PICO 6 – IS THERE ANY EVIDENCE OF BETTER COST-EFFECTIVENESS OF tsDMARD (JAK INHIBITORS) COMPARED TO csDMARD?

The clinical question is: "Is there evidence of better cost-effectiveness of JAK inhibitors compared to synthetic DMARDs?"

The eligibility elements of the studies are:

1. Adult patients (>16 years) meeting the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) RA classification criteria; patients with new-onset RA (symptoms < 6 months) and established RA (symptoms ≥ 6 months), regardless of disease activity.

2. Treated with JAK inhibitors (tofacitinib, baricitinib, upadacitinib, other JAK inhibitors) as monotherapy or in combination with or other drugs that modify the course of rheumatic disease.

3. Compared with patients treated with synthetic DMARDs (Methotrexate, Hydroxychloroquine, Chloroquine Diphosphate, Sulfasalazine, Leflunomide);

4. Outcomes:

• Cost-effectiveness, cost-effectiveness or cost-utility outcomes were evaluated.

• Studies with only budget impact assessment were not included

5. Clinical trials or observational studies.

6. No period or language limit.

7. Full text available for access.

The search for evidence was carried out in the virtual scientific information bases using the search strategies:

Medline/PubMed:

#1 – (Arthritis, Rheumatoid OR Rheumatoid Arthritis OR Sjogren's Syndrome OR Caplan Syndrome OR Felty Syndrome OR Rheumatoid Nodule OR Rheumatoid Vasculitis OR Still Disease OR Arthritis, Juvenile OR Juvenile Arthritis OR Polyarthritis, Juvenile) – 322217

#2 – (JAK inhibitor OR JAK inhibitors OR Janus Kinases Inhibitors OR Janus Kinase Inhibitors OR Upadacitinib OR Protein Kinase Inhibitors OR Tofacitinib OR Baricitinib) – 208052

#3 – (Economics OR Cost OR Costs OR Costs and Cost Analysis OR Cost Effectiveness OR Cost Benefit) – 1312429

1. CENTRAL (Cochrane):

(JAK inhibitor OR JAK inhibitors OR Janus Kinases Inhibitors OR Janus Kinase Inhibitors OR Upadacitinib OR Protein Kinase Inhibitors OR Tofacitinib OR Baricitinib) AND (Economics OR Cost OR Costs OR Costs and Cost Analysis OR Cost Effectiveness OR Cost Benefit)

2. EMBASE:

#5. #4 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

#4. #1 AND #2 AND #3

#3. jak AND inhibitor OR (jak AND inhibitors) OR (janus AND kinases AND inhibitors) OR (janus AND kinase AND inhibitors) OR upadacitinib OR (protein AND kinase AND inhibitors) OR tofacitinib OR Baricitinib

#2. ((((((((((arthritis, AND rheumatoid OR rheumatoid) AND arthritis OR sjogren) AND syndrome OR caplan) AND syndrome OR felty) AND syndrome OR rheumatoid) AND nodule

OR rheumatoid) AND vasculitis OR still) AND disease OR arthritis,) AND juvenile OR juvenile) AND arthritis OR polyarthritis,) AND juvenile

#1. ((('economics'/exp OR economics OR 'cost'/exp OR cost OR costs) AND ('cost'/exp OR cost) AND ('analysis'/exp OR analysis) OR 'cost'/exp OR cost) AND effectiveness OR 'cost'/exp OR cost) AND benefit

4. LILCAS BVS

(JAK inhibitor OR JAK inhibitors OR Janus Kinases Inhibitors OR Janus Kinase Inhibitors OR Upadacitinib OR Protein Kinase Inhibitors OR Tofacitinib OR Baricitinib) AND (Economics OR Cost OR Costs OR Costs and Cost Analysis OR Cost Effectiveness OR Cost Benefit)

Searches ended on June 09, 2020.

The studies were assessed for risk of bias using the Critical Appraisal Skills Programme - *CASP (economic) evaluation checklist* [1].

RESULTS

Figure 1 shows the selection of retrieved papers. The included studies are in Table 1.

