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Biologics for psoriatic arthritis: network meta-analysis in review

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Abstract. – OBJECTIVE: A review of network meta-analysis to assess efficacy and safety of biologics for the treatment of psoriatic arthritis (PsA).

MATERIALS AND METHODS: A systematic search was conducted on electronic databases to identify Bayesian meta-analysis reporting clinical parameters of efficacy, safety and cost-effectiveness of biologics that are approved for the treatment of PsA patients.

RESULTS: We identified 19 studies and included them for review. There is insufficient statistical evidence to demonstrate clear differences in effectiveness between available biologic agents for PsA due to many differences in methods and clinical parameters reported in the studies. Old biologics are reported to be safe.

CONCLUSIONS: New molecules approved for the treatment of PsA appear promising treatments but further comparative studies methodologically well-conducted are necessary. It is also necessary to follow strictly international recommendations to conduct NMA to better help physicians and decision-makers in making appropriate decisions.

Key Words:
Biologics, Comparative effectiveness, Network meta-analysis, Psoriatic arthritis.

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory autoimmune joint disorder and mainly affects people between 20 to 55 years of age. This disease is commonly associated with skin psoriatic lesions and if not properly treated, can lead to severe disability[1,2]. Efficacy and safety profiles of biologics indicate it is reasonable to use anti TNF-α agents such as Adalimumab, Certolizumab pegol, Etanercept, Golimumab and Infliximab to control disease progression for patients not responding to Nonsteroidal anti-inflammatory drugs (NSAIDs) and disease-modifying antirheumatic drug (DMARD) therapy[3]. For new drugs, such as Ustekinumab, Secukinumab, Ixekizumab and Apremilast, similar results were obtained in clinical trials, making it difficult for physicians to make a choice based on efficacy, safety and prognosis[4]. Only one head-to-head trial is available, so indirect comparison technique can be adopted with network meta-analysis (NMA) for comparative studies applying statistical probability[5,6].

The objective of the study was to review all network meta-analysis comparing Randomized Clinical Trials (RCT's) and comparing the efficiency of biologics such as Adalimumab (ADA), Apremilast (APR), Certolizumab pegol (CZP), Etanercept (ETA), Golimumab (GOL), Infliximab (IFX), Secukinumab (SEC), Ustekinumab (USK), Ixekizumab (IXE), Tofacitinib (TOF), Guselkumab (GUS) that are approved for the treatment of Psoriatic Arthritis (PsA) and mixed treatment options by performing Bayesian statistical approach and evaluating improvements following the reduction in severity based on criteria of the American College of Rheumatology (ACR), PASI (Psoriasis Area and Severity Index), PsARC (Psoriatic Arthritis Response Criteria), and HAQ (Health Assessment Questionnaire).

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Materials and Methods

An extensive literature search was performed in MEDLINE and EMBASE to assess the efficacy of different biologics in patients with PsA, from 2006 to 2020. Both engines were intensively searched, and search terms included a combination of the following terms: "Indirect comparison" OR "Bayesian" OR "Network metanalysis" OR "Mixed treatment comparison" AND "Psoriatic Arthritis" AND "Biologic" OR "anti TNF" OR "Biosimilar" OR "Adalimumab" OR "Apremilast", OR "Certolizumab pegol" OR "Etanercept" OR "Golimumab" OR "Infliximab" OR "Secukinumab" OR "Ustekinumab" OR "Ixekizumab" OR "Tofacitinib" OR "Guselkumab".

The first screening was performed by a single reviewer for identifying and excluding from further analysis all duplicates. Consequently, the remaining papers were analysed independently by three reviewers. A second screening was performed by each reviewer by title. Then, all three reviewers analysed the remaining abstracts, and papers that were only published as abstracts without full text, and articles published in a language different from English, were excluded. In a further step, the remaining abstracts were analysed in full text. All included meta-analysis were then analysed for main characteristics, such as the number of included studies, characteristics of patients and treatment arms of analysed studies, methodology of analysis, clinical parameters, length of follow-up, safety and economic evaluation and presentation of results in the light of ISPOR guidelines[7] (Table I). Results obtained from included studies were then analysed and discussed.

Results

After an extensive literature search, a total of 41 articles were selected for the studies, which included 13 on indirect comparison, 13 on Bayesian method, 9 on network meta-analysis, and 6 on mixed treatment comparison (MTC). After title screening, 15 were excluded and another 7 were excluded since they were duplicates, and for final analysis 19 studies were included (Figure 1).

