PICO 7 – IS THERE ANY EVIDENCE OF BETTER COST-EFFECTIVENESS OF tsDMARD (JAK INHIBITORS) COMPARED TO bDMARD?

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

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 bDMARDs (adalimimab, certolizumab pegol, etanercept, Golimumab, Infliximab, Rituximab, Tocilizumab, Abatacept.

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:

1. 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

2. 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)

3. 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:

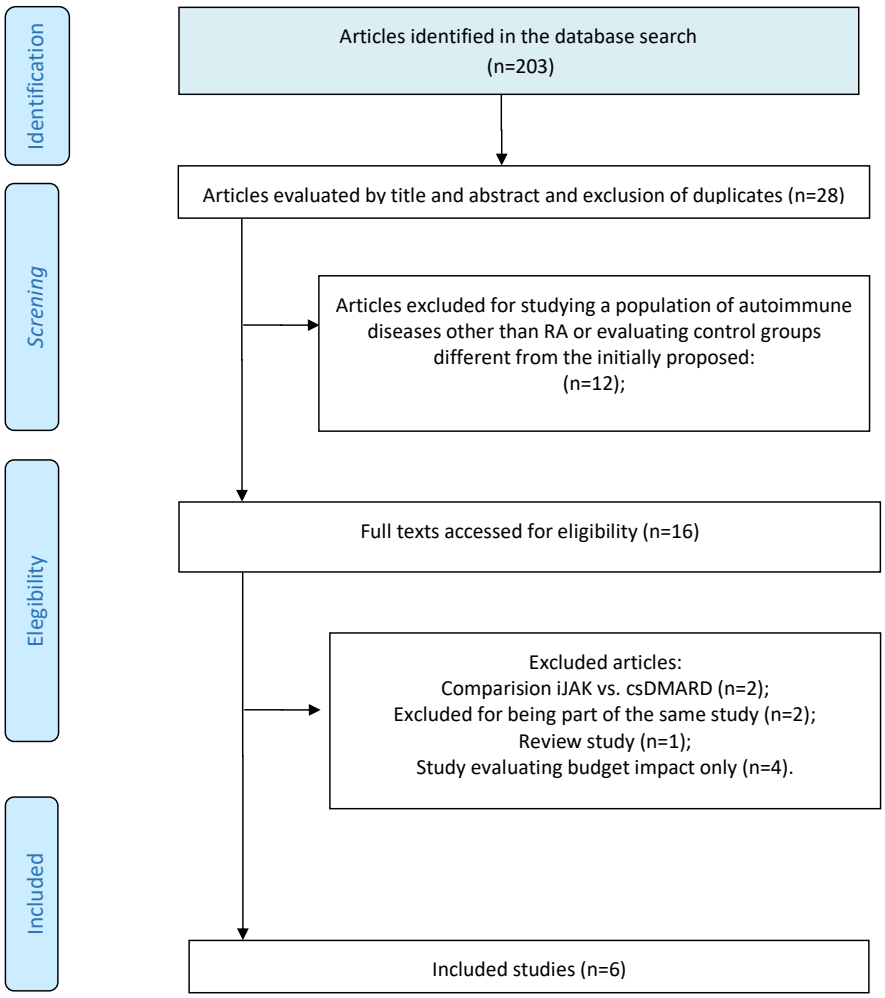

Table 1. Characteristics of the included studies

Author,yr	Country	Decision model	Population level	Data	RA severity	Currency	tsDMARD	bDMARD
Chen,2019	Taiwan	Markov	Individual	Secondary	Moderate to severe	New Taiwan dollar (NTD)	Tofacitinib	Adalimumab
Claxton, 2016	USA	Decision tree	Individual	Secondary	Moderate to severe	American Dollar	Tofacitinib	Adalimumab, etanercept, certolizumab tocilizumab
Lee, 2015	South Korea	Markov	Individual	Secondary	Moderate to severe	Korean won (KRW)	Tofacitinib	Adalimumab
Navarro, 2020	Spain	Microssimulation	Individual	Secondary	Moderate to severe	Euro	Tofacitinib, baricitinib	Adalimumab, rituximab, tocilizumab, etanercept, abacacept, certolizumab
Schlueter,2020	Spain	Adverse events simulation	Individual	Secondary	Moderate to severe	Euro	Baricitinib	Adalimumab
Van De Laar,2020	Holland	Markov	Individual	Secondary	Moderate to severe	Euro	Baricitinib	Adalimumab, etanercept, rituximab, infliximab, abatacept, tocilizumab

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.

