Wu 2019)[88], including the aforementioned studies, quantified the relative efficacy of various treatments in ankylosing spondylitis (see Evidence Summary Tables), including 25 double-blind studies of anti-TNF with 2514 patients and 4 RCTs of IL17 inhibitors (specifically secukinumab) with 568 patients. Three mathematical models with non-parametric placebo estimates were used to describe the longitudinal profile of efficacy measures, finding significant differences between treatments, with infliximab and golimumab as the most effective agents on all measures reviewed. These findings must be viewed in light of the lack of direct evidence for comparisons.

Evidence Profiles

Ixekizumab versus Adalimumab to achieve activity control or slow radiological progression in patients with ankylosing spondylitis.

Certainty assessment						Results summary					Overall certainty of evidence
Nº of patients (studies)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Events rate (%)		Relative effect (95% CI)	Expected absolute effects		
						With Adalimumab	With Ixekizumab		Risk with Adalimumab	Risk differences with Ixekizumab	
Disease activity IXE 4 weeks (follow-up median, 16 weeks, assessed by: Proportion of patients achieving ASAS40)											
171 (1 RCT)[83]	Not serious	Not serious	Not serious	Not serious	None	36/90 (40.0%)	48/81 (59.3%)	RR 1.48 (1.08, 2.02)	400 per 1000	192 more per 1000 (32, 408)	⊕⊕⊕⊕ High
Disease activity IXE 2 weeks (follow-up median, 16 weeks, assessed by: Proportion of patients achieving ASAS40)											
173 (1 RCT) [83]	Not serious	Not serious	Not serious	Not serious	None	36/90 (40.0%)	52/83 (62.7%)	RR 1.56 (1.15, 2.11)	400 per 1000	224 more per 1000 (60, 444)	⊕⊕⊕⊕ High
Disease activity IXE 2 weeks (follow-up median, 16 weeks, assessed by: Proportion of patients achieving ASAS20)											
171 (1 RCT) [83]	Not serious	Not serious	Not serious	Not serious	None	59/90 (65.6%)	69/81 (85.2%)	RR 1.29 (1.09, 1.54)	656 per 1000	190 more per 1000 (59, 354)	⊕⊕⊕⊕ High
Disease activity IXE 4 weeks (follow-up median, 16 weeks, assessed by: Proportion of patients achieving ASAS <2.1)											
168 (1 RCT)[84]	Not serious	Not serious	Not serious	Not serious	None	38/89 (42.7%)	43/79 (54.4%)	RR 1.25 (0.91, 1.72)	427 per 1000	107 more per 1000 (38, 307)	⊕⊕⊕⊕ High
Disease activity IXE 4 weeks (follow-up median, 16 weeks, assessed by: Proportion of patients achieving ASAS Hi >3)											
168 (1 RCT) [84]	Not serious	Not serious	Not serious	Not serious	None	43/89 (48.3%)	42/79 (53.2%)	RR 1.10 (0.81, 1.48)	483 per 1000	48 more per 1000 (-92, 232)	⊕⊕⊕⊕ High
Disease activity IXE 2 weeks (follow-up median, 16 weeks, assessed by: Proportion of patients achieving ASAS Hi >3)											
168 (1 RCT) [84]	Not serious	Not serious	Not serious	Not serious	None	43/89 (48.3%)	51/79 (64.6%)	RR 1.33 (1.02, 1.75)	483 per 1000	159 more per 1000 (10, 362)	⊕⊕⊕⊕ High
Disease activity IXE 4 weeks (follow-up median, 16 weeks, assessed by: Proportion of patients achieving ASAS Hi <5)											
168 (1 RCT) [84]	Not serious	Not serious	Not serious	Not serious	None	47/89 (52.8%)	46/79 (58.2%)	RR 1.10 (0.84, 1.44)	528 per 1000	53 more per 1000 (-84, 232)	⊕⊕⊕⊕ High
Disease activity IXE 2 weeks (follow-up median, 16 weeks, assessed by: Proportion of patients achieving ASAS Hi <5)											
168 (1 RCT) [84]	Not serious	Not serious	Not serious	Not serious	None	47/89 (52.8%)	45/79 (57.0%)	RR 1.07 (0.81, 1.04)	528 per 1000	37 more per 1000 (-100, 21)	⊕⊕⊕⊕ High

CI: Confidence interval; RR: Risk ratio.

Estimates of relative efficacy (response models based on RCTs) of anti-TNF and IL17 inhibitors in patients with ankylosing[88]

Intervention	Studies	N° of patients	ASAS 20	% of patients with ASAS20	BASDAI change*	BASFI change*
TNFα inhibitors						
Adalimumab	3	475	1.41 (1.19, 1.62)	59.5 (54.2, 64.3) *	-1.65 (-1.92, -1.39)	−1.44 (−1.65, −1.24)
Certolizumab pegol	1	121	200 mg: 1.21 (0.83, 1.59) 400 mg: 1.42 (1.02, 1.82)	60 (50, 68.5) *	-1.66 (-2.03, -1.28)	−1.02 (−1.25, −0.80)
Etanercept	12	1072	1.49 (1.32, 1.67)	51.5 (57.5, 65.5) *	-2.05 (-2.36, -1.74)	−1.58 (−1.85, −1.31)
Golimumab	5	525	1.32 (1.11, 1.54)	76.97 (61.58, 87.34)	-2.11(-2.4, -1.8)	−1.83 (−2.07, −1.59)
Infliximab	5	321	2.08 (1.77, 2.39)	74.48 (67.94, 79.89)	-2.46 (-2.8, -2.1)	−1.89 (−2.22, −1.55)
IL17 inhibitors						
Secukinumab	4	568	150 mg: 1.10 (0.92, 1.28) 75 mg: 0.77 (0.43, 1.11)	51.5 (47.5, 56) *	150 mg: -1.3 (-1.53, -1.07) 75 mg: -1.09 (-1.49, -0.70)	−1.09 (−1.33, −0.84)

* Estimated from the graphical representation, figure 2 in Wu, Y., et al, 2019, vol. 105, no 5, p. 1244-1255.[88]

Small molecules for the management of axial spondyloarthritis

Three PICO questions were posed in this topic:

In adults with active axial spondyloarthritis despite NSAID treatment, is small molecule treatment more effective than no treatment in improving outcomes?
In adults with active axial spondyloarthritis despite NSAID treatment, is small molecule treatment more effective than anti-TNF treatment in improving outcomes?
In adults with active axial spondyloarthritis despite NSAID treatment and who have contraindications to anti-TNF, is treatment with a non-anti-TNF biologic more effective than treatment with a small molecule in improving outcomes?

PICO 6.1 In adults with active axial spondyloarthritis despite NSAID treatment, is small molecule treatment more effective than no treatment in improving outcomes?

Summary

4 RCTs and a post-hoc analysis directly addressed this PICO question. Two RCTs and one post-hoc analysis for tofacitinib, one RCT for upadacitinib, and one RCT for filgotinib.

Tofacitinib

The first RCT evaluating tofacitinib (van der Heijde 2017)[89], included 207 patients with active AD. Patients were randomized 1:1:1:1 to placebo or tofacitinib at 2, 5, and 10 mg twice daily for 12 weeks (results from the 5 mg group included in this report). Tofacitinib at a dose of 5 mg twice daily demonstrated significantly greater clinical efficacy versus placebo in reducing symptoms and response criteria such as ASAS 20 80.8% versus 41.2% for placebo; p<0.001. Improvement in SPARCC scores of the sacroiliac joint and spine was also reported. The safety profile was also favorable for 12 weeks.

In the second RCT (Deodhar 2022)[90] 269 patients were randomized and treated (tofacitinib 5 mg twice daily = 133 and placebo = 136) for 16 weeks. At week 16, the ASAS 20 response rate was significantly higher with tofacitinib (56.4%, 75 of 133) versus placebo (29.4%, 40 of 136) (p<0.0001) and similar to the ASAS 40 response rate, 40.6% (54 of 133) with tofacitinib versus 12.5% (17 of 136) placebo (p<0.0001). 73 of 133 (54.9%) tofacitinib patients and 70 of 136 (51.5%) placebo patients had adverse events; 2/133 (1.5%) on tofacitinib and 1/136 (0.7%) on placebo had serious adverse events. During 48 weeks of follow-up, there were no deaths, malignancies, major cardiovascular events, thromboembolic events, or opportunistic infections.

The third study (Maksymowych 2018)[91] is a post-hoc analysis that assessed minimally important changes (MIC) in SPARCC scores for the sacroiliac joint and spine. MICs were assessed in sacroiliac joint and spine SPARCC scores (N= 164; 79%) at week 12. A greater proportion of patients achieved MIC with tofacitinib 2, 5, and 10 mg twice daily versus placebo for the sacroiliac joint (28.6, 38.6, 29.6 vs 11.8%) and for the spine (29.3, 36.4, 40.9 vs 11.8%). A greater proportion of patients treated with tofacitinib or placebo who achieved MIC for the sacroiliac joint and spine achieved ASAS20 versus patients who did not achieve MIC. In conclusion, approximately one-third of tofacitinib-treated patients experienced clinically significant reductions in MIC at week 12. Patients who achieved MIC had a greater clinical response.

Upadacitinib

A clinical trial was identified that evaluated the efficacy and safety of upadacitinib in axial spondyloarthritis. This RCT (Van der Heijde 2019)[92] is a randomized, double-blind, placebo-controlled study that included 187 patients randomized to upadacitinib 15 mg daily or placebo for a period of 14 weeks. A greater proportion of patients achieved an ASAS 40 response in the upadacitinib versus placebo arm at week 14 (48 [52%] of 93 patients vs 24 [26%] of 94 patients; p=0 0003; difference 26% [95% CI 13–40]). Adverse events were reported in 58 (62%) of 93 patients in the upadacitinib group versus 52 (55%) of 94 in the placebo group. The most common adverse event in the upadacitinib group was increased CPK in 9% of patients in the upadacitinib group vs. 2% in the placebo group). Not seriousus infections, herpes zoster, malignancy, venous thromboembolic events, or deaths were reported; one serious adverse event was reported in each group.

Filgotinib

One randomized, double-blind, placebo-controlled phase 2 clinical trial (Van der Heijde 2018)[93] investigating the efficacy and safety of filgotinib for the treatment of patients with axial spondyloarthritis was identified. One hundred and sixteen patients were randomized to filgotinib 200 mg once daily (n=58) or placebo (n=58)

for 12 weeks. The mean change in ASDAS from baseline to week 12 was -1.47 (SD 1.04) in the filgotinib group and -0.57 (0.82) in the placebo group; p<0.0001). Treatment-emergent adverse events were reported in 18 patients in each group, the most common being nasopharyngitis (in two patients in the filgotinib group and four patients in the placebo group). Adverse events led to permanent treatment discontinuation in two patients (one case of grade 3 pneumonia in the filgotinib group and one case of high CPK in the placebo group).

Evidence Profiles

Tofacitinib (5 mg twice daily) versus placebo

Certainty assessment							№ of patients		Effect		Certainly
Nº of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Tofacitinib	Placebo	Relative (95% CI)	Absolute (95% CI)	
Disease response (follow-up, range 12-16 weeks, assessed by: ASAS 20)											
2	Randomized clinical trials	Not serious	Not serious	Not serious	Not serious	None	108/185 (58.4%)	60/187 (32.1%)	RR 1.80 (1.42, 2.29)	257 more per 1000 (135, 414)	⊕⊕⊕⊕ High
Disease response (follow-up, range 12-16 weeks, assessed by: ASAS 40)											
2	Randomized clinical trials	Not serious	Not serious	Not serious	Not serious	None	78/185 (42.2%)	27/187 (14.4%)	RR 2.88 (1.95, 4.23)	271 more per 1000 (137, 466)	⊕⊕⊕⊕ High
Performance status: (follow-up, range 12-16 weeks, assessed by BASFI change)											
2	Randomized clinical trials	Not serious	Serious[a]	Not serious	Not serious	None	185	187	-	MD 1.12 lower (-1.34, -0.89)	⊕⊕⊕◯ Moderate
Performance status: (follow-up, range 12-16 weeks, assessed by BASDAI change)											
2	Randomized clinical trials	Not serious	Serious[a]	Not serious	Not serious	None	185	187	-	MD 1.22 lower (-1.6, -0.79)	⊕⊕⊕◯ Moderate
Disease activity (follow-up, range 12-16 weeks, assessed by: ASDAS change)											
2	Randomized clinical trials	Not serious	Serious[a]	Not serious	Not serious	None	185	187	-	MD 0.83 lower (-1.1, -0.57)	⊕⊕⊕◯ Moderate
Disease activity (follow-up mean, 12 weeks, assessed by: SPARCC change on sacroiliac joints)											

1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[b]	None	52	51	-	MD 2.4 lower (-4.62, -0.18)	⊕⊕⊕◯ Moderate
Disease activity (follow-up mean, 12 weeks, assessed by: SPARCC change on spine)											
1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[b]	None	52	51	-	MD 5.4 lower (-8.45, -2.35)	⊕⊕⊕◯ Moderate

CI: Confidence interval; MD: Median differences; RR: Risk ratio.
Explanations
[a]. High heterogeneity.
[b] Data of single study. Wide confidence intervals.

Upadacitinib (15 mg/day) versus PBO

Certainty assessment							№ of patients		Effect		Certainly
Nº of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Upadacitinib	Placebo	Relative (95% CI)	Absolute (95% CI)	
Disease response (follow-up mean, 14 weeks, assessed by: ASAS 40)											
1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[a]	None	48/93 (51.6%)	24/94 (25.5%)	RR 2.02 (1.36, 3.00)	260 more per 1000 (92, 511)	⊕⊕⊕◯ Moderate
Disease activity (follow-up mean, 14 weeks, assessed by: ASDAS change)											
1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[a]	None	93	94	-	MD 0.91 lower (-1.14, -0.68)	⊕⊕⊕◯ Moderate
Performance status (follow-up mean, 14 weeks, assessed by: BASFI change)											
1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[a]	None	93	94	-	MD 1 lower (-1.6, -0.39)	⊕⊕⊕◯ Moderate
Disease response (follow-up mean, 14 weeks, assessed by: ASAS 20)											
1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[a]	None	60/93 (64.5%)	38/94 (40.4%)	RR 1.59 (1.19, 2.12)	239 more per 1000 (77, 453)	⊕⊕⊕◯ Moderate
Disease activity (follow-up mean, 14 weeks, assessed by: SPARCC change on sacroiliac joints)											
1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[a]	None	93	94	-	MD 3.69 lower (-5.31, -2.08)	⊕⊕⊕◯ Moderate
Disease activity (follow-up mean, 14 weeks, assessed by: SPARCC change on spine)											

1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[a]	None	93	94	-	MD 6.71 lower (-9.01, -4.41)	⊕⊕⊕◯ Moderate

CI: Confidence interval; MD: Mean differences; RR: Risk ratio.
Explanations
[a] Data of a single study.