The included studies analyze a variable number of RCTs ranging from 44 to 3, using as main outcomes clinical efficacy assessed by the ACR response (specifically ACR20 in 16 studies, ACR50 in 11 studies and ACR70 in 9 studies) and PsARC (10 studies). PASI index was evaluated only in 11 studies and the HAQ was evaluated in 8 studies. The included studies considered a period of follow-up ranging between 12 weeks and 50 weeks, 10 studies assessed also the safety profile of the treatments, and 6 studies performed an economic evaluation. 9 studies had evaluated old biologics therapies authorized for the treatment of the PsA (anti-tumor necrosis factor biologics – anti TNF-α), and 10 studies had included new molecules (SEC, USK, APR, IXE, TOF, GUS). Only studies on molecules authorized in Europe for the treatment of psoriatic arthritis were considered.

In 2006 Woolacott et al[8], compared results of 40 studies on efficacy, safety and tolerability of ETA and IFX in PsA patients DMARDs IR. The probability of response to both treatments was similar (0.7705) and ETA was preferred due to acquisition, administration costs, and cost-effectiveness.

In 2007, Bravo et al[9] published results on studies relating to relative efficacy and cost-effectiveness of ETA, IFX and palliative care. Long term cost-effectiveness was studied from NHS (National Health Service) UK perspective for 10 years reporting ETA cost-effective. Saad et al[10] in 2007 conducted a meta-analysis evaluating clinical efficacy (ACR 20, PsARC, PASI and HAQ outcomes) and safety of ADA, ETA and IFX for the treatment of PsA. All three TNF-α inhibitors were found to be more effective than placebo in achieving ACR response and PsARC. No significant difference was noticed between the TNF-α inhibitors for achieving ACR20 response. Regarding safety and tolerability, a difference was noticed with reactions compared with ADA. Rodgers et al[11] in 2011 published reports of studies from the UK, regarding clinical effectiveness, safety and cost-effectiveness of ETA, IFX and ADA. Based on PsARC ETA had RR 2.60, IFX RR 3.44, and ADA RR 2.24. This was consistent with the results from pooled estimates of ACR20. In terms of PASI response, at 24-weeks all three TNF-α inhibitors demonstrated effectiveness on skin disease. For evaluating the safety, 32 studies were identified, and rates of serious infection were 0.6%-13.2% for ETA, 0.8%-13.8% for IFX and 0.4%-5.1% for ADA. The rates of malignancy were 1%-5.7% for ETA, 0.16%-5.1% for IFX and 0.1%-1.1% for ADA. The rates of activation of TB for the treatment were 0%-1.4% for ETA, 0.06%-4.6% for IFX and 0%-0.4% for ADA. Regarding cost-effectiveness, six studies revealed that ETA is likely to be cost-effective at a thresh-