Figure 01 - FLOW DIAGRAM

The selection of works retrieved from the virtual databases of scientific information is detailed in the flowchart below:

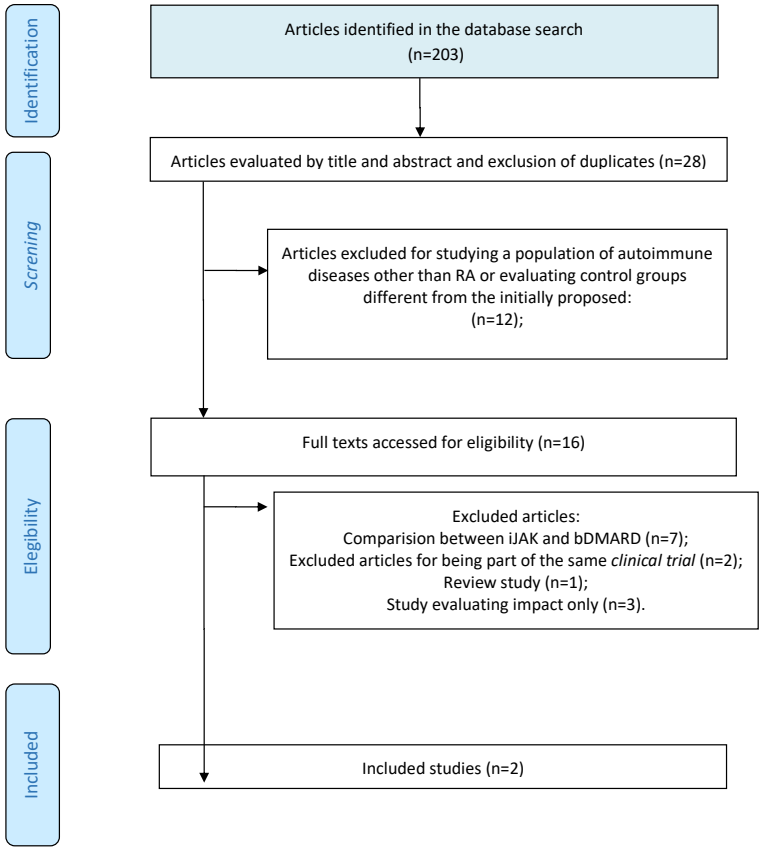

Table 1. Characteristics of the included studies

Author_yr	Country	Design	Currency	JAKi	csDMARD
Jansen_2017	USA	Modeling	Dolar americano	Tofacitinib	MTX
Wehler_2020	Holanda	Modeling	Dolar americano	Baricitinib	MTX

NR: not reported

Bias risk assessment

The included studies were evaluated using the Critical Appraisal Skills Program. CASP economic evaluation checklist[1]. The results can be seen in table 2.

Table 2. *Assessment of the quality of evidence. Critical Appraisal Skills Programme (2018). CASP (insert name of checklist i.e. Economic Evaluation).*

Study		**Jansen**	**Wehler**
Year		**2017**	**2020**
Section A Is the economic evaluation valid?	*Was a well-defined question posed?*	+	+
	Was a comprehensive description of the competing alternatives given?	+	-
	Does the paper provide evidence that the programme would be effective? (i.e. would the programme do more good than harm?)	+	+
	Were the effects of the intervention identified, measured and valued appropriately?	+	-
Section B How were consequences and costs assessed and compared?	*Were all important and relevant resources required, and health outcome costs for each alternative identified, measured in appropriate units and valued credibly?*	-	-
	Were costs and consequences adjusted for different times at which they occurred (discounting)?	+	+
	What were the results of the evaluation?	+	+
	Was an incremental analysis of the consequences and cost of alternatives performed?	+	+
	Was an adequate sensitivity analysis performed?	+	+
Section C Will the results help in purchasing fo local people?	*Is the programme likely to be equally effective in your context or setting?*	-	-
	Are the costs translatable to your setting?	-	-
	Is it worth doing in your setting?	-	-

Yes: + ; Can't tell: - ; No: X .

Jansen et al.[2], in 2017 published an economic study delineated by modeling, in which nine scenario simulations containing biological DMARDs, Tofacitinib (iJAK) and methotrexate (MTX) were created. The comparator for all scenarios was synthetic conventional DMARDs.

Tofacitinib used after failure of biological therapy. Active moderate to severe rheumatoid arthritis were included.