Filgotinib (200 mg/day) versus PBO

Certainty assessment							№ of patients		Effect		Certainly
Nº of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Upadacitinib	Placebo	Relative (95% CI)	Absolute (95% CI)	
Disease response (follow-up mean, 12 weeks, assessed by: ASAS 40)											
1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[a]	None	22/58 (37.9%)	11/58 (18.9%)	RR 2 (1.07, 3.74)	190 more per 1000 (13, 520)	⊕⊕⊕◯ Moderate
Disease activity (follow-up mean, 12 weeks, assessed by: ASDAS change)											
1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[a]	None	58	58	-	MD 0.85 lower (-1.17, -0.53)	⊕⊕⊕◯ Moderate
Performance status (follow-up mean, 12 weeks, assessed by: BASFI change)											
1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[a]	None	58	58	-	MD 1.11 lower (-1.78, -0.43)	⊕⊕⊕◯ Moderate
Disease response (follow-up mean, 12 weeks, assessed by: ASAS 20)											
1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[a]	None	44/58 (75.8%)	23/58 (39.6%)	RR 1.91 (1.35, 2.71)	361 more per 1000 (139, 678)	⊕⊕⊕◯ Moderate
Disease activity (follow-up mean, 12 weeks, assessed by: SPARCC change on sacroiliac joints)											
1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[a]	None	58	58	-	MD 2.33 lower (-4.20, -0.46)	⊕⊕⊕◯ Moderate
Disease activity (follow-up mean, 12 weeks, assessed by: SPARCC change on spine)											
1	Randomized clinical trials	Not serious	Not serious	Not serious	Serious[a]	None	58	58	-	MD 5.69 lower (-9.75, -1.62)	⊕⊕⊕◯ Moderate

CI: Confidence interval; MD: Mean differences; RR: Risk ratio.
Explanations
[a] Data of a single study.

PICO 6.2 In adults with active axial spondyloarthritis despite NSAID treatment, is small molecule treatment more effective than anti-TNF treatment in improving outcomes?

Summary

This PICO question was not directly addressed by any study. Very indirect evidence of this PEAK can be obtained by qualitatively comparing clinical responses between patients treated with tofacitinib versus placebo with patients treated with anti-TNF vs. placebo.
A systematic review (Ungprasert 2017)[85] indirectly compared tofacitinib and anti-TNF. This study did not identify differences in ASAS20 response between tofacitinib and the older anti-TNFs (adalimumab, infliximab, etanercept, and golimumab) or between tofacitinib and certolizumab pegol. However, this meta-analysis did not include several published RCTs, making comparisons very difficult.

PICO 6.3 In adults with active axial spondyloarthritis despite NSAID treatment and who have contraindications to anti-TNF, is treatment with a non-anti-TNF biologic more effective than treatment with a small molecule?

Summary

This peak question was not directly addressed by any study. Very indirect evidence of this PEAK can be obtained by qualitatively comparing clinical responses between patients treated with tofacitinib versus placebo with patients treated with no anti-TNF versus placebo.

One systematic review (Ungprasert 2017)[85] indirectly compared tofacitinib and secukinumab. This study did not identify differences in ASAS20 response between tofacitinib and secukinumab. However, this meta-analysis did not include several published RCTs, making comparisons very difficult.

Combination therapy (add conventional DMARDs to treatment with biologicals)

PICO 7.1. In adults with active or stable spondyloarthritis on anti-TNF therapy, is low-dose methotrexate co-treatment more effective than no low-dose methotrexate co-treatment in improving outcomes?

Summary

This PICO question was directly addressed in two small RCTs (Mulleman 2011 and Li 2008)[94,95] and two observational studies (Perez-Guijo 2007, Nissen 2016)[96,97] reporting clinical outcomes. Direct evidence from RCTs found that combined treatment with MTX and infliximab has similar efficacy and safety to infliximab

monotherapy. In the first observational study (Nissen 2016)[97], no difference in BASDAI (mean decrease of 2.0 in both groups) or ASDAS (mean decrease of 1.1 in both groups) was evident at 1 year in patients taking MTX or SSZ versus those not taking co-treatment. Half of the studies (5 of 10, including Nissen and 9 other studies) showed greater drug persistence/less discontinuation with co-treatment, particularly for the combination of infliximab and methotrexate. Pérez-Guijo[96] was a small, open-label, prospective, observational study of 19 patients with active spondyloarthritis who had a previous incomplete response to NSAIDs, methotrexate (MTX), and sulfasalazine. Two groups of patients were treated with infliximab and MTX (n = 9) or infliximab alone (n = 10), however patient assignments were based on prior treatment; patients previously treated with MTX had infliximab added to their regimen, while those treated with NSAIDs alone were treated with infliximab alone. They found that MTX in combination with infliximab increased the efficacy of the therapeutic response.

This PICO question was indirectly addressed by one RCT (Breban 2008)[5] and 15 observational studies. Indirect evidence from the RCT (Breban 2008)[5] was presented in the subset of patients randomized to on-demand (non-continuous) infliximab treatment, who were randomized to receive methotrexate together with infliximab or infliximab alone (without methotrexate). On-demand treatment with infliximab was given only after recurrence of symptoms (relapse) with a minimum interval of 4 weeks between infusions (after an initial loading regimen) while the methotrexate dose was limited to 12.5 mg. At 58 weeks, the addition of methotrexate to infliximab had no significant effect on primary outcomes compared to on-demand infliximab. Low strength of evidence for outcomes was attributed to limited data from a single study with a small patient population (imprecision) and lack of direct comparison, as infliximab was provided as needed rather than continuously.

A retrospective study (Nair 2017)[98] of 45 patients who achieved mean BASDAI of 1.9 (standard deviation 1.1) on a short course of infliximab with methotrexate (91% of the cohort) and sulfasalazine (96% of the cohort). After 4 doses of infliximab, the infusions were stopped, but methotrexate and sulfasalazine were continued. The relapse rate (BASDAI ≥ 4) was 20% at one year and 40% at 2 years.

Of the remaining 13 observational studies (Nissen 2016; Glintborg 2010; Heiberg 2008; Kristensen 2010; Favalli 2017; Rahman 2016; Heinonen 2015; Lie 2015; Sepriano 2016; Scire 2013)[97, 99-107], with indirect evidence, nine assessed persistence drug regimen (drug interruption) among those receiving co-treatment versus no co-treatment) or assessed for the presence of anti-drug antibodies (four studies; most compared antibodies among those on co-treatment versus no co-treatment) (de Vries 2009; de Vries 2007; deVries 2007;Kneepkens 2015)[108-111]. Among all these studies, clinical outcomes were not reported (reported only by Nissen, et al, although results were not stratified by MTX or SSZ).
As part of additional evidence, Heinonen et al.[112] was a prospective cohort study that described the effectiveness and survival of anti-TNF drugs in the treatment of ankylosing spondylitis and the effect of concomitant treatment with conventional DMARDs. There, in the multivariate analysis, the concomitant use of sulfasalazine (244 patients) and methotrexate (266 patients) reduced the risk of treatment discontinuation (SSZ HR 0.70, 95% CI 0.49 to 0.99; MTX HR 0.80 , 95% CI 0.64 to 0.99).
Some of the four anti-drug antibody studies included clinical outcomes, however, they compared the outcomes of those with antibodies to those without, rather than the outcomes of patients receiving or not receiving co-treatment. One infliximab and two adalimumab studies showed a lower response in the presence of anti-drug antibodies, however, no anti-drug antibodies were identified in a fourth etanercept study.

Infliximab plus Methotrexate versus Infliximab alone, for patients with active spondyloarthritis, 18 - 30 weeks (randomized trials; direct evidence). Mulleman 2011; Li 2008[94,95].

Certainty assessment						Event rate (%)		Effect			Certainly
Nº of patients (N° of studies and study design)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Infliximab alone	Infliximab + MTX	Relative effect (95% CI)	Expected absolute effects		
									Infliximab alone	Risk difference with Infliximab + MTX	
ASAS20, 18 o 30 weeks											
64 (2 RCT)	Not serious	Not serious	Not serious	Serious [a]	None	20/31 (64.5%)	22/33 (66.7%)	OR 1.10 (0.39, 3.07)	645 per 1000	22 more per 1000 (-230, 203)	⊕⊕⊕◯ Moderate
ASAS40, 30 weeks											
38 (1 RCT)	Not serious	Not serious [b]	Not serious	Serious [c]	None	5/19 (26.3%)	5/19 (26.3%)	OR 1.00 (0.24, 4.24)	263 per 1000	o less per 1000 (-184, 339)	⊕⊕⊕◯ Moderate
BASDAI, 18 weeks											
28 (1 RCT)	Serious [d]	Not serious [b]	Not serious	Serious [c]	None	7/14 (50.0%)	8/14 (57.1%)	OR 1.33 (0.30, 5.91)	500 per 1000	71 more per 1000	⊕⊕◯◯ Low
Partial remission, 30 weeks											
38 (1 RCT)	Not serious	Not serious [b]	Not serious	Serious [c]	None	15/19 (78.9%)	15/19 (78.9%)	OR 1.00 (0.21, 4.76)	789 per 1000	o less per 1000 (-349, 157)	⊕⊕⊕◯ Moderate
Adverse events, 30 weeks											
38 (1 RCT)	Not serious	Not serious [b]	Not serious	Serious [c]	None	13/19 (68.4%)	15/19 (78.9%)	OR 1.73 (0.40, 7.51)	684 per 1000	105 more per 1000 (-220, 258)	⊕⊕⊕◯ Moderate

CI: Confidence interval; OR: Odds ratio

[a] Wide confidence interval and overlaps the line with no difference

[b] Does not apply, single study.

[c] Single study, small sample size. Wide confidence interval 95%.

[d] Open-label study.

Infliximab plus methotrexate versus Infliximab, for patients with active spondyloarthritis, *30 weeks (observational study; direct evidence). Perez-Guijo 2007*[96]

Certainty assessment						Event rate (%)		Effect			Certainly
Nº of patients (N° of studies and study design)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Infliximab + MTX	Infliximab alone	Relative effect (95% CI)	Expected absolute effects		
									Infliximab alone	Risk difference with Infliximab + MTX	
BASDAI 50, 30 weeks											
19 (1 observational study)	Serious [a]	Not serious [b]	Not serious	Serious [c]	None	8/9 (88.9%)	1/10 (10.0%)	OR 72.00 (3.84, 1349.55)	100 per 1000	789 more per 1000 (199, 893)	⊕◯◯◯ Very low
ASAS 20, 30 weeks											
19 (1 observational study)	Serious [a]	Not serious [b]	Not serious	Serious [c]	None	8/9 (88.9%)	2/10 (20.0%)	OR 32.00 (2.39, 427.74)	200 per 1000	689 more per 1000 (174, 791)	⊕◯◯◯ Very low
ASAS 50, 30 weeks											
19 (1 observational study)	Serious [a]	Not serious [b]	Not serious	Serious [c]	None	5/9 (55.6%)	0/10 (0.0%)	OR 25.67 (1.16, 568.91)	0 per 1000	0 less per 1000	⊕◯◯◯ Very low
Remisión parcial, 30 weeks											
19 (1 observational study)	Serious [a]	Not serious [b]	Not serious	Serious [d]	None	3/9 (33.3%)	0/10 (0.0%)	OR 11.31 (0.50, 256.20)	0 per 1000	0 less per 1000	⊕◯◯◯ Very low

CI: Confidence intervals; OR: Odds ratio
[a] Observational study.
[b] Does not apply; single study.
[c] Single study; small sample size, Wide CI 95%.
[d] Single study; small sample size. Wide confidence interval and overlaps the line with no difference.

Infliximab with methotrexate versus Infliximab alone for treatment of active or ankylosing spondylitis *(indirect evidence). Breban 2008*[5]

Certainty assessment						N° of patients (Event rate, %)		Effect		Certainly
Nº of patients (N° of studies and study design)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Infliximab + MTX	Infliximab alone	Relative (95% CI)	Absolute (95% CI)	

ASAS20, 58 weeks										
123 (1 RCT)	Not serious	Not serious [a]	Serious [b]	Serious [c,d]	None	31/61 (50.8%)	25/62 (40.3%)	OR 1.53 (0.75, 3.12)	105 more per 1000 (-67, 275)	⊕⊕◯◯ Low
ASAS40, 58 weeks										
123 (1 RCT)	Not serious	Not serious [a]	Serious [b]	Serious [c,d]	None	22/61 (36.1%)	15/62 (24.2%)	OR 1.77 (0.81, 3.86)	119 more per 1000 (-37, 310)	⊕⊕◯◯ Low
Partial remission, 58 weeks										
123 (1 RCT)	Not serious	Not serious [a]	Serious [b]	Serious [c,e]	None	6/61 (9.8%)	3/62 (4.8%)	OR 2.15 (0.51, 9.00)	50 more per 1000 (-23, 266)	⊕⊕◯◯ Low
Pain assessment (scale 0-10), 58 weeks										
123 (1 RCT)	Not serious	Not serious [a]	Serious [b]	Serious [c,d]	None	61	62	-	MD 0.3 lower (-1.24, 0.64)	⊕⊕◯◯ Low
Patient global assessment, change (scale 0-10), 58 weeks										
123 (1 RCT)	Not serious	Not serious [a]	Serious [b]	Serious [c,d]	None	61	62	-	MD 0.8 lower (-1.68, 0.08)	⊕⊕◯◯ Low
BASDAI change, 58 weeks										
123 (1 RCT)	Not serious	Not serious [a]	Serious [b]	Serious [c,d]	None	61	62	-	MD 0.2 higher (-0.49, 0.89)	⊕⊕◯◯ Low
BASFI change, 58 weeks										
123 (1 RCT)	Not serious	Not serious [a]	Serious [b]	Serious [c,d]	None	61	62	-	MD 0.5 lower (-1.19, 0.19)	⊕⊕◯◯ Low
SF-36, physical component, 58 weeks										
123 (1 RCT)	Not serious	Not serious [a]	Serious [b]	Serious [c,d]	None	61	62	-	MD 0.1 lower (-2.98, 2.78)	⊕⊕◯◯ Low
Muerte, 58 weeks										
123 (1 RCT)	Not serious	Not serious [a]	Serious [b]	Serious [c,e,f]	None	1/61 (1.6%)	0/62 (0.0%)	OR 3.10 (0.12, 77.57)	0 less per 1000	⊕⊕◯◯ Low
Severe infection, 58 weeks										
123 (1 RCT)	Not serious	Not serious [a]	Serious [b]	Serious [c,e]	None	3/61 (4.9%)	1/62 (1.6%)	OR 3.16 (0.32, 31.21)	33 more per 1000 (-11, 322)	⊕⊕◯◯ Low

CI: Confidence interval; OR: Odds ratio; MD: Mean differences.

[a] Does not apply, single study.

[b] Indirect comparison: infliximab treatment as needed.

[c] Single study, small sample size.

[d] Confidence interval overlaps the line with no difference.

[e] Wide confidence interval and overlaps the line with no difference.
[f] Event with low incidence.

In addition, for non-radiographic axial spondyloarthritis, one RCT directly addressed the analysis of co-treatment with methotrexate. Ducourau et al.[113], a 26-week, prospective, open-label, multicenter study with 107 patients who received adalimumab 40 mg subcutaneously every two weeks, were randomized to receive methotrexate 10 mg subcutaneously or not. Adalimumab concentration was significantly higher in the methotrexate group than in the non-methotrexate group at weeks 4, 8, 12, and 26. The two groups did not differ in adverse events or efficacy. In the follow-up study, co-treatment with MTX versus no MTX, greater than 26 weeks, was significantly associated with long-term adalimumab maintenance (HR 0.46 CI 0.22 to 0.95, p = 0.04).
Additionally, indirect evidence can be derived from a single observational study (Gulfe 2014)[114] that examined the efficacy and persistence of anti-TNF medication in non-radiographic axial spondyloarthritis. In this study of 119 people, "concomitant use of nonbiologic DMARDs" was not associated with medication persistence. Results were not reported separately for methotrexate nor were efficacy results compared between those who received methotrexate and those who did not.