Study		Chen	Claxton	Lee	Navarro	Schlueter	Van De Laar
Year		***2019***	***2016***	***2015***	***2020***	***2020***	***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	*Were all important and relevant resources required, and health outcome costs for each alternative identified,*	+	+	+	+	+	+

consequences and costs assessed and compared?	*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 for 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?	-	-	-	-	-	-

Table 2. *Assessment of the quality of evidence. Critical Appraisal Skills Programme (2018). CASP (insert name of checklist i.e. Economic Evaluation).Yes: + ; Can't tell: - ; No: X.*

In the study by Chen et al.[2], a simulation model was used to project cost of living and quality-adjusted life years (QALYs) in Taiwan in patients with moderate to severe rheumatoid arthritis. Second-line treatment with Tofacitinib 5 mg twice daily plus methotrexate (MTX) was compared to Adalimumab 40 mg every 2 weeks plus MTX. The model was based on data from a randomized, double-blind clinical trial (ClinicalTrials.gov NCT00853385) and Taiwan's National Health Insurance Research Database between 2007 and 2011.In that study, treatment with Tofacitinib plus MTX is a cost-effective treatment strategy compared to Adalimumab plus MTX. The difference in treatment between Tofacitinib and Adalimumab resulted in a cost-effectiveness of NT$ 429.367/LY; and cost-utility of NT$143,122/QALY (in 2015, 1 NT$ = 0.026–0.030 EUR, and 0.030–0.033 US$).

In the study by Claxton et al.[3], they evaluated, using an economic model, the treatment costs of a strategy for the treatment of moderate to severe rheumatoid arthritis. This strategy includes Tofacitinib, compared to biological treatment strategies (Adalimumab, etanercept, certolizumab and tocilizumab) in the US setting. Effectiveness was determined by the ACR. Patients with inadequate response to MTX and TNF were evaluated.This study suggests that Tofacitinib is cost-effective compared to biological therapies. For patients on the Tofacitinib regimen, the ACR20 cost per patient was $57,424 (12 months) and $115,286 (24 months) in a patient with an inadequate response to MTX monotherapy. For patients on the Adalimumab regimen, the ACR20 cost per patient was $86,096 (12 months) and $157,072 (24 months) in a patient with inadequate response to MTX monotherapy. For patients on the Etanercept regimen, the ACR20 cost per patient was $75,335 (12 months) and $144,025 (24 months) in a patient with an inadequate response to MTX monotherapy. For patients on the Certolizumab regimen, the ACR20 cost per patient was $79,418 (12 months) and $146,919 (24 months) in a patient with an inadequate response to MTX monotherapy. For patients on the Tofacitinib regimen, the ACR20 cost per patient was $62,690 (12 months) and $124,309 (24 months) in a patient with an inadequate response to MTX monotherapy. For patients with an inadequate response to TNF, the ACR20 cost per patient was $69,575 (12 months) and $132,500 (24 months) for Tofacitinib plus MTX. For patients using Adalimumab associated with MTX, the cost per ACR20 patient was $86,164 (12 months) and $1157,273 (24 months).

In the study by Lee et al.[4], in a cohort model for cost-utility analysis in South Korea, the use of Tofacitinib against Adalimumab was compared as first-line treatments in different settings. Efficacy was

assessed using the ACR and usefulness was calculated using the QALYs. The inclusion of Tofacitinib as a treatment strategy for moderate to severe rheumatoid arthritis is cost-effective. Following Adalimumab, the total cost per patient was KRW 116200667, and the QALY gained per patient was 5.01 (US$1 = 1055 KRW; 2013). The addition of Tofacitinib as a first-line treatment resulted in higher costs and greater gains in QALYs per patient (KRW 135849396 and 6.50 QALYs, respectively). Thus, the incremental cost-effectiveness was estimated at KRW 13228910 per QALY gained in the baseline scenario analysis.

Navarro et al.[5], in a study evaluating rheumatoid arthritis in Spain, compared scenarios containing Tofacitinib followed by biological versus biological only. In this study, the inclusion of Tofacitinib appears to be a dominant strategy in patients with moderate to severe rheumatoid arthritis after failure of synthetic DMARDs. Tofacitinib as initial third-line therapy has proven to be a cost-saving strategy (€ - 337,489/QALY gained) in patients with rheumatoid arthritis with an inadequate initial response to TNF.

Schlueter et al.[6], also in the Spanish context, compared Baricitinib with Adalimumab. Baricitinib was cost-effective, being associated with a 0.09-year QALY gain, at an incremental cost of - €558 against Adalimumab.

In the study by Van De Laar et al.[7], a cost-utility analysis was carried out from the Dutch social perspective. The sensitivity analysis results showed that the Baricitinib strategy generated lower costs and greater utility over a 5-year period. The incremental cost-effectiveness index (ICER) was estimated at €238,418.

REFERENCES

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