The nine scenarios were:

1. etanercept + MTX → adalimumab + MTX → abatacept subcutaneous (SC) + MTX → tocilizumab + MTX → tofacitinib + MTX → rituximab + MTX → non-biological therapy

2. adalimumab + MTX → etanercept + MTX → abatacept SC + MTX → tocilizumab + MTX → tofacitinib + MTX → rituximab + MTX → non-biological therapy

3. abatacept SC + MTX → etanercept + MTX → adalimumab + MTX → tocilizumab + MTX → tofacitinib + MTX → rituximab + MTX → non-biological therapy

4. abatacept SC + MTX → adalimumab + MTX → etanercept + MTX → tocilizumab + MTX → tofacitinib + MTX → rituximab + MTX → non-biological therapy

5. etanercept + MTX → certolizumab pegol + MTX → abatacept SC + MTX → tocilizumab + MTX → tofacitinib + MTX → rituximab + MTX → non-biological therapy

6. adalimumab + MTX → certolizumab pegol + MTX → abatacept SC + MTX → tocilizumab + MTX → tofacitinib + MTX → rituximab + MTX → non-biological therapy

7. certolizumab pegol + MTX → etanercept + MTX → tocilizumab + MTX → abatacept SC + MTX → tofacitinib + MTX → rituximab + MTX → non-biological therapy

8. certolizumab pegol + MTX → adalimumab + MTX → tocilizumab + MTX → abatacept SC + MTX → tofacitinib + MTX → rituximab + MTX → non-biological therapy

9. certolizumab pegol + MTX → golimumab + MTX → tofacitinib + MTX → tocilizumab + MTX → abatacept SC + MTX → rituximab + MTX → non-biological therapy

The model estimated costs and quality-adjusted life years (QALYs) over the lifetime of patients. The American College of Rheumatology (ACR) scores; European League Against Rheumatism (EULAR); Health Assessment Questionnaire (HAQ); and patient characteristics were estimated. Costs were estimated using the US dollar. The cost of any serious infection event was considered equivalent to the cost of hospitalization for pneumonia, based on Medicare[4]. Wolfe et al. provided an estimate of the annual loss of income in relation to the HAQ scores, which was inflated by 34% to reflect the costs for the year 2016.[5]

The analysis included costs associated with procurement, administering medical appointments, chest X-rays, tuberculosis testing for some interventions, and hospitalization.

The incremental cost-effectiveness ratio ranged across scenarios from 125,609 (scenario 9) to 139.985 (scenario 2) dollars per QALY earned.

Wehler et al.[3] developed an analysis in a hypothetical North American population. We performed a retrospective observational study using data from Truven Health MarketScan Research to assess market share of advanced therapies in rheumatoid arthritis by therapy line. Drug acquisition costs for all treatments were calculated based on drug dosage and unit costs (2019 Wholesale Acquisition Cost) of Medispan Price Rx. All costs were based on the US dollar in 2019. Effectiveness was assessed using the ACR.

The cost per additional responder for baricitinib, compared with synthetic DMARDs, in patients who failed anti-TNF, was substantially lower than all other treatments for all three endpoints assessed for efficacy (ACR) at 12 weeks (ACR20: US $129,672; ACR50: $237,732; ACR70: $75,464) and 24 weeks (ACR20: $167,811; ACR50: $259,344; ACR70: $570,557).

REFERENCES

1. Critical Appraisal Skills Programme. CASP economic evaluation checklist.
2. Jansen JP, Incerti D, Mutebi A, Peneva D, MacEwan JP, Stolshek B, Kaur P, Gharaibeh M, Strand V. Cost-effectiveness of sequenced treatment of rheumatoid arthritis with targeted immune modulators. Journal of Medical Economics. 2017 Jul 3;20(7):703-14.
3. Wehler E, Boytsov N, Nicolay C, Herrera-Restrepo O, Kowal S. A Budget Impact and Cost Per Additional Responder Analysis for Baricitinib for the Treatment of Moderate-to-Severe Rheumatoid Arthritis in Patients with an Inadequate Response to Tumor Necrosis Factor Inhibitors in the USA. PharmacoEconomics. 2020 Jan 1;38(1):39-56.
4. Centers for Medicare & Medicaid Services. FY 2016 Final Rule, Correction Notice and Consolidated Appropriations Act of 2016 Tables. 2016. Available at: https://www.cms.gov/Medicare/Medicare-Fee-for-Service- Payment/AcuteInpatientPPS/FY2016-IPPS-Final-Rule-Home-Page-Items/FY2016-IPPS-Final-Rule-Tables.html?DLPage=1&DLEntries=10&DLSort=0&DLSortDir=ascending. [Accessed February 15, 2017.]
5. Wolfe F, Michaud K, Choi HK, et al. Household income and earnings losses among 6,396 persons with rheumatoid arthritis. J Rheumatol 2005;32:1875-83