Adalimumab plus MTX versus adalimumab alone for axial spondyloarthritis, 26 weeks (randomized trial; direct evidence). Ducourau et al.[113]

Certainty assessment						№ of patients		Effect		Certainly
N° of studies and study design)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Adalimumab + methotrexate	Adalimumab alone	Relative (95% CI)	Absolute (95% CI)	
Disease activity (follow-up median, 26 weeks; assessed by: ASDAS response)										
1 RCT	Serious[c,d]	Not serious	Not serious	Serious[a,b]	None	25/46 (54.3%)	31/50 (62.0%)	RR 0.8766 (0.62, 1.23)	77 less per 1000 (-234, 145)	⊕⊕◯◯ Low
Disease activity, inactivity (follow-up median, 26 weeks; assessed by: ASDAS)										
1 RCT	Serious[c,d]	Not serious	Not serious	Serious[a,b]	None	17/46 (37.0%)	21/52 (40.4%)	RR 0.915 (0.55, 1.51)	34 less per 1000 (-180, 206)	⊕⊕◯◯ Low
Immunogenicity (follow-up median, 26 weeks; assessed by: anti-drug antibodies)										
1 RCT	Not serious	Not serious	Not serious	Serious[a,b]	None	26/55 (47.3%)	13/52 (25.0%)	RR 0.53 (0.31, 0.91)	118 less per 1000 (-173, 22)	⊕⊕⊕◯ Moderate

CI: Confidence interval; RR: relative risk.
[a] Does not apply, single study.
[b] Single study, small sample size.
[c] The effect measure includes the possibility that there are no differences.
[d] Open-label study.

Observational data (Indirect evidence). Gulfe 2014[114]

Reference, Author, year	Study design	Extension	Population description	Treatment administered to the relevant population	Results
Gulfe 2014[114]	Observational, prospective.	6 months	112 patients with non-radiographic axial spondyloarthritis and high disease activity (inadequate response or intolerance to nonsteroidal anti-inflammatory drugs (NSAIDs) and first course of anti-TNF treatment) The mean duration of illness was 6 years and 10 months.	Anti-TNF therapy recommended doses used, except infliximab (3 mg/kg infusion at 0, 2, 6, and then every 8 weeks) Not direct: 38% of patients used cDMARDs before anti-TNF therapy	BASDAI median: decreased from 5.6 to 3.2 (p=0.002) BASFI median: decreased from 3.9 to 1.8 (p=0.005) C-reactive protein (CRP): decreased from 4.4 to 1.7 mg/L (p = 0.001) Kaplan–Meier for drug survival at 2 years of follow-up: 65%.

Biosimilars in axial spondyloarthritis

Two PICO questions were raised in this topic:

In adults with axial spondyloarthritis, what is the efficacy and safety of biosimilars compared to innovator biologics?
In adults with stable axial spondyloarthritis on an innovator anti-TNF, what is the efficacy and safety of switching to a biosimilar compared to continuing treatment with the innovator?

PICO 8.1 In adults with axial spondyloarthritis, what is the efficacy and safety of biosimilars compared to innovator biologics?

Summary

This PICO question was addressed by three RCTs (Park 2013 and 2016, Xu 2019, Su 2020)[115-118] and one observational study from a registry (Lindström 2019)[119]. The first RCT (Park 2016 and 2013)[115,116] compared the biosimilar CT-P13 versus the innovative molecule infliximab. The results of this randomized, double-blind, multicenter, parallel-group trial in patients with axial spondyloarthritis indicate that there are no significant differences between CT-P13 and infliximab for most major efficacy outcomes or adverse event rates. The second RCT (Xu 2019)[117] compared adalimumab and a biosimilar IBI303 with a follow-up of 24 weeks. The ASAS 20 response and the change in BASDAI, BASFI, safety and tolerability scores were similar in the two groups. The third RCT identified (Su 2020)[118] evaluated the equivalence between ADA and a biosimilar HS016; No significant differences were identified in the ASAS 20, ASAS 40 response, or in the change in BASDAI scores, or in quality of life outcomes.

An observational study (Lindström 2019)[119] compared treatment retention in patients with axial spondyloarthritis who started treatment with the infliximab and etanercept biosimilar or innovator products. Information was obtained from five Nordic biological/rheumatological registries. We included 1319 patients who started infliximab (24% innovator/76% biosimilar) and 1015 patients who started etanercept (49% innovator/51% biosimilar). Baseline patient characteristics were similar for patients treated with the innovators compared to the corresponding biosimilars. The survival curves of the innovators and biosimilars were very similar, as were the retention rates at two years: infliximab innovator 44% (95% CI 38% to 50%), biosimilar 46% (95% CI 42% to 51%); and at one year: innovator

etanercept 66% (95% CI 61% to 70%), biosimilar 73% (95% CI 68% to 78%), with similar clinical responses, indicating comparable effectiveness in clinical practice. GRADE tables for this study are not presented due to a high proportion of missing disease activity measures, thus statistical comparisons were not performed.

Evidence Profiles

CT-P13 versus infliximab, 30 weeks

Certainty assessment							Conclusions summary				
Nº of patients (studies)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	CertainlyIN	Event rate (%)		Relative effect (95% CI)	Expected absolute effects	
							Infliximab	CT-P13		Risk with IFX 30 weeks	Risk difference with CT-P13
ASAS 20, 30 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	84/125 (67.2%)	79/125 (63.2%)	OR 0.84 (0.50, 1.41)	672 per 1000	40 less per 1000 (-166, 71)
ASAS 40, 30 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	55/125 (44.0%)	58/125 (46.4%)	OR 1.10 (0.67 a 1.81)	440 per 1000	24 more per 1000 (-95, 147)
ASDAS-CRP (change), 30 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	116	113	-	-	MD 0.1 lower (-0.41, 0.21)
Treatment-emergent AE in general, 30 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	78/122 (63.9%)	83/128 (64.8%)	OR 1,04 (0.62 a 1.75)	639 per 1000	9 more per 1000 (-116, 117)
Urinary tract infection, 30 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [c]	None	⊕⊕⊕◯ Moderate	0/122 (0.0%)	5/128 (3.9%)	OR 10.91 (0.60, 199.46)	0 per 1000	0 less per 1000
Tonsillitis, 30 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [c]	None	⊕⊕⊕◯ Moderate	2/122 (1.6%)	0/128 (0.0%)	OR 0.19 (0.01, 3.95)	16 per 1000	13 less per 1000 (-16, 45)
Tuberculosis, 30 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [c]	None	⊕⊕⊕◯ Moderate	1/122 (0.8%)	2/128 (1.6%)	OR 1.92 (0.17, 21.46)	8 per 1000	7 more per 1000 (-7, 142)
Adverse cardiac event, 30 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [c]	None	⊕⊕⊕◯ Moderate	1/122 (0.8%)	1/128 (0.8%)	OR 0.95 (0,06 a 15,40)	8 per 1000	0 less per 1000 (-8, 105)
Appendicitis, 30 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [c]	None	⊕⊕⊕◯ Moderate	1/122 (0.8%)	0/128 (0.0%)	OR 0,32 (0.01, 7.81)	8 per 1000	6 less per 1000 (-8, 52)
Carcinoma, 30 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [c]	None	⊕⊕⊕◯ Moderate	0/122 (0.0%)	1/128 (0.8%)	OR 2.88 (0.12, 71.44)	0 per 1000	Uncalculable

CI: Confidence interval; OR: Odds ratio; AE: adverse event; RCT: Randomized control trial.

Explanations

a. Does not apply, single study.

b. Single study; CI includes the possibility that there are no differences.
c. Single study; low event rate, wide CI 95% that includes the possibility that there are no differences.

CT-P13 versus infliximab, 54 weeks

Certainty assessment							Conclusions summary				
Nº of patients (studies)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Certainly	Event rate (%)		Relative effect	Expected absolute effects	
							Infliximab	CT-P13	(95% CI)	Risk with INX, 54 weeks	Risk difference with CT-P13
ASAS20											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	82/125 (65.6%)	73/125 (58.4%)	OR 0,74 (0.44, 1.23)	656 per 1000	71 less per 1000 (-200, 45)
ASAS40, 54 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	56/125 (44.8%)	59/125 (47.2%)	OR 1.10 (0.67, 1.81)	448 per 1000	24 more per 1000 (-96, 147)
Partial response ASAS, 54 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	18/125 (14.4%)	18/125 (14.4%)	OR 1.00 (0.49, 2.03)	144 per 1000	0 less per 1000 (-68, 111)
BASDAI, change, 54 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	125	125	-	-	MD 0.3 lower (-0.86, 0.26)
BASFI, change, 54 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	125	125	-	-	MD 0.2 lower (-0.75, 0.35)
BASMI, change, 54 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	125	125	-	-	MD 0.2 lower (-0.58, 0.18)
All serious adverse events, 54 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	8/122 (6.6%)	10/128 (7.8%)	OR 1.21 (0.46, 3.17)	66 per 1000	13 more per 1000 (-34, 116)
All treatment-emergent AE, 54 weeks											

250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	5/122 (4.1%)	4/128 (3.1%)	OR 0.75 (0.20, 2,88)	41 per 1000	10 less per 1000 (-33, 69)
Active tuberculosis, 54 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [c]	None	⊕⊕⊕◯ Moderate	1/122 (0.8%)	2/128 (1.6%)	OR 1.92 (0.17, 21.46)	8 per 1000	7 more per 1000 (-7, 142)
Malignancy, 54 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [c]	None	⊕⊕⊕◯ Moderate	0/122 (0.0%)	1/128 (0.8%)	OR 2.88 (0.12, 71.44)	0 per 1000	0 less per 1000
Latent tuberculosis, 54 weeks											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [c]	None	⊕⊕⊕◯ Moderate	6/122 (4.9%)	9/128 (7.0%)	OR 1.46 (0.50, 4.24)	49 per 1000	21 more per 1000 (-24, 131)
SAE associated with treatment and discontinuation											
250 (1 RCT)	Not serious	Not serious [a]	Not serious	serio [b]	None	⊕⊕⊕◯ Moderate	9/122 (7.4%)	11/128 (8.6%)	OR 1.18 (0.47,2.96)	74 per 1000	12 more per 1000 (-38, 117)

CI: Confidence interval; OR: Odds ratio; MD: Mean differences; AER: adverse event; SAE: serious adverse event; RCT: Randomized control trial.

Explanations

a. Does not apply, single study.
b. Single study; CI includes the possibility that there are no differences.
c. Single study; low event incidence. Wide CI that includes the possibility that there are no differences.

HS016 versus adalimumab, 24 weeks

Certainty assessment						№ of patients		Effect		Certainly
N° of studies and study design)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	HS016	Adalimumab	Relative (95% CI)	Absolute (95% CI)	
Disease response (assessed by: proportion of patients achieving ASAS20)										
1 RCT	Not serious	Not serious	Not serious	Serious[a]	None	364/416 (87.5%)	209/232 (90.1%)	RR 0.97 (0.92, 1.03)	26 less per 1000 (-74, 24)	⊕⊕⊕◯ Moderate
Disease response (follow-up median, 24 weeks, assessed by: proportion of patients achieving ASAS 40)										

1 RCT	Not serious	Not serious	Not serious	Serious[a]	None	296/416 (71.2%)	175/232 (75.4%)	RR 0.94 (0.86, 1.04)	43 less per 1000 (-108, 29)	⊕⊕⊕◯ Moderate
Disease response (follow-up median, 24 weeks, assessed by: proportion of patients achieving ASAS 5/6)										
1 RCT	Not serious	Not serious	Not serious	Serious[a]	None	262/416 (63.0%)	156/232 (67.2%)	RR 0.94 (0.83, 1.05)	43 less per 1000 (-112, 35)	⊕⊕⊕◯ Moderate
Disease activity (follow-up: median 24 weeks; assessed by: Percentage of patients improving ≥50 on BASDAI)										
1 RCT	Not serious	Not serious	Not serious	Serious[a]	None	318/416 (76.4%)	182/232 (78.4%)	RR 0.97 (0.89, 1.06)	20 less per 1000 (-83, 49)	⊕⊕⊕◯ Moderate
Adverse events (follow-up median, 24 weeks, assessed by: proportion of patients with treatment-emergent adverse event)										
1 RCT	Not serious	Not serious	Not serious	Serious[a]	None	352/416 (84.6%)	200/232 (86.2%)	RR 0.98 (0.91, 1.04)	16 less per 1000 (-70, 41)	⊕⊕⊕◯ Moderate
Adverse events (follow-up median, 24 weeks, assessed by: proportion of patients with serious adverse event)										
1 RCT	Not serious	Not serious	Not serious	Serious[b]	None	18/416 (4.3%)	6/232 (2.6%)	RR 1.67 (0.67, 4.15)	17 more per 1000 (-8, 82)	⊕⊕⊕◯ Moderate

CI: Confidence interval; RR: Risk ratio; RCT: Randomized control trial.

Explanations

a. Single study; 95% CI includes the possibility that there are no differences.
b. Single study; wide 95% CI that includes the possibility that there are no differences.

IBI303 versus adalimumab, 24 weeks

Certainty assessment						№ of patients		Effect		Certainly
N° of studies and study design)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	IBI303	Adalimumab	Relative (95% CI)	Absolute (95% CI)	
Disease response (assessed by: proportion of patients achieving ASAS20)										
1 Randomized control trial	Not serious	Not serious	Not serious	Serious[a]	None	165/220 (75.0%)	158/218 (72.5%)	RR 1.03 (0.92, 1.15)	25 more per 1000 (-54, 114)	⊕⊕⊕◯ Moderate
Disease response (follow-up median, 24 weeks, assessed by: proportion of patients achieving ASAS 40)										

1 Randomized control trial	Not serious	Not serious	Not serious	Serious[a]	None	137/220 (62.3%)	134/218 (61.5%)	RR 1.01 (0.87, 1.17)	8 more per 1000 (-77, 107)	⊕⊕⊕◯ Moderate
Disease response (follow-up median, 24 weeks, assessed by: proportion of patients achieving ASAS 5/6)										
1 Randomized control trial	Not serious	Not serious	Not serious	Serious[a]	None	144/220 (65.5%)	140/218 (64.2%)	RR 1.02 (0.89, 1.17)	12 more per 1000 (-72, 109)	⊕⊕⊕◯ Moderate
Disease response (follow-up median, 24 weeks; assessed by: proportion of patients achieving ASAS partial response)										
1 Randomized control trial	Not serious	Not serious	Not serious	Serious[a]	None	65/220 (29.5%)	74/218 (33.9%)	RR 0.87 (0.66, 1.15)	44 less per 1000 (-115, 50)	⊕⊕⊕◯ Moderate
Adverse events (follow-up median, 24 weeks, assessed by: treatment-emergent adverse event)										
1 Randomized control trial	Not serious	Not serious	Not serious	Serious[a]	None	174/220 (79.1%)	178/218 (81.7%)	RR 0.97 (0.88, 1.06)	25 less por 1000 (-96, 51)	⊕⊕⊕◯ Moderate
Adverse events (follow-up median, 24 weeks, assessed by: serious adverse events)										
1 Randomized control trial	Not serious	Not serious	Not serious	Serious[a]	None	7/220 (3.2%)	8/218 (3.7%)	RR 1.59 (0.59, 4.27)	22 more per 1000 (-15, 120)	⊕⊕⊕◯ Moderate

CI: Confidence interval; RR: Risk ratio.

Explanations

a. Single study; 95% CI includes the possibility that there are no differences.

PICO 8.2 In adults with stable axial spondyloarthritis on an innovator anti-TNF, what is the efficacy and safety of switching to a biosimilar compared to continuing treatment with the innovator?

Summary

This peak question was directly addressed by an observational study (Kaltsonoudis 2019)[120] and by an RCT (Jorgensen 2017)[121]. In the phase 4, double-blind, non-inferiority RCT (Jorgensen 2017), subjects with stable rheumatologic disease treated with lead infliximab were randomized to continue lead infliximab or CT-P13, a biosimilar of infliximab. A total of 482 patients (241 to the infliximab innovator, 241 to the CT-P13 group) were recruited and randomized; and 408 were included in per-protocol analysis (202 in the infliximab innovator group and 206 in the CT-P13 group). 155 (32%) patients in the total population had Crohn's disease, 93 (19%) ulcerative colitis, 91 (19%) spondyloarthritis, 77 (16%) rheumatoid arthritis, 30 (6%) psoriatic arthritis, and 35 (7%) chronic plaque psoriasis. Disease worsening occurred in 53 (26%) patients in the infliximab innovator group and 61 (30%) patients in the CT-P13 group (per protocol analysis; adjusted treatment difference -4.4%, 95% CI: -12.7 to 3.9). The frequency of adverse events was similar between groups (for serious adverse events, 24 [10%] for the infliximab innovator vs 21

[9%] for CT-P13; for general adverse events, 168 [70%] vs 164 [68%]; and for adverse events leading to discontinuation, nine [4%] vs eight [3%], respectively). Specifically for axial spondyloarthritis, the results at 52 weeks did not differ for ASDAS, ASDAS-inactivity, and BASDAI between the two therapeutic agents.

The observational study (Kaltsonoudis 2019)[120] evaluated patients with axial spondyloarthritis (AS) in clinical remission who were on the lead infliximab and switched to biosimilar infliximab. Those who switched to biosimilar infliximab were compared with a matched control group who continued on the lead infliximab, with a follow-up of at least 18 months. 88% of the patients were evaluated (21 excluded for different reasons). Of these, 45 switched to biosimilar infliximab, while 43 continued to receive infliximab innovator. No differences were observed between the groups regarding demographic, clinical, and laboratory parameters. All patients were in clinical remission. During follow-up, five patients in the biosimilar group (4 nocebo patients, 1 recurrent infection) and three in the maintenance group (2 recurrent infection, 1 loss of efficacy) discontinued the study. After 18 months of treatment, all patients in both groups remained in clinical remission with low BASDAI, low ASDAS, as well as low erythrocyte sedimentation rate (ESR) and CRP. No significant adverse events were observed between the groups. In conclusion, the infliximab biosimilar was equivalent to the infliximab innovator in maintaining AD in clinical remission for at least 18 months.

Evidence Profiles

Continue with infliximab innovator versus switch to CT-P13 in stable axial spondyloarthritis, 52 weeks

Nº of patients (study design)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Certainly	Event rate (%)		Relative effect (95% CI)	Absolute effect
							Switch to CT-P13	Continue with Infliximab		
ASDAS, change										
408 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	202	206	-	MD 0.01 lower (-0.27, 0.24)
ASDAS, inactive disease										
408 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [c]	None	⊕⊕⊕◯ Moderate	10 (23%)	7 (17%)	RR 1.36 (0.57, 3.23)	61 more per 1000 (-73, 381)
BASDAI, change										
408 (1 RCT)	Not serious	Not serious [a]	Not serious	Serious [b]	None	⊕⊕⊕◯ Moderate	202	206	-	MD 0.5 lower (-0.74, 0.26)

CI: Confidence interval; MD: Mean differences; OR: Odds ratio; RCT: Randomized control trial.

Explanations

[a] Does not apply, single study.

[b] Single study; small sample size of patients with axial spondyloarthritis.

[c] Single study; wide 95% CI that overlaps the line with no difference.

Therapeutic Failure

To answer this clinical question, a PICO question was posed:

PICO 9.1 In adults with active axial spondyloarthritis despite treatment with the first anti-TNF used, is switching to a different anti-TNF more effective than switching to a non-anti-TNF biologic in improving outcomes?

Summary

No RCTs comparing anti-TNF with non-anti-TNF in patients with axial spondyloarthritis unresponsive to anti-TNF were identified. However, one observational study (Micheroli 2020)[122] directly addressing this PICO question was identified, with low certainty of evidence. This observational study (Micheroli 2020)[122] compared the effectiveness of secukinumab and other anti-TNFs in patients with axial spondyloarthritis with prior anti-TNF failure. Information was obtained from the Swiss clinical quality management cohort. 106 patients who had started secukinumab after failure and 284 who had started another anti-TNF were included. A comparable risk of drug discontinuation was found for secukinumab versus anti-TNF (HR 1.14, 95% CI 0.78 to 1.68). No significant differences were found in the BASDAI50 response at one year between the two groups (OR for secukinumab vs anti-TNF 0.76; 95% CI 0.26 to 2.18), nor in the secondary outcomes change in BASDAI >2, ASDAS <2.1, change in ASDAS >1.1.

There is evidence of the efficacy of other anti-TNFs, secukinumab and ixekizumab, in patients with biologic failure, but it is not of a comparative nature.

Treatment of axial spondyloarthritis with extra-articular manifestations

Two PICO questions were raised in this topic:

1. In adults with axial spondyloarthritis and uveitis, are some biological drugs more effective than others in reducing recurrences of uveitis?
2. In adults with axial spondyloarthritis and inflammatory bowel disease (IBD), are certain biologics more effective than others in improving outcomes?

PICO 10.1 In adults with axial spondyloarthritis and uveitis, is there any biologic more effective in reducing uveitis flares?

Summary

In the literature review of this PICO question for the ACR 2019 guideline, no RCTs were identified and the evidence was obtained from four observational studies or pooled analyzes of clinical trials (Guignard 2006, Braun 2005, Cobo-Ibáñez 2008, Fouache 2009, Rudwaleit 2009)[123-127] comparing uveitis rates between patients treated with etanercept, infliximab, or adalimumab. All studies reported higher rates of uveitis among patients treated with etanercept than with infliximab or adalimumab. Compared with pretreatment periods evaluated, the anti-TNFs adalimumab and infliximab produced lower rates of anterior uveitis (AU) flares, while rates with the introduction of etanercept remained stable or increased.

Our search update identified three observational studies that directly addressed this question (Lee 2019, Choi 2020 and Lindström 2021, see table)[128-130]. In Lee et al. 54 patients with spondyloarthritis with at least one episode of AU were included. Anti-TNF-α drugs were more effective in reducing AU recurrence than etanercept. Etanercept patients tended to develop UA for the first time less than a year after starting the drug, and their spondyloarthritis was generally well controlled at the time of UA flares. Patients with an UA flare before their medication was changed had no recurrence, and five of eight patients had no relapse after dose increase.

In the study by Choi et al.[129] the appearance of non-infectious uveitis (de novo and recurrent) was compared according to the anti-TNF used to treat spondyloarthritis (adalimumab [ADA], infliximab [IFX], etanercept [ETN] and golimumab [GOL]). Cumulative rates of onset of uveitis at three years were significantly different according to the type of anti-TNF used (23.1% in IFX, 18.5% in ETN, and 11.9% in the ADA+GOL group) (p =0.020). The risk of de novo uveitis was similar for the different drugs. However, the IFX group showed a recurrence risk 5.4 times higher than the ADA+GOL group (p=0.022). After adjusting for other confounders, IFX use was independently associated with a more frequent occurrence of uveitis (HR 2.01, p 0.011).

In the study by Lindström et al.[130] The objective was to compare the risk of AU during treatment with secukinumab versus anti-TNF, based on information from Swedish Registries: Rheumatology Quality Registry and National Outpatient Registry. Based on 4,851 treatment initiations (456 secukinumab; 4,395 any anti-TNF), the rate of AU diagnoses per 100 patient-years was 6.8 (95% CI 5.2 to 8.7) for secukinumab. Among anti-TNFs, the rate ranged from 2.9 (95% CI 2.1 to 3.7) for infliximab, 4.0 (95% CI 3.3 to 4.9) for adalimumab, and 7.5 (95% CI 3.3 to 4.9) for 95%: 6.7 to 8.4) for etanercept. The adjusted risks for the first AU (adalimumab as reference) were: secukinumab 2.32 (95% CI 1.16 to 4.63), infliximab 0.99 (95% CI 0.49 to 1.96), etanercept 1, 82 (95% CI 1.13 to 2.93), golimumab 1.59 (95% CI 0.90 to 2.80) and certolizumab 1.12 (95% CI 0.44 to 2.83).

In general, the highest rates of uveitis were reported for secukinumab and etanercept and the lowest rates for adalimumab and golimumab, based on low-quality evidence with a high risk of bias due to differences in the baseline characteristics of the patients in each group.

Evidence Profiles

Author, year	Study design	Extension	Population	Treatment	Results
Lee 2019[128]	Retrospective cohort	10 years	54 patients with spondyloarthritis with at least 1 episode of anterior uveitis: - 39 prior anti-TNF	39 prior anti-TNF: - ADA 25 patients - IFX 7 patients - ETN 6 patients	Uveitis (episodes per 100 patient-years) In patients with uveitis prior to starting anti-TNF (before/after):

			- 15 after anti-TNF	- GOL 1 patients 15 after anti-TNF: - ETN 5 patients - ADA 3 patients - IFX 6 patients - GOL 1 patients	- ADA, 59.78 ± 61.11 vs. 7.53 ± 14.63 (P = 0.001) - IFX, 39.78 ± 33.29 vs. 8.93 ± 14.44 (P = 0.046) - ETN, 102.25 ± 92.21 vs. 71.95 ± 23.83 (P = 0.465) Treatment with anti-TNF-α resulted in a significantly higher relapse-free survival rate than with ETN (ADA vs. ETN, P < 0.001; IFX vs. ETN, P = 0.048). No se observaron diferencias entre ADA e IFX (P = 0.506). In patients without uveitis prior to starting anti-TNF (after): Onset of AU occurred within 1 year after initiation of anti-TNF in 4 of 5 patients (80%) treated with ETN and 2 of 10 patients (20%) treated with anti-TNF-α (P = 0.089).
Choi 2020[129]	Retrospective cohort	3 years	175 patients with spondyloarthritis treated with anti-TNF (ADA, ETN, IFX, and GOL) for more than 6 months	- ADA 62 patients - IFX 49 patients - ETN 37 patients - GOL 27 patients 23 patients (37.1%) had a history of one or more episodes of uveitis before receiving ADA, 11 (29.7%) before ETN, 14 (28.6%) before IFX, and 7 patients (25.9 %) before GOL (p= 0.54).	Uveitis rate - IFX: 4.8% at 1 year, 13.8% at 2 years and 23.1% at 3 years - ETN: 3.0% at 1 year, 3.8% at 2 years, and 18.5% at 3 years - ADA + GOL: 2.4% at 1 year, 4.3% at 2 years, and 11.9% at 3 years Adjusted HR for uveitis vs. ADA + GOL: - ETN 1.53 [0.51, 3.58]; p = 0.44 - IFX [0.85,4.15]; p = 0.011
Lindström 2021[130]	Retrospective cohort	2 years	Patients with spondyloarthritis receiving treatment with secukinumab or an anti-TNF (adalimumab, certolizumab, etanercept, golimumab or infliximab)	- SEC 456 patients - ADA 1006 patients - IFX 783 patients - ETN 1800 patients - GOL 500 patients - CTZ 306 patients	Uveitis (episodes per 100 patient-years) - SEC 6.8 - ADA 4.0 - IFX 2.9 - ETN 7.5 - GOL 6.8 - CTZ 4.5 Adjusted HR for uveitis vs. ADA - SEC 2.32 (1.16, 4.63) - IFX 0.99 (0.49,1.96) - ETN 1.82 (1.13, 2.93) - GOL 1.59 (0.90, 2.80) - CTZ 1.12 (0.44, 2.83)

ADA= Adalimumab, ETN= Etanercept, IFX= Infliximab, GOL= Golimumab, CTZ= Certolizumab, SEC= Secukinumab, HR= Hazard ratio.

PICO 10.2 In adults with axial spondyloarthritis and inflammatory bowel disease (IBD), are some biologics more effective than others in improving outcomes?

Summary

In the ACR guideline search this PICO question was directly addressed by a study that pooled data from multiple RCTs and two open label studies of anti-TNF for patients with axial spondyloarthritis (Braun 2007)[131]. Reports indicated that infliximab was superior to etanercept and, on the other hand, adalimumab was not statistically different from either. The results showed wide confidence intervals and a high risk of bias. This PICO was indirectly addressed by an RCT that demonstrated the inefficacy of etanercept in patients with inflammatory bowel disease without a diagnosis of axial spondyloarthritis (Sandborn 2001)[132].
Our search update identified three observational studies (Üsküdar 2018, Korzenic 2019, Onac 2021)[133-135] that provide additional information. The Üsküdar 2018 study looked for the likely association with anti-TNF administration and de novo development of IBD in patients with spondyloarthritis from medical records. A total of 420 patients were included, 154 patients receiving anti-TNF treatment (etanercept = 52, infliximab = 50, adalimumab = 41 and golimumab = 11). De novo IBD was identified in 10 patients; 3 cases in patients treated with non-anti-TNF agents (1.1%) and 7 in the anti-TNF group (4.5% p 0.042). No significant difference was detected between the different anti-TNFs in relation to the risk of developing IBD, with an incidence for etanercept of 1.6 per 100 patient-years, for infliximab 1.59 per 100 patient-years, and for adalimumab 0.8 per 100 patient-years.
The second observational study (Korzenic 2019)[134] evaluated the risk of developing Crohn's disease (CD) and ulcerative colitis (UC) in patients with rheumatoid arthritis, psoriasis/psoriatic arthritis, ankylosing spondylitis, among others, treated with anti-TNFα agents. In total, 17,018 individuals with autoimmune diseases were exposed to anti-TNFα (the vast majority had infliximab, etanercept, and adalimumab), and 63,308 individuals were unexposed. Patients treated with etanercept had an increased risk of being diagnosed with CD and UC while on treatment (adjusted HR 2.0 [95% CI 1.4-2.8] and 2.0 [95% CI 1.5-2 .8], respectively, compared with infliximab 1.3 [95% CI 0.8-2.2] and 1.0 [95% CI 0.6-1.6] and adalimumab 1.2 [95% CI 0 0.8-1.8] and 0.6 [95% CI 0.3-1.0]. The nature of this association is uncertain.
The third study (Onac 2021)[135], although not comparative, provides descriptive evidence of a non-anti-TNF biologic, secukinumab. Based on data obtained from records of 306 patients in 10 UK hospitals (40.5% with spondyloarthritis and 59.5% with psoriatic arthritis), 24 patients (7.8%) experienced gastrointestinal adverse events after starting secukinumab. Among these, four (1.3%) had definite IBD, seven (2.3%) probable IBD, and 13 (4.2%) possible IBD. All definite cases were patients with spondyloarthritis, two had preexisting IBD, and two (0.7%) were de novo cases requiring surgical intervention. The absolute rates of de novo IBD in patients starting secukinumab are low.

Evidence Profile

Certainty assessment							**Nº of patients**		**Effect**		**Certainly**
Nº of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Infliximab	Etanercept	Relative (95% CI)	Absolute	
IBD flares (follow-up, 14-156 weeks; assessed by: onset or flare IBDs; Lower values are considered better)											
1	Randomized clinical trials[a]	Very serious[b]	Very serious[c]	Very serious[d]	Very serious[e]	Reporting bias[d]	366	419	-	mean 2 lower (0, 9)	⊕◯◯◯ Very low

[a] Pooled data from 8 RCTs (1 added later for adalimumab) + 2 open-label studies.

[b] Double-blind and open-label studies are included.
[c] Literature review: multiple studies of unknown quality.
[d] Part of the rationale is based on the observed low efficacy of these agents in IBD without spondyloarthritis. It is unclear whether this effect translates to outcomes for IBD in the setting of spondyloarthritis.
[e] Post hoc analysis (Gao)[136] published with the support of the pharmaceutical company that markets adalimumab substantially changed the result for adalimumab. These revised results suggest that adalimumab produced results between infliximab and etanercept, but was not statistically different from either.

Summary of observational studies

Author, year	Study design	Extension	Population	Treatment	Results
Üsküdar 2018[133]	Retrospective cohort	From 1998 to 2016	420 patients with AS according to the modified New York criteria of 1984 - 154 (36.7%) exposed to anti-TNFα - 266 (63.3%) not exposed	With anti-TNF Etanercept: 52 (33.8%) Infliximab 50 (32.5%) Adalimumab 41 (26.6%) Golimumab 11 (7.1%) Without anti-TNF NSAIDs 131 (49,2%) Sulfasalazine and NSAIDs 132 (49,6%) No medication 3 (0,7%)	- The incidence of IBDs (all cases were Crohn's disease) in the entire patient population was 2.4%. - 7 patients were from anti-TNF group (4.5%) - 3 patients were from without anti-TNF group (1.1%) - In the anti-TNF group, of 7 patients with new-onset IBDs, 3 were on etanercept, 3 on infliximab, and 1 on adalimumab. Incidence of de novo IBDs - Etanercept 1.6 per 100 patient-years - Infliximab 1.59 per 100 patient-years - Adalimumab 0.8 per 100 patient-years. -
Korzenic 2019[134]	Retrospective cohort	From 2004 to 2018	Patients with autoimmune diseases (rheumatoid arthritis, psoriasis/psoriatic arthritis, spondyloarthritis, others): - 17018 exposed to anti-TNFα - 6308 not exposed	Infliximab 7344 (43.2%) Etanercept 9072 (53.3%) Adalimumab 8355 (49.1%) Golimumab 1973 (11.6%) Certolizumab pegol 2503 (14.7%)	Risk of Crohn's disease during treatment (adjusted HR) - Infliximab 1.3 (0.8,2.2) - Etanercept 2.0 (1.4,2.8) - Adalimumab 1.2 (0.8,1.8) - Golimumab 2.0 (1.0,3.9) - Certolizumab pegol 2.2 (1.0,4.9) Risk of ulcerative colitis during treatment (adjusted HR) - Infliximab 1.0 (0.6,1.6) - Etanercept 2.0 (1.5,2.8) - Adalimumab 0.6 (0.3,1.0) - Golimumab 1.0 (0.4,2.6) - Certolizumab pegol 1.3 (0.5,3.4)
Onac 2021[135]	Retrospective cohort	3 years	306 patients who started treatment with secukinumab were analyzed: 124 (40.5%) with spondyloarthritis and 182 (59.5%) with psoriatic arthritis.	Secukinumab	- 4/24 patients had gastrointestinal AEs consistent with a definitive diagnosis of IBD, and all of them had a history of AS. - With a total follow-up time of 331 person-years, the incidence of IBD was 1.3 per 100 person-years (95% CI: 0.9, 2.0). - Two of these patients had known IBD and two were de novo cases, who developed symptoms of IBD after 5 and 12 months of treatment duration, respectively. - One patient diagnosed with Crohn's disease required surgical treatment (drainage of a perianal abscess) and the other underwent medical treatment for ulcerative colitis. - All definite cases of IBD discontinued secukinumab treatment. - In total, seven of the 24 gastrointestinal AEs were probable cases of IBD. Among these, secukinumab was discontinued in six patients. These included three patients with AS.

Strategy to optimize therapy (reduce the dose or extend the intervals) in patients with therapeutic objective achieved

Two PICO questions were raised in this topic:

1. In adults with stable spondyloarthritis treated with a biologic, is gradually decreasing the biologic dose more effective than not decreasing it in improving outcomes?
2. In adults with stable spondyloarthritis treated with a biologic, is stopping the biologic more effective than not stopping it in improving outcomes?

PICO 11.1. In adults with stable spondyloarthritis treated with a biologic, is tapering the biologic dose more effective than not tapering it to improve outcomes?

Summary

This PICO question was directly addressed by 10 RCTs, three from the ACR source guideline review (Yates 2015, Cantini 2013, Li 2016)[137-139], one RCT added by this review[140] and six RCTs included in a recent meta-analysis (Lawson 2021)[141]. Several observational studies also provided indirect evidence based on prospective (Arends 2015, Lee 2008, DeStefano 2014, Almirall 2015)[142-145] and retrospective studies (Plasencia 2015, Zavada 2016, Navarro-Compan 2011, Lee 2010, Paccou 2012, Fong 2016, Park 2016; Morck 2013, Chen 2018)[146-154]. These studies were generally small (n<50) and one of the studies (Plasencia)[146] included only 74% of patients with spondyloarthritis.

The RCT by Cantini et al.[138] included patients who had achieved remission with the use of etanercept and randomized them to continue treatment with a dose of 50 mg weekly (n = 21) or twice weekly (n = 22) (see Table 1). The RCT by Yates et al (2015)[137] randomized patients who responded to 50 mg/week of etanercept for 6 months to continue with this dose of etanercept or reduce it to 25 mg/week (see Table 2). These two studies showed that approximately 90% and 50%, respectively, of the cohorts who lowered their anti-TNF maintained their remission.

Lian 2018[155] included patients with axial spondyloarthritis who achieved clinical remission for at least 6 months after receiving a standard dose of etanercept treatment and compared discontinuation, 25% reduction, and 50% reduction. The 25% taper protocol was to space 25% every 3 months until complete suspension and the 50% taper protocol was to space 50% every 3 months until complete suspension. Almost all patients (103/107, 96.3%) in the 25% dose taper group and more than 80% (71/88, 80.7%) of patients in the dose taper group 50% of the dose maintained low disease activity or clinical remission during the first year. At the end of the 2-year follow-up, the percentage of patients who maintained low activity or remission was 55.7% (50% dose reduction) and 84.1% (25% dose reduction). Activity rates were significantly lower in the 25% taper group compared to the other two groups (see Evidence Summary Tables).

A recent systematic review and meta-analysis (Lawson 2021)[141] investigated the efficacy and safety of dose reduction of anti-TNF therapy in the treatment of axial spondyloarthritis compared to usual care. Six randomized trials with 747 participants (442 with ankylosing spondylitis and 305 with non-radiographic axial

spondyloarthritis) were included. Compared with the standard dose, there were fewer events with the reduced dose for the ASAS criteria for 40% improvement (RR 0.62 [95% CI 0.49, 0.78]) and for ASAS partial remission (RR 0 .17 [95% CI 0.06, 0.46]). There was an increase in BASDAI score (mean difference 0.35 [95% CI 0.10, 0.60]) and no difference in C-reactive protein levels at the reduced dose. There were more disease flares/relapses (RR 1.73, 95% CI 1.32 to 2.27) with the reduced dose. There were no differences in infection rates or injection/infusion reactions.
In general, the results of observational studies suggest that changes to reduced treatment regimens with biologics for patients with stable disease do not have a significant effect on most of the main outcomes. Approximately 50-90% of subjects remained in clinical remission 1 year after frequency or dose was halved.

Quality of evidence: Low ⊕⊕◯◯

Evidence Profiles

Standard treatment versus tapering with anti-TNF (etanercept): F/U to long time to improve outcomes in patients with stable spondyloarthritis (direct evidence) Cantini 2013[138]

Certainty assessment							Conclusions summary				
Nº of patients (studies)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Overall certainty of evidence	Event rate (%)		Relative effect (95% CI)	Expected absolute effects	
							Anti-TNF tapering treatment	Anti-TNF standard treatment		Risk with tapering treatment	Differences with anti-TNF standard treatment
Time to disease relapse											
43(1 RCT)	Serious [a]	Not serious [b]	Not serious	Serious [c]	None	⊕⊕◯◯ Low	21	22	-	-	MD 2 lower (-3.42,-0.58)
Relapse											
43(1 RCT)	Serious [a]	Not serious [b]	Not serious	Serious [d]	None	⊕⊕◯◯ Low	2/21 (9.5%)	3/22 (13.6%)	**OR 1,50** (0.22, 10.02)	95 per 1000	41 more per 1000 (-73, 418)
Remission											
43(1 RCT)	Serious [a]	Not serious [b]	Not serious	Serious [d]	None	⊕⊕◯◯ Low	19/21 (90.5%)	19/22 (86.4%)	**OR 0.67** (0.10, 4.45)	905 per 1000	41 less per 1000 (-418, 72)
BASDAI, mean of change, 2 years											
43(1 RCT)	Serious [a]	Not serious [b]	Not serious	Serious [c]	None	⊕⊕◯◯ Low	21	22	-	-	MD 0.1 higher (-0.31, 0.51)
BASFI, mean of change,2 years											
43(1 RCT)	Serious [a]	Not serious [b]	Not serious	Serious [c]	None	⊕⊕◯◯ Low	21	22	-	-	MD 0 (-0.71, 0.71)
BASMI, change, 2 years											
43(1 RCT)	Serious [a]	Not serious [b]	Not serious	Serious [c]	None	⊕⊕◯◯ Low	21	22	-	-	MD 0.1 higher (-0.56, 0.76)
Modified Schober test, 2 years											

43(1 RCT)	Serious [a]	Not serious [b]	Not serious	Serious [c]	None	⊕⊕◯◯ Low	21	22	-	-	MD **0.2 higher** (-0.86, 1.26)
Fingertip to floor distance, 2 years											
43(1 RCT)	Serious [a]	Not serious [b]	Not serious	Serious [c]	None	⊕⊕◯◯ Low	21	22	-	-	MD **0.1 higher** (-1.38, 1.58)
Chest expansion, 2 years											
43(1 RCT)	Serious [a]	Not serious [b]	Not serious	Serious [c]	None	⊕⊕◯◯ Low	21	22	-	-	MD **0** (-0.31, 0.31)
Urinary infection, 2 years											
43(1 RCT)	Serious [a]	Not serious [b]	Not serious	Serious [d]	None	⊕⊕◯◯ Low	1/21 (4.8%)	2/22 (9.1%)	**OR 2.00** (0.17, 23.86)	48 per 1000	**43 more per 1000** (-39, 496)
Upper respiratory tract infections, 2 years											
43(1 RCT)	Serious [a]	Not serious [b]	Not serious	Serious [d]	None	⊕⊕◯◯ Low	5/21 (23.8%)	7/22 (31.8%)	**OR 1,49** (0.39, 5.74)	238 per 1000	**80 more per 1000** (-129, 404)

CI: Confidence interval; MD: Mean differences; OR: Odds ratio.

Explanations

a. Unblinded study. Most methodologies were not cleary explained.
b. Does not apply, single study.
c. Results of a single small study.
d. Single study. Wide 95% CI includes the possibility that there are no differences.
e. Single study. 95% CI includes the possibility that there are no differences.
f. Low event rates. Wide CI includes the possibility that there are no differences.

ETN 50 mg/week versus 25 mg/weeks (6 months) for stable spondyloarthritis patients (direct evidence) Yates 2015[137]

Certainty assessment							Conclusions summary				
							Event rate (%)			Expected absolute effects	
Nº of patients (studies)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Overall certainty of evidence	ETN 25 mg/week, 6 months	ETN 50 mg/weeks	Relative effect (95% CI)	Risk with ETN 25 mg/week, 6 months	Risk differences with ETN 50 mg/week
ASAS20, 6 months											
47(1 RCT)	Serious [a]	Not serious [b]	Not serious	Serious [c]	None	⊕⊕◯◯ Low	20/24 (83.3%)	14/23 (60.9%)	**OR 0.31** (0.08, 1.21)	833 per 1000	225 less per 1000 (-548, 25)
ASAS partial remission, 6 months											
47(1 RCT)	Serious [a]	Not serious [b]	Not serious	Serious [d]	None	⊕⊕◯◯ Low	7/24 (29.2%)	1/23 (4.3%)	**OR 0.11** (0.01, 0.99)	292 per 1000	248 less per 1000 (-288, -2)
BASDAI50, 6 months											
47(1 RCT)	Serious [a]	Not serious [b]	Not serious	Serious [d]	None	⊕⊕◯◯ Low	16/24 (66.7%)	8/23 (34.8%)	**OR 0.27** (0.08,0.89)	667 per 1000	316 less per 1000 (-529, -26)
Complete clinical response, 6 months											
47(1 RCT)	Serious [a]	Not serious [b]	Not serious	Serious [d]	None	⊕⊕◯◯ Low	20/24 (83.3%)	12/23 (52.2%)	**OR 0.22** (0.06, 0.84)	833 per 1000	310 less per 1000 (-603, -26)
CRP (mg/l), change, 6 months											
47(1 RCT)	Serious [a]	Not serious [b]	Not serious	Serious [c]	None	⊕⊕◯◯ Low	24	23	-	-	MD 0.2 lower (-0.78, 0.39)

Serious adverse events, 6 months											
47(1 RCT)	Serious [a]	Not serious [b]	Not serious	Serious [e]	None	⊕⊕◯◯ Low	0/24 (0.0%)	0/23 (0.0%)	Not estimable	0 per 1000	Not estimable

CI: Confidence interval; OR: Odds ratio; MD: Mean differences.

Explanations

a. Unblinded study.
b. Does not apply, single study.
c. Single study; small sample size. 95% CI overlaps the line with no difference.
d. Single study; small sample size.
e. Events were not reported.

Standard treatment versus tapering with anti-TNF (Etanercept/Infliximab/Adalimumab) to improve outcomes for stable spondyloarthritis patients (direct evidence). Lawson 2021[141]; Chen 2018[140]

Interventions: Etanercept 50 mg/week versus 50 mg every 2 weeks or 25 mg /week; Adalimumab 40 mg every 2 weeks or Adalimumab 40 mg every 3 weeks; Infliximab 5 mg/kg in weeks 4, 6 y 10 (load), then 5 mg/kg every 6 weeks or 5 mg/kg in weeks 4, 6 y 10 (load), then 5 mg/kg on if it is necessary.

Certainty assessment							**Conclusions summary**				
							Event rate (%)			Expected absolute effects	
Nº of patients (studies)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Overall certainty of evidence	Standard treatment	ETN/ADA/INF Tapering treatment	Relative effect (95% CI)	Risk with tapering treatment	Risk difference with standard treatment
ASDAS											
(1 RCT)[1]	Serious [a]	Not serious [b]	Not serious	Serious [c]	None	⊕⊕◯◯ Low	24	23			MD 0.52 higher (0.15, 0.87)
ASAS 40 (Yates 2015, Landewé 2018, Moreno 2019)[137,156,157] *											
(3 RCT)	Serious [a]	Not serious	Not serious	Not serious	None	⊕⊕⊕◯ Moderate	181/300	95/238	RR 0,62 (0.49,0.78)	62 per 100	285 less per 1000 (-390, 165)
BASDAI (Breban 2002, Cantini 2013, Li 2016)[158,138,139] *											
(3 RCT)	Serious [a]	Not serious	Not serious	Not serious	None	⊕⊕⊕◯ Moderate	162	110			MD 0.35 higher (-0.10, 0.60)
Relapse (Breban 2002, Cantini 2013, Moreno 2019, Landewé 2018)[158,138,157,156] *, Chen 2018[140]											
(4 RCT)	Serious [a]	Serious	Not serious	Not serious	None	⊕⊕◯◯ Low	96/389	62/333	RR 1. 32 (0.99, 1.76)	132 per 1000	240 more per 1000 (-8,570)
Any adverse (Breban 2002, Cantini 2013, Moreno 2019, Landewé 2018, Yates 2015, Li 2016)[158,138,157,156,137,139] *											
(6 RCT)	Serious [a]	Not serious	Not serious	Not serious	None	⊕⊕⊕◯ Moderate	130/397	125/347	RR 0.98 (0.76, 1.25)	98 per 100	15 less per 1000 (-180,188)

*Studies from systematic review of Lawson *et al.* 2021[141]
CI: Confidence interval; OR: Odds ratio; MD: Mean differences.

Explanations

a. Unblinded study.
c. Single study; small sample size. 95% CI overlaps the line with no difference.
d. Single study; small sample size.
e. Event were not reported.

f. Inconsistent results between studies.

Gradual tapering of Etanercept to 50% versus 25% in patients with axial spondyloarthritis in clinical remission (direct evidence). Lian 2018[155]

Certainty assessment							Conclusions summary				
Nº of patients (studies)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Overall certainty of evidence	Event rate (%)		Relative effect (95% CI)	Expected absolute effects	
							With 50% reduction	With 25% reduction		Risk with 50% reduction	Risk difference with gradual 25% reduction
Maintenance of LDA or remission, 2 years											
(1 cohort study)	Very serious [a, d]	Not serious [b]	Not serious	Serious [e]	None	⊕◯◯◯ Very low	71/88	103/107	RR 1.72 (1.42, 2.09)	172 per 1000	540 more per 1000 (315, 817)
LDA or clinical remission, 1 year											
(1 cohort study)	Very serious [a, d]	Not serious [b]	Not serious	Serious [e]	None	⊕◯◯◯ Very low	49/88	90/107	RR 1.19 (1.07, 1.33)	119 per 1000	142 more per 1000 (53, 248)
BASDAI, 2 years											
(1 cohort study)	Very serious [a, d]	Not serious [b]	Not serious	Serious [e]	None	⊕◯◯◯ Very low	88	107			MD -2.0 (-2.47, 1.53)
ASDAS-CRP, 2 years											
(1 cohort study)	Very serious [a, d]	Not serious [b]	Not serious	Serious [e]	None	⊕◯◯◯ Very low	88	107			MD -0.30 (-0.52, 0.08)

CI: Confidence interval; MD: Mean differences; LDA: Low disease activity.

Explanations

a. Unblinded study. Methodological details are missing.
b. Does not apply, single study.
c. Single study; small sample size.
d. Study was not randomized.
e. Single study.

Standard anti-TNF treatment versus gradual tapering to long time to improve outcomes in stable spondyloarthritis (Indirect evidence). Plasencia 2015[146]; Zavada 2016[147]

Certainty assessment							Conclusions summary				
Nº of patients (studies)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Overall certainty of evidence	Event rate (%)		Relative effect (95% CI)	Expected absolute effects	
							Tapering treatment: long time	Anti-TNF standard treatment		Risk with gradual tapering treatment: long time	Risk difference with anti-TNF standard treatment
BASDAI, change, 2 years											
253(2 observational studies)	Serious [a]	Not serious	Not serious	Not serious	None	⊕◯◯◯ Very low	126	127	-	-	MD 0.03 higher (-0.22, 0.28)

BASFI, change, 2 years											
136(1 observational study)	Serious [a]	Not serious [b]	Not serious	Not serious	None	⊕◯◯◯ Very low	83	53	-	-	MD 0.02 higher (-0.4, 0.44)
Flare diseases											
117(1 observational study)	Serious [a]	Not serious [b]	Not serious	Serious [c]	None	⊕◯◯◯ Very low	8/43 (18.6%)	22/74 (29.7%)	**OR 1.85** (0.74, 4.62)	186 per 1000	111 more per 1000 (-41, 328)

CI: Confidence interval; MD: Mean differences; OR: Odds ratio.

Explanations

a. One of the two observational studies were retrospective.
b. Does not apply, single study.
c. Wide 95% CI, overlaps the line with no difference.

Additional observational data (indirect evidence)

Author, year	Study design	Extension	Population description	Treatment	Results
Chen 2018[154]	Observational	1 year	N=450 patients (120 with ankylosing spondylitis; 330 with RA)	Tapering or discontinuation of bDMARDs treatment (adalimumab, etanercept, golimumab, tocilizumab, abatacept y rituximab) Indirect evidence: There is no direct comparison of tapering treatment with non-tapering treatment.	SF-36 and Global Quality of Life (GQL): DMARD tapering or discontinuation resulted in significant decreases in all SF-36 and GQL domains in the ankylosing spondylitis and RA groups. Relapse rate: 50% for patients with ankylosing spondylitis; 90% for RA patients
Almirall 2016[145]	Observational	Mean 42 months (±18.8 months)	N=20 patients with axial spondyloarthritis with disease in remission >1 year after tapering of infliximab or adalimumab	Infliximab tapering to 3 mg/kg every 8 weeks; extension of the interval between doses of adalimumab to 40 mg every 3 weeks Indirect evidence: There is no direct comparison of tapering treatment with non-tapering treatment.	The data could support the tapering of biological drugs in patients with low disease activity. 18/20 had therapeutic drug levels, no patients had anti-drug antibodies, no patients had active sacroiliitis on MRI
Fong 2011[151]	Observational retrospective	24 weeks	N=48 patients with ankylosing spondylitis (n=33) or PsA (n=15) who achieved stable disease on anti-TNF treatment	Tapering of the anti-TNF dose by approximately one third; the dose was reduced or the interval between doses extended Anti-TNF used: adalimumab, etanercept, infliximab or certolizumab Indirect evidence: There is no direct comparison of tapering treatment with non-tapering treatment.	Approximately 60% of patients with severe ankylosing spondylitis or PsA who achieve low disease activity can reduce their anti-TNF dose by a third over a median of 1 year. Disease activity at 24 weeks was similar in patients with ankylosing spondylitis with and without tapering of anti-TNF treatment: BASDAI 2,3 ± 1,8 vs 2,4 ± 1,0, respectively (p = 0,811). 19 of 33 (58%) patients with ankylosing spondylitis and 9 of 15 (60%) patients with PsA maintained an anti-TNF dose reduction for a mean of 1.0 ± 0.8 years. In all patients who did not achieve tapering, reestablishing the standard dose of anti-TNF allowed achieving low disease activity.

Park 2016[152]	Retrospective cohort	2 years	165 patients with ankylosing spondylitis	Etanercept or adalimumab Standard dose (n=49) vs. tapering (n=116) Direct evidence: Individualized tapering in all patients at the discretion of the physician. Recruitment restricted to patients with cervical and lumbar radiographs.	Baseline characteristics between two groups were comparable, except for a higher BASDAI for the standard-dose group (7.1 vs. 6.3, p = 0.003). mSASSS progression: similar for standard dose and tapering groups; the subgroup of patients with baseline syndesmophytes progressed significantly faster in the tapering group, after adjustment for baseline status (1.23 vs. 1.72 mSASSS units/year, p = 0.023).
Arends 2015[142]	Observational	24 months	58 patients with ankylosing spondylitis	Individualized tapering of etanercept (n = 39), infliximab (n = 10) or adalimumab (n = 9) Direct evidence: There is no direct comparison of tapering treatment with non-tapering treatment. Tapering was at the discretion of the physicians.	74%, 62%, and 53% sustained tapering after 6, 12, and 24 months, respectively. ASDAI < 4 after maintaining tapering for 24 months.
De Stefano 2014[144]	Prospective cohort	48 weeks	N=21 patients who achieved partial remission with etanercept 50 mg/week (ETN)	ETN tapering from 25 mg, from 2/week (12w) to 1/week Direct evidence: There is no direct comparison of tapering treatment with non-tapering treatment.	24 weeks: 20/21 patients with tapering (95.2%) remained in remission 36 weeks: 16/21 patients (76.2%) in remission with tapering at 24 weeks sustained remission. 48weeks: 16/21 patients (76.2%) in remission with tapering at 24 weeks sustained remission.
Morck 2013[153]	Prospective cohort	2 years	N=18 patients who completed 56 weeks of IFX treatment	Dose reduction and interval extension of IFX Reduced to 3 mg/kg every 8 weeks after 5 mg/kg every 6 weeks Direct evidence: There is no direct comparison of tapering treatment with non-tapering treatment.	BASDAI: No significant increase in BASDAI median, 2.1 (IQR 0.6 to 3.6) vs. 3.2 (0.4 to 4.2) after tapering. CRP (mg/L): median 8 (IQR 8 to 8) vs. 8 (5 to 8) after tapering.
Paccou 2012[150]	Observational retrospective	Mean 43.5 months (±17.9)	N=65 patients with ankylosing spondylitis who achieved remission	Tapering of adalimumab, etanercept o infliximab Direct evidence: There is no direct comparison of tapering treatment with non-tapering treatment.	Dose adjustment and reduction in treatment frequency were effective in maintaining remission. Follow-up at 6 months after tapering: ADA: sustained remission in 5 of 5 patients (100%) ETN: sustained remission in 12 of 17 patients (70.6%) IFX: sustained remission in 26 of 27 patients (96.3%) The cumulative probability of continuing with anti-TNF after tapering was 79% at 12 months, 70.5% at 24 months, and 58.8% at 36 months.
Navarro-Compan 2011[148]	Case series	Mean 26.1 months	16 patients switched to low-dose etanercept	Dose reduction with etanercept (from 50 mg/week) to lower dose, variable between patients. Direct evidence: There is no direct comparison of tapering treatment with non-tapering treatment.	Median scores and ranges at the start of the low-dose regimen and 6 months later, respectively: BASDAI: 1.6 (0.9 to 2.4) and 1.4 (0.3 to 3.2) BASFI: 2.2 (0.8 to 3.9) and 2.5 (0.8 to 3.2) Patient global assessment: 15 (10 to 30) and 10 (2.5 to 20) Patients with follow-up at 12 months (n = 12), 24 months (n = 7), or longer (n = 5) remained in clinical remission with BASDAI values <2 and normal CRP values (<5 mg/L). No serious adverse events were reported.
Lee 2008[143]	Observational retrospective	6 months	N=18 patients with active ankylosing spondylitis	ETN 25mg/week; Previous dose: 50 mg/week for 3 months	Etanercept 25 mg/week per week is effective in maintaining remission.

			who achieved remission with etanercept 50 mg/week (ETN)	Direct evidence: There is no direct comparison of tapering treatment with non-tapering treatment.	Values at the end of 50 mg/week and after 25 mg/week BASDAI: from 2.1 ± 1.0 to 2.1 ± 1.3 ESR (mm/h): from 8.7 ± 9.9 to 6.7 ± 5.5 CRP (mg/dl): from 0.2 ± 0.7 to 0.2 ± 0.2

PICO 11.2. In adults with stable spondyloarthritis treated with a biologic, is discontinuation of the biologic more effective than not discontinuation in improving outcomes?

Summary

This PICO question was directly addressed by three studies. Lian et al. 2018[155] evaluated the efficacy of different etanercept reduction or discontinuation strategies in an axial spondyloarthritis cohort from southern China. They reported significantly more patients in the discontinuation group (19%) than in the taper group (5.4%, p<0.001) with relapses as early as 6 months. Almost all patients (103/107, 96.3%) in the 25% dose reduction group and more than 80% (71/88, 80.7%) in the 50% reduction group of the dose maintained low disease activity or clinical remission during the first year. At the end of the 2-year follow-up, the percentage of patients who discontinued medication and maintained low activity or remission was 28.6% (see Evidence Summary Tables).

Landewé R.[156] explored the ability to withdraw adalimumab treatment in patients with non-radiographic axial spondyloarthritis who achieved sustained clinical remission. They reported that a greater proportion of patients who continued adalimumab versus those who received placebo did not experience a flare (107/152, 70% of patients vs. 72/153, 47% of patients; p<0.0001) at follow-up through week 68. Moreno 2019[157] evaluated the time free of flares in patients with ankylosing spondylitis with persistent clinical remission after withdrawal of the anti-TNF infliximab. After stopping treatment, 21 of 36 patients (58%) experienced clinical relapse at some point during follow-up (see Evidence Summary Tables).

On the other hand, this PICO question was indirectly addressed by an RCT (Deng 2013)[159], which examined discontinuation versus use of a DMARD as a comparator. Five observational studies also provided relevant indirect data (Breban 2002, Brandt 2003, Baraliako 2004, Heldman 2011, Zhao 2017)[158,160-163]. Overall, the results of this indirect evidence suggest that discontinuation of anti-TNF results in a high rate of buds. (see evidence summary tables)

Quality of evidence: Low ⊕◯◯◯

Effectiveness of different reduction or interruption strategies of etanercept in axial spondyloarthritis cohort (direct evidence).

Certainty assessment							Conclusions summary				
Nº of patients (studies)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Overall certainty of evidence	Event rate (%)		Relative effect (95% CI)	Expected absolute effects	
							25% or 50% gradual reduction	Discontinuation		Risk with 25% or 50% reduction	Risk difference with discontinuation
Relapse, 6 months											
(1 cohort study)[155]	Very serious [a, d]	Not serious [b]	Not serious	Serious [e]	None	⊕◯◯◯ Very low	11/195	12/63	RR 3,37 (1. 56, 7.27)	337 per 1000	1000 more per 1000 (420, 1000)
LDA or clinical remission, 2 years											
(1 cohort study) [155]	Very serious [a, d]	Not serious [b]	Not serious	Serious [e]	None	⊕◯◯◯ Very low	139/195	30/63	RR 0,66 (0.50, 0.87)	66 per 100	255 less per 1000 (-375, -98)

CI: Confidence interval; MD: Mean differences; LDA: Low disease activity.

Explanation.

a. Unblinded study. Methodological details are missing.
b. Does not apply, single study.
c. Single study; small sample size.
d. Study was not randomized.
e. Single study.

Withdrawal of adalimumab treatment in the maintenance remission in patients with axial spondyloarthritis

Certainty assessment							Conclusions summary				
Nº patients (studies)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Overall certainty of evidence	Event rate (%)		Relative effect (95% CI)	Expected absolute effects	
							Adalimumab	Placebo		Risk with 50% reduction	Risk difference with 25% gradual reduction
Proportion of patient without relapses (defined by ASDAS ≥2·1 in 2 consecutive visits), 68 weeks											
1 (RCT)[156]	Serious	Not serious [b]	Not serious	Not serious	None	⊕⊕⊕◯ Moderate	107/152	72/153	RR 1.49 (1.22, 1.82)	149 per 1000	368 more per 1000 (165,615)

CI: Confidence interval; MD: Mean differences.

Explanations

a. Methodological details are missing.
b. Does not apply, single study.
c. Single study; small sample size.
d. Study was not Randomized.
e. Single study.

Effectiveness of infliximab interruption in axial spondyloarthritis (direct evidence)

Author, year	Study design	Extension (weeks)	Risk of bias	Primary outcome	Indirect	Imprecision	Consistency	Certainty assessment	N	Flare/ Relapse %	Extension (years)
Moreno 2019[157]	Observational	48	Serious	Clinical remission without flare	Uncontrolled	Not serious	Not serious	Low	36	21/58	6 months

Summary of observational data (all Indirect evidence)

Author, year	Study design	Extension (weeks)	Risk of bias	Primary outcome	Indirect	Imprecision	Consistency	Certainty assessment	N	Flare/ Relapse %	Extension (years)
Breban 2002[158]	Observational	24	Serious	GAP/ASAS20	Uncontrolled	Serious (Measures of dispersion are missing in multiple studies)	Not serious	Very low	48	73	Mean 13
Brandt 2003[160]	Observational	36	Serious	BASDAI	vs. baseline; active patients				26	100	14.9
Baraliakos 2004[161]	Observational	48	Serious	BASDAI	vs. baseline, uncontrolled				42	98	15
Deng 2013[159]	RCT	52	Serious	BASDAI	Compared to DMARD, without continuation of anti-TNF				111	79	9
Heldmann, 2011[162]	Observational	Mean 64	Serious	BASDAI					14	64	-----
Sebastian 2017[164]	Observational	36+	Serious	BASDAI	vs. baseline, uncontrolled				54	74	N/A
Zhao 2018[163]	Observational	52	Serious	BASDAI	vs. baseline, uncontrolled				35	46	7.7
								Total/Mean	330 Patients	76.3%	7.7

Descriptive summary of studies (all indirect evidence)

Author, year	Study design	Extension	Population description	Treatment	Results
Sebastián 2017[164]	Observational	9 to 40 months	65 patients with axial spondyloarthritis	Discontinuation of anti-TNF treatment after achieving low disease activity	Relapse: 40 patients (74% of patients with low disease activity had increased activity after a median of 14 weeks. Low disease activity recovered in all patients after a median of 7 weeks after restarting anti-TNF treatment.
Zhao 2018[163]	Observational	3 years	35 patients with ankylosing spondylitis who achieved ASAS 20 remission with etanercept	Etanercept discontinuation after remission	Relapse: 21 of 35 (60.0%) patients relapsed after etanercept withdrawal Median time to relapse: 15 months (IQR, range 3.7 to 26.3 months)
Deng 2013[159]	Randomized control trial	1 year maximum; follow-up mean 5.1 ± 3.9 months	111 patients with ankylosing spondylitis achieving an ASAS20 response after treatment with etanercept	Thalidomide (150mg/day); Sulfasalazine (1 g, 2 times a day); or NSAIDs	Regardless of maintenance treatment, the majority of patients who completed etanercept treatment experienced disease recurrence. <u>Recurrence rates:</u> NSAIDs: 33 of 37 patients (89.2%) Sulfasalazine: 28 of 33 (84.8%) Thalidomide: 18 of 30 (60%)
Heldmann 2011[162]	RCT/ Observational	Mean 1,3 years	103 patients (n=14 with withdrawn treatment)	Discontinue/Continue IFX	9 of 14 patients (64.3%) who discontinued infliximab after the primary study experienced ankylosing spondylitis relapse
Baraliakos 2005[161]	Single arm, observational study	1-year follow-up after discontinuation	42 patients with ankylosing spondylitis	Infliximab discontinuation after 3 years of treatment	The BASADI value after drug discontinuation at the time of relapse was 3.6 (± 1.7). The mean time between discontinuation and relapse was 17.5 weeks (±7.9 range 7 to 45), and the median time was 15 weeks.

					At 3 weeks after the last patient relapsed, 41 of the 42 patients had restarted infliximab treatment (the first patient relapsed at 7 weeks; the last patient more than 52 weeks) 41 patients who were reinfused responded well to reinitiation of infliximab treatment. BASDAI improved from 6.1 ± 1.4 to 3.2 ± 2.6 at 6 weeks and to 2.9 ± 2.1 at 12 weeks after reinfusion
Brandt 2003[160]	RCT/ Observational	24 weeks (observational phase)	38 patients with active ankylosing spondylitis	Etanercept (ETN) discontinuation after 12 weeks of treatment	Relapse: 18/24 patients (75%) relapsed after discontinuation of ETN treatment. The mean (SD) time to relapse was 6.2 (3.0) weeks. The remaining 6 patients (25%) relapsed later.
Breban 2002[158]	Observational	6 months	50 patients with active ankylosing spondylitis	Infliximab (3 infusions 5mg/kg at weeks 0, 2 and 6)	Relapse was reported in 73% of patients who completed treatment. Median delay of 14 weeks after the last infusion.

Non-pharmacological interventions in adults with axial spondyloarthritis.

Seven PICO questions were posed in this topic:

1. In adults with axial spondyloarthritis, is any form of physical therapy more effective than no physical therapy in improving health and functional status?
2. In adults with axial spondyloarthritis, are aquatic physiotherapy interventions more effective than land-based physiotherapy interventions in improving health status and functional status?
3. In adults with axial spondyloarthritis, are aerobic exercises more effective than physiotherapy in improving health status and functional status?
4. In adults with axial spondyloarthritis, is high-intensity exercise more effective than no high-intensity exercise in improving health and functional status?
5. In adults with axial spondyloarthritis, is an exercise program (home exercise plan, pilates, or any exercise with prescription parameters) more effective than no exercise program in improving health and functional status?
6. In adults with stable axial spondyloarthritis, is unsupervised back exercise more effective than no exercise in improving health and functional status?
7. In adults with spondyloarthritis and spinal fusion or advanced spinal osteoporosis, is spinal manipulation (chiropractic or osteopathic) more effective than no spinal manipulation in improving health and functional status?

PICO 12.1. In adults with axial spondyloarthritis, is any form of physical therapy more effective than no physical therapy in improving health and functional status?

Summary

In active spondyloarthritis, two small RCTs answered this question (Kjeken, Bulstrode)[165,166]. There were some significant differences between groups, with BASFI and SF-36 physical outcomes in favor of the intervention, at high risk of bias (see Evidence Summary Tables). Two others small RCTs addressed this question in adults with active non-radiographic axial spondyloarthritis (Cozzi, Viitanen)[167,168], showing significant differences, with 4 out of 5 response outcomes favoring intervention, wide confidence intervals, but without serious risk of bias (see evidence summary tables).
In stable spondyloarthritis, 10 RCTs reported in 11 articles answered this question[169-179]. There were some significant differences between groups, with 5 of the 7 response outcomes assessed in favor of the intervention, with narrow confidence intervals, and substantial variation in study quality (see Evidence Summary Tables).

Evidence Profiles

Evidence of physiotherapy versus no physiotherapy in active radiographic axial spondyloarthritis[165,166]

Certainty assessment							No. of patients		Effect		Certainly
N. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Any physiotherapy	Control: no physiotherapy	Relative (95% CI)	Absolute	
BASDAI (follow-up mean, 12 weeks; Lower values are considered better)											
1	Randomized control trial	Serious[1]	Not serious	Not serious	Not serious	None	46	49	-	MD 14.3 lower (-22.64, 5.96)	⊕⊕⊕◯ Moderate
Performance status: BASFI (follow-up mean, 12 weeks; Lower values are considered better)											
1	Randomized control trial	Serious[1]	Not serious	Not serious	Not serious	None	46	49	-	MD 6 lower (-12.82, 0.82)	⊕⊕⊕◯ Moderate
Performance status: SF-36, physical functioning, role physical (follow-up mean, 12 weeks; Higher values are considered better)											
1	Randomized control trial	Serious[1]	Not serious	Not serious	Not serious	None	46	49	-	MD 11.8 higher (2.02, 21.58)	⊕⊕⊕◯ Moderate
BAS-G (follow-up mean, 12 weeks; Lower values are considered better)											
1	Randomized control trial	Serious[1]	Not serious	Not serious	Not serious	None	46	49	-	MD 6.4 lower (-14.8, 2)	⊕⊕⊕◯ Moderate

Explanations
[1] Small sample size.
[2]Lack of allocation concealment. Low number of patients

Evidence of physiotherapy versus no physiotherapy in active non-radiographic axial spondyloarthritis [167,168]

Certainty assessment							No. of patients		Effect		Certainly
N. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Any physiotherapy	Control: no physiotherapy	Relative (95% CI)	Absolute	
BASDAI, mean differences (follow-up mean, 3 weeks; Lower values are considered better)											
1	Randomized control trial	Not serious	Not serious	Not serious	Very serious[1]	None	25	18	-	MD 18 lower (-26.65, -9.35)	⊕⊕◯◯ Low
Dolor (follow-up mean, 2 weeks; Lower values are considered better)											
1	Randomized control trial	Not serious	Not serious	Not serious	Very serious[1]	None	12	12	-	MD 22.7 lower (-38.48, -6.92)	⊕⊕◯◯ Low
Performance status: BASFI, mean differences (follow-up mean, 3 weeks; Lower values are considered better)											
1	Randomized control trial	Not serious	Not serious	Not serious	Very serious[1]	None	25	18	-	MD 1 lower (-1.76, -0.24)	⊕⊕◯◯ Low
Performance status: HAQ-S, mean differences (follow-up mean, 3 weeks; Lower values are considered better)											
1	Randomized control trial	Not serious	Not serious	Not serious	Very serious[1]	None	25	18	-	MD 0.11 lower (-0.46,0.24)	⊕⊕◯◯ Low
BAS-G, mean differences (follow-up mean, 2 weeks; Lower values are considered better)											
1	Randomized control trial	Not serious	Not serious	Not serious	Very serious[1]	None	25	18	-	MD 17 lower (-28.42, -5.58)	⊕⊕◯◯ Low

Explanations
[1] Small sample size.

Evidence of physiotherapy versus no physiotherapy in patient with axial spondyloarthritis[169-179]

Certainty assessment	No. of patients	Effect	Certainly

N. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Other considerations	Any physiotherapy	Control: no physiotherapy	Relative (95% CI)	Absolute	
BASDAI, mean difference (follow-up mean, 13.5 weeks; Lower values are considered better)											
4	Randomized control trial	Serious[1]	Serious	Not serious	Not serious	None	450	433	-	MD 0.67 lower (-1.2, -0.14)	⊕⊕◯◯ Low
Pain, mean difference (follow-up mean, 13.75 weeks; Lower values are considered better)											
4	Randomized control trial	Serious[1]	Serious	Not serious	Not serious	None	432	424	-	MD 1.26 lower (-2.8, 0.28)	⊕⊕◯◯ Low
ASQOL, mean difference (follow-up mean 24 weeks; Lower values are considered better)											
2	Randomized control trial	Not serious	Serious	Not serious	Not serious	None	410	399	-	MD 0.31 lower (-1.48, 0.86)	⊕⊕⊕◯ Moderate
Performance status: BASFI, mean difference (follow-up mean 13.5 weeks; Lower values are considered better)											
4	Randomized control trial	Serious[1]	Serious	Not serious	Not serious	None	503	486	-	MD 0.47 lower (-0.90, -0.04)	⊕⊕◯◯ Low
Performance status: SF-36 physical functioning (follow-up mean, 12 weeks; Higher values are considered better)											
1	Randomized control trial	Serious[1]	Not serious	Not serious	Not serious	None	25	18	-	MD 0.18 higher (0.07, 0.29)	⊕⊕⊕◯ Moderate
Performance status: BASMI, mean difference (follow-up mean 7 weeks; Lower values are considered better)											
3	Randomized control trial	Not serious	Not serious	Not serious	Not serious	None	103	98	-	MD 0.26 lower (-0.36, 0.15)	⊕⊕⊕⊕ High
Patient global disease activity, mean difference (follow-up mean 24 weeks; Lower values are considered better)											
1	Randomized control trial	Not serious	Not serious	Not serious	Not serious	None	381	375	-	MD 0.39 lower (-0.71, -0.07)	⊕⊕⊕⊕ High

Explanations

[1] 1 study with unclear randomization and assessor blinding.

[2] 1 study used a 3-arm design comparing 2 interventions with a control group.

[3] Small sample size, short follow-up.

PICO 12.2. In adults with axial spondyloarthritis, are aquatic physiotherapy interventions more effective than land-based physiotherapy interventions in improving health status and functional status?

Summary

This PICO was directly addressed by 5 RCTs[180-184]. There were some significant differences between groups, with 4 of 6 outcomes examined favoring the intervention, with confidence intervals of variable width, and not serious risks of bias for most outcomes. A review of evidence[185] of exercise in ankylosing spondylitis included 35 studies (30 of exercises on land and 5 of exercises in water, combined or not with biological drugs), with a total of 2515 patients, in which the majority showed a positive effect of exercise on the BASDAI, BASFI, pain, mobility, function and quality of life.

Evidence Profiles

Certainty assessment							No. of patients		Effect		Certainly
N. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Others consideration	Aquatic physiotherapy	Land-based physiotherapy	Relative (95% CI)	Absolute	
BASDAI (follow-up mean, 4 weeks; Lower values are considered better)											
5	Randomized control trial	Not serious	Not serious	Serious[1]	Not serious	None	185	140	-	MD 0.37 lower (-0.69, 0.04)	⊕⊕⊕◯ Moderate
Dolor (follow-up mean, 3.5 weeks; Lower values are considered better)											
2	Randomized control trial	Not serious	Serious	Not serious	Not serious	None	108	66	-	MD 0.51 lower (-1.52, 0.49)	⊕⊕⊕◯ Moderate
ASQOL, mean difference (follow-up mean, 3 weeks; Lower values are considered better)											
1	Randomized control trial	Not serious	Not serious	Not serious	Not serious	None	29	28	-	MD 2.07 lower (-3, -1.14)	⊕⊕⊕⊕ High
Patient global disease activity, mean difference (follow-up mean, 3 weeks; Lower values are considered better)											
1	Randomized control trial	Not serious	Not serious	Not serious	Not serious	None	28	26	-	MD 0.54 lower (-1, 0.08)	⊕⊕⊕⊕ High
Performance status: BASFI (follow-up mean 4 weeks; Lower values are considered better)											
5	Randomized control trial	Not serious	Not serious	Serious[1]	Not serious	None	185	140	-	MD 0.22 lower (-0.51, 0.07)	⊕⊕⊕◯ Moderate
Performance status: HAQ, mean difference (follow-up mean, 4 weeks; Lower values are considered better)											
1	Randomized control trial	Not serious	Not serious	Serious[1]	Not serious	None	80	80	-	MD 0.24 lower (-0.33, 0.15)	⊕⊕⊕◯ Moderate

Explanations

[1] 1 Study was a 3-arms study comparing 2 types of spa therapy versus control group.

PICO 12.3. In adults with axial spondyloarthritis, are aerobic exercises more effective than physical therapy in improving health status and functional status?

Summary

This PICO was directly addressed by 6 RCTs included in the meta-analysis by Verhoeven et al.[186] According to the studies, in activity and function in spondyloarthritis no significant differences were found between the interventions evaluated in terms of disease activity and functionality, although serious risk of bias and low quality of evidence were found in the outcomes reported.

Evidence Profiles

Certainty assessment						Results summary				Overall certainty of evidence
Patients (studies)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Event rate (%) Control	Event rate (%) With Exercise / Physical Activity / Rehabilitation	Relative effect (95% CI)	Absolute effect	
Disease activity, intervention: aerobic exercise vs physiotherapy[1] (follow-up: range 3-12 weeks; assessed by: BASDAI)										
300 (6 [RCT])	Serious[a]	Not serious	Not serious	Serious[b]	None	152	148	-	MD 0.25 lower (-0.83, 0.32)	⨁⨁◯◯ Low
Functional improvement, intervention: aerobic exercise vs physiotherapy 1 (follow-up: range 3-12 weeks; assessed by: BASFI)										
300 (6 [RCT])	Serious[a]	Not serious	Not serious	Serious[b]	None	152	148	-	MD 0.41 lower (-1.09, 0.27)	⨁⨁◯◯ Low

Explanations
a. High risk of bias.
b. Wide confidence intervals.

PICO 12.4. In adults with axial spondyloarthritis, is high-intensity exercise more effective than no high-intensity exercise in improving health and functional status?

Summary

This PICO was directly addressed by 2 RCTs[187,188]. Activity and function outcomes showed advantages of the evaluated intervention, with narrow confidence intervals and low risk of bias for reported outcomes.

Evidence Profiles

Certainty assessment							Results summary			
Patients (studies)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Overall certainty of evidence	Event rate (%) Control	Event rate (%) Intervention	Relative effect (95% CI)	Absolute effect Risk difference with intervention

Disease activity, intervention: high intensity exercise vs control[1] (follow-up: range 1-3 months, assessed by: BASDAI)										
97 (1 RCT)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High	49	48	-	MD 0.95 lower (-1.61, -0.29)
Adherence: high intensity exercise vs control[1-2] (follow-up: range 1-3 months, assessed by: percentage of patients who attended 80% of the activities)										
117 (2 RCT)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High	Sveaas 2019 reported adherence of 76% (38) in the exercise group. Per protocol analysis included [n = 38], of experimental group and [n = 44]) of control group. This did not change any of the results. Sveaas 2017, reported adherence of 100%.			
Functional improvement: high intensity exercise vs control[2] (follow-up: range 1-3 months, assessed by: BASFI change)										
117 (2 RCT)	Not serious	Not serious	Not serious	Not serious	None	⊕⊕⊕⊕ High	59	58	-	MD 1.15 lower (-1.86, -0.44)

PICO 12.5. In adults with axial spondyloarthritis, is an exercise program (home exercise plan, pilates, or any exercise with prescription parameters) more effective than no exercise program in improving health and functional status?

Summary

This PICO was directly addressed by 11 RCTs, included in the meta-analysis by Hu et al.[189] There were significant differences between groups, benefits of the exercise program in terms of disease activity, function and pain, with wide confidence intervals and a serious risk of bias reported results.

Evidence Profiles

Certainty assessment							Results summary			
Patients (studies)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Overall certainty of evidence	Event rate (%)		Relative effect (95% CI)	Risk difference with intervention
							Control	Exercise program		
Disease activity, intervention: exercise program (home exercise plan, pilates, or any exercise with prescription parameters) vs control (follow-up: range 1-3 months, assessed by: BASDAI)										
534 (11 [RCT])	Serious	Not serious	Not serious	Serious	None	⊕⊕◯◯ Low	256	278	-	MD 0.85 lower (-1.09, -0.61)
Functional improvement, intervention: exercise program (home exercise plan, pilates, or any exercise with prescription parameters) vs control (follow-up: range 1-3 months, assessed by: BASFI)										

421 (11 [RCT])	Serious[a]	Not serious	Not serious	Serious[b]	None	⨁⨁◯◯ Low	199	222	-	MD 0.66 lower (-0.95, -0.88)
Pain: exercise program (home exercise plan, pilates, or any exercise with prescription parameters) vs control (follow-up: range 1-3 months, assessed by: Visual analogue scale)										
399 (11 [RCT])	Serious[a]	Not serious	Not serious	Serious[b]	None	⨁⨁◯◯ Low	193	206	-	MD 1.02 lower (-1.5, -0.55)

Explanations
a. High risk of bias.
b. Wide confidence intervals.

PICO 12.6. In adults with stable axial spondyloarthritis, are unsupervised back exercises more effective than no exercise in improving health and functional status?

Summary

This PICO was directly addressed by 2 RCTs[190,191]. The reports found no difference in health status outcomes between the unsupervised exercise intervention compared with no exercise. Confidence intervals were narrow and risk of bias was assessed as serious.

Evidence Profiles

Certainty assessment							No. of patient		Effect		Certainty
N. of studies	Study design	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Others consideration	Unsupervised exercise	Control: no exercise	Relative (95% CI)	Absolute	
BASDAI, mean differences (follow-up mean, 4.5 weeks; Lower values are considered better)											
2	Randomized control trial	Serious[1]	Not serious	Not serious	Serious	None	104	111	-	MD 0.33 higher (-0.09, 0.74)	⨁⨁◯◯ Low
Self Efficacy Scale Pain: mean differences (follow-up mean, 6 months; Lower values are considered better)											
1	Randomized control trial	Serious[1]	Not serious	Not serious	Serious	None	75	80	-	MD 0.1 higher (-0.38, 0.58)	⨁⨁◯◯ Low
Performance status: BASFI, mean differences (follow-up mean 13.5 weeks; Lower values are considered better)											

2	Randomized control trial	Serious[1]	Not serious	Not serious	Serious	None	104	111	-	MD 0.58 higher (-1.17,2.33)	⊕⊕◯◯ Low
BAS-G, mean differences (follow-up mean, 6 months; Lower values are considered better)											
1	Randomized control trial	Serious[1]	Not serious	Not serious	Serious	None	75	80	-	MD 0.14 higher (-0.72, 1)	⊕⊕◯◯ Low

Explanations

[1] Randomization, allocation concealment and blinding not detailed.

PICO 12.7. In adults with active or stable spondyloarthritis and spinal fusion or advanced spinal osteoporosis, is spinal manipulation (chiropractic or osteopathic) more effective than no spinal manipulation in improving health and functional status?

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Summary

This PICO was not directly addressed by any RCTs. Several systematic reviews have identified adverse events associated with spinal manipulation (Ernst 2007, Hebert 2015, Carnes 2010)[192-194] and some case series (Rinsky 1976, Liao 2007)[195,196] have reported adverse events resulting from spinal manipulation specifically in people with spondyloarthritis.

Quality of evidence: Very low ⊕◯◯◯

Clinimetric, paraclinical and imaging scales in the follow-up of axial spondyloarthritis

Seven PICO questions were posed for this topic:

1. In adults with axial spondyloarthritis, is screening for osteopenia/osteoporosis with periodic DEXA scanning (annually, every two or five years) more effective than screening after insufficiency fractures or no screening in improving outcomes?
2. In adults with axial spondyloarthritis and syndesmophytes or spinal fusion, is screening for osteopenia/osteoporosis with DEXA scanning of the hip or other non-vertebral sites more effective than DEXA scanning of the spine in improving outcomes?
3. In adults with axial spondyloarthritis, is screening for cardiac conduction defects or valvular heart disease with electrocardiogram or echocardiogram, respectively, at diagnosis, and periodically more effective than no screening in improving outcomes?
4. In adults with axial spondyloarthritis, is the use at regular intervals and monitoring of BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), ASDAS (Ankylosing Spondylitis Disease Activity Score) or another index, more effective than usual care without monitoring? any index to improve results?
5. In adults with axial spondyloarthritis, is use at regular intervals and monitoring of C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) levels more effective than usual care without regular monitoring of CRP or ESR for improve results?
6. In adults with stable axial spondyloarthritis, is performing an MRI of the spine or pelvis to confirm inactivity more effective than not obtaining an MRI in improving outcome?
7. In adults with axial spondyloarthritis on any treatment, is getting repeat spinal radiographs at a scheduled interval (eg, every 2 years) more effective than not getting scheduled radiographs in improving outcomes?

PICO 13.1. In adults with axial spondyloarthritis, is screening for osteopenia/osteoporosis with periodic DEXA scanning (annually, every two or five years) more effective than screening after insufficiency fractures or no screening in improving outcomes?

Summary: This PICO question was not directly addressed by any study.

PICO 13.2. In adults with axial spondyloarthritis and syndesmophytes or spinal fusion, is screening for osteopenia/osteoporosis with DEXA scanning of the hip or other non-vertebral sites more effective than DEXA scanning of the spine in improving outcomes?

Summary

This PICO question was not directly addressed by any study. The validity of several imaging studies in patients with axial spondyloarthritis has been evaluated. Some observational studies have found that low bone density may be significantly more common in the femoral neck (measured by DEXA) than in the lumbar spine, but others have found the opposite[197,198].

Quality of evidence: very low ⊕◯◯◯

PICO 13.3. In adults with axial spondyloarthritis, is screening for cardiac conduction defects or valvular heart disease with electrocardiogram or echocardiogram, respectively, at diagnosis and periodically more effective than no screening in improving outcomes?

Summary

This PICO question was not directly addressed by any RCTs and was indirectly addressed by 1 observational cohort study [Roldan][199]. A cross-sectional component of this study examined aortic and valvular abnormalities in patients with axial spondyloarthritis (n=44) and controls (n=30). Abnormalities were detected in 82% (axial spondyloarthritis) versus 27% (controls). Follow-up of 25 patients revealed new aortic valve or root abnormalities in 24%, worsening of existing valve regurgitation in 12%, and resolution of abnormalities in 20%. Twenty percent of patients developed heart failure, underwent valve replacement, had a stroke, or died, compared with 3% of control subjects (length of follow-up unclear).

Quality of evidence: very low ⊕◯◯◯

PICO 13.4. In adults with axial spondyloarthritis, is the use at regular intervals and monitoring of BASDAI (Bath Ankylosing Spondylitis Disease Activity Index), ASDAS (Ankylosing Spondylitis Disease Activity Score) or another index, more effective than usual care without control of any index? to improve results?
Summary

This PICO question was not directly addressed by any study. Many studies have evaluated the validity of these measures. Four RCTs included in a systematic review[200] used the BASDAI and ASDAS measures as a decision point to determine subsequent treatment, but it was not in regular interval use. More recently, Hong Ki Min et al[201] compared several PRO (patient report outcomes) in an observational study considered to have a serious risk of bias, which included 453 patients with radiographic and non-radiographic axial spondyloarthritis. The ASAS HI showed a significant correlation with self-reported instruments for evaluating quality of life EQ-5D-TTO (Rho =0.71, $p < 0.001$) and functional evaluation in spondyloarthritis BASFI (Rho = 0.65, $p <0.001$). In addition, positive correlations between 0.53 and 0.58 were found with other self-report instruments such as BADAI, ASDAS, PGA, and the Physician Global Assessment (PhyGA). ASAS HI was higher in patients with radiographic axial spondyloarthritis than in those with non-radiographic.

Quality of evidence: very low ⊕◯◯◯

PICO 13.5. In adults with axial spondyloarthritis, is use at regular intervals and monitoring of C-reactive protein (CRP) or erythrocyte sedimentation rate (ESR) levels more effective than usual care without regular monitoring of CRP or ESR in improving outcomes?

Summary

This PICO question was not directly addressed by any study. Two RCTs used these measures as a decision point to determine subsequent therapy, but without using regular interval[200]. Many studies have evaluated the validity of these measures.

Quality of evidence: very low ⊕◯◯◯

PICO 13.6. In adults with stable axial spondyloarthritis, is performing an MRI of the spine or pelvis to confirm inactivity more effective than not obtaining an MRI in improving outcome?

Summary

This PICO question was not directly addressed by any study. Although a considerable literature documents correlations between magnetic resonance imaging (MRI) findings and disease progression, studies do not address the effects of performing pelvic or spinal MRI on patient outcomes. A recent meta-analysis[202] evaluated the effect of anti-TNF alpha on MRI inflammation score in the spine and sacroiliac joints, and its correlation with parameters used in daily practice. At 12-week follow-up, studies reported a non-significant decrease in MRI score between the anti-TNF group and the control group, except for the sacroiliac joint SPARCC (Spondyloarthritis Research Consortium of Canada) score at 12 weeks ($p<0.0001$) (see Table). The correlation between the MRI scores of the spine and sacroiliac joints, with the clinical and biological data, was very heterogeneous between the different reports. However, an association between MRI scores and CRP, ESR, and ASDAS was generally reported.

Although not provided as evidence in this report, recommendations have been published to guide the use of imaging in the context of spondyloarthritis. With regard to activity monitoring of axial spondyloarthritis, EULAR established that MRI of the sacroiliac joints and/or the spine can be used to assess and monitor disease activity, providing additional information in addition to clinical and biochemical assessments[203]. The decision on when to repeat MRI depends on the clinical circumstances, however, the limitations of imaging have recently been addressed, and the importance of active and structural lesions for prognostic risk assessment and selection of appropriate treatment is currently a research area[204].

In non-radiographic axial spondyloarthritis, observational MRI studies at 0 and 12 weeks during anti-TNF treatment have shown that decreases in MRI scores (SPARCC of sacroiliac joints) moderately correlate with several patient-reported outcomes. (ASDAS, BASDAI and BASFI) at 48 weeks according to data from an RCT[205].

Evidence Profiles

Certainty assessment							Results summary			
Patients (studies)	Risk of bias	Inconsistency	Indirect evidence	Imprecision	Publication bias	Overall certainty of evidence	Event rate (%)		Relative effect (95% CI)	Absolute effect, risk difference with IRM
							Control	MRI in anti-TNF patients		
Disease activity, (follow-up mean, 12 weeks; assessed by: the Spondyloarthritis Research Consortium of Canada (SPARCC) score in spine)										
293 (3 [RCT])	Not serious	Not serious	Not serious	Serious[b]	None	⊕⊕⊕◯ Moderate	145	148	-	MD 4.85 lower (-10.99, 1.28)
Disease activity, (follow-up mean, 12 weeks; assessed by: the Spondyloarthritis Research Consortium of Canada (SPARCC) score in sacroiliac joint)										
307 (3 [RCT])	Not serious	Not serious	Not serious	Serious[b]	None	⊕⊕⊕◯ Moderate	152	155	-	MD 3.19 lower (-4.8, -1.58)
Disease activity; assessed by: Spondylitis spine Magnetic Resonance Imaging activity (ASspiMRI-a) (follow-up mean, range 12-14 weeks)										
115 (2 [RCT])	Not serious	Serious[a]	Not serious	Serious[b]	None	⊕⊕◯◯ Low	34	81	-	MD 1.67 lower (-5.2, 1.87)
Disease activity; assessed by: Spondylitis spine Magnetic Resonance Imaging activity (ASspiMRI-a) (follow-up mean, 2 years)										
115 (2 [RCT])	Not serious	Serious[a]	Not serious	Serious[b]	None	⊕⊕◯◯ Low	34	81	-	MD 1.34 higher. (-6.3, 8.98)

MD: mean differences; CI: Confidence interval.

Explanations

a. One study favors the control and the other the experimental group.

b. Wide confidence intervals.

PICO 13.7. In adults with axial spondyloarthritis on any treatment, is getting repeat spinal radiographs at a scheduled interval (eg, every 2 years) more effective than not getting scheduled radiographs in improving outcomes?

Summary

This PICO question was not directly addressed by any study. Six studies (seven publications) provided indirect evidence, clarifying that progression can be documented within a 2-year interval; 5 studies show that 20-48% of patients with axial spondyloarthritis show a progression of ≥2 mSASSS over 2 years[206-210]. Among these, an observational study (Poddubnyy 2016)[206] with 60 patients and mSASSS every two years, in which after initial improvement, BASFI and BASMI remained remarkably stable at low levels for up to 10 years despite radiographic progression of the spine.

In non-radiographic axial spondyloarthritis, indirect evidence is available from 5 observational studies (six publications)[211-216]. Two reports based on the GESPIC observational cohort (Poddubnyy 2011 and Poddubnyy 2012)[211,212] reported definite radiographic progression (increase of ≥2 mSASSS units) in 7.4% of patients during the initial 2 years of follow-up. Additionally, data on progression of non-radiographic to radiographic axial spondyloarthritis (mNY criteria) in the sacroiliac joint are reported in 5 studies, where approximately 2 to 8% progressed per year and 20 to 30% in 10 years.

Quality of evidence: very low ⊕◯◯◯

Evidence Profiles

Summary of mSASSS progression in axial SpA

Author, year	Extension	Population description	mSASSS rate unit/year	% progression ≥2 mSASSS to 2 years	% progression ≥5 mSASSS to 2 years
Park 2017[207]	2 years	N=31 patients; 20 men with axial SpA; 11 controls matched by sex and age	1.25 (median)	35	-------
Maas 2016[208]	4, 6, 8, 10 years F/U	N=210 patients with active axial SpA, who started anti-TNF; largest numbers reported at 4 years F/U (results in this table refer to this time point)	0.88	25	-------
Podubbnyy 2016[206]	10 years	N=60 patients; of 2 long-term open-label extensions of anti-TNF clinical trials	0.6	-------	-------
Ramiro 2013[209]	12 years (every 2 years)	N=186 patients with axial SpA (n=68 completed at 12 years); 95% of patients were treated with NSAIDs and 22% anti-TNF (5% exposed before year 8).	0.98	48 (1ª 2 years F/U) 29 (all 2 years F/U)	25 (1ª 2 years F/U)
Podubbnyy 2012[212]	2 years	N=210 patient with axial SpA (GESPIC cohort)	0.95	20	-------

mSASSS, modified stoke ankylosing spondylitis spinal score

Additional observational data in axial SpA

Author, year	Extension	Population description	Treatment administered to the relevant population	Results
Sepriano 2016[210]	Mean 4.4 years	357 patients with undiagnosed chronic back pain or peripheral symptoms	Pelvic radiographs	62 of 357 (17.4%) met criteria for axial SpA at baseline versus 80 of 357 (22.4%) at follow-up. 36/62 (58.1%) considered mNY positive at baseline were mNY negative at follow-up.
Poddubnyy 2011[211]	2 years	N=210 patients with axial SpA	Sacroiliac joints radiographs	115 patients (54.8%) met the modified NY criteria for axial SpA; 95 patients (45.2%) were classified as non-radiographic. The rate of progression from non-radiographic to radiographic axial spondyloarthritis was 11.6% at 2 years. The mean rate of progression of radiographic sacroiliitis at 2 years was low: 0.07 (95% CI -0.05 to 0.19) and 0.09 (95% CI -0.03 to 0.21) grades for the left and right sacroiliac joints, respectively.

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