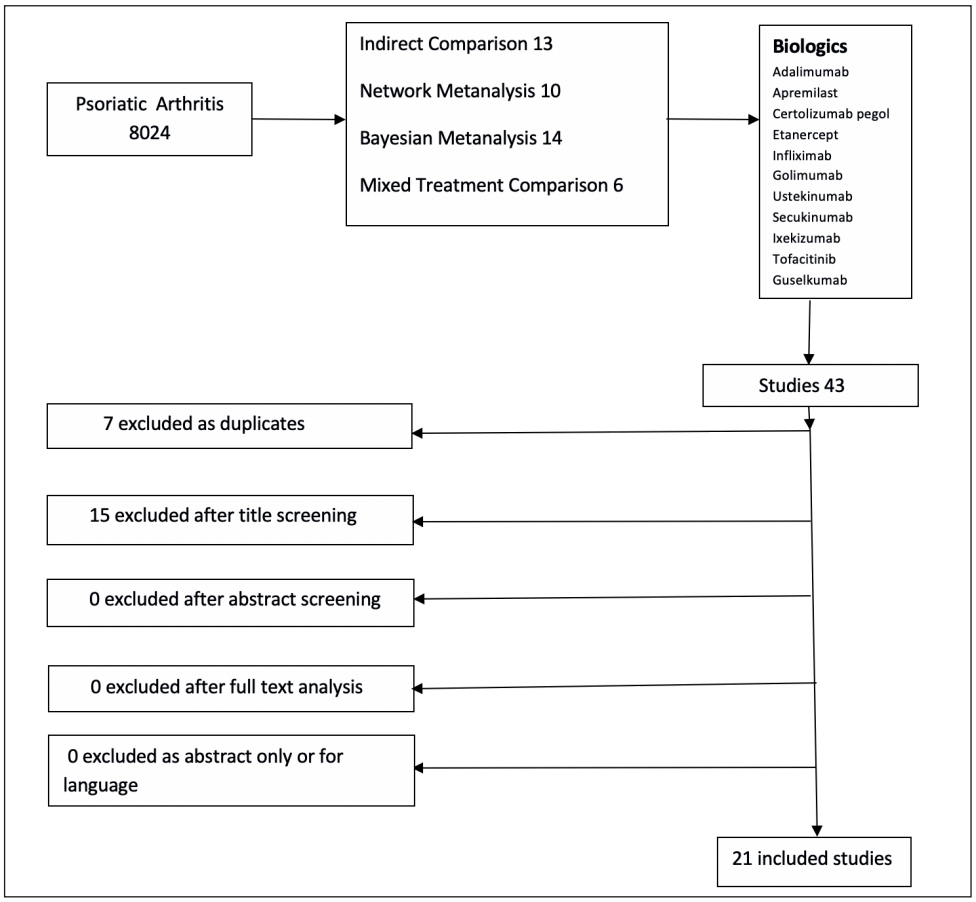

Figure 1. Flow diagram for the selection of studies.

old of £20,000 or £30,000 per QALY for patients with mild-to-moderate psoriasis, who have failed with ADA or IFX as first-line therapy. In 2012, Migliore et al[12] published an indirect mixed treatment comparing ACR20 responses of ETA, IFX and ADA for patients DMARDs IR and the rank of treatments was made. The results revealed that ETA provided the greatest probability of ACR20 response showing a probability of 71%, for achieving ACR20 response followed by IFX (24.7%) and ADA (4.3%). In 2012, Thorlund et al[13] from Canada, compared ETA, IFX, ADA and GOL for patients DMARD IR. In terms of PsARC response, GOL yielded the highest relative risk (RR 3.45,) and ETA the second highest (RR 3.19,). As far as HAQ is concerned, ETA and IFX yielded the largest mean difference (MD) among PsARC responders (0.43 and 0.41, respectively) and regarding PASI, IFX yielded the largest MD and GOL the second largest (6.44 and 4.90, respectively), while ETA yielded the smallest MD (3.13). Kirson et al[14] performed a matching adjusted indirect comparison of ADA with ETA and IFX. Outcomes on patients were accessed based on ACR20, ACR50, ACR70, PsARC, PASI, HAQ at an interval of 12 to 24 weeks. Numbers needed to treat (NNT) was calculated as the inverse of risk reduction measured by differences in placebo-adjusted response rates. Patients treated with ADA are likely to achieve better improvements in joint symptoms (ACR70) at 12 weeks (p=0.055) and 24 weeks (p=0.002). Compared with IFX, treated patients with ADA have a greater chance of relieving joint symptoms (ACR70) at 14 weeks with no significant difference at 24 weeks. In 2012, Fenix-Caballero et al[15] from Spain studied the efficacy and safety of ADA, ETA, IFX and GOL for the treatment of PsA using IFX as a reference drug. The Indirect comparison was made utilizing the Bucher method. ACR50 was taken as the primary outcome and ACR 20 and ACR70 as secondary outcomes. By comparing the four drugs, relative efficacy was analysed. Outcomes from secondary efficacy from indirect treatment comparison re-

Table I. Main characteristics and results of the included studies.

Author, Year/ Journal	Compared Biologics	Method	Length of follow up	Evaluation		Economic	N. of studies	Results
			Clinical efficacy parameters		Safety			
Woolacott et al[8], 2006	IFX, ETA	Bayesian York model for economic evaluation	50W	ACR20, ACR50, ACR70, PsARC, HAQ, PASI	Yes	QALY, ICER	40 RCT	No significant statistical difference in terms of efficacy. ETA preferred in terms of QALY and ICER.
Bravo-Vergel et al[9], 2007	IFX, ETA	Bayesian	12W	PsARC, HAQ	No	ICER, QALY	2 NMA	ETA is cost-effective for a period of 10 years.
Saad et al[10], 2008	ADA, ETA, IFX	Bayesian randomized model	12-24W	ACR20, ACR50, ACR70, PsARC, PASI, HAQ	Yes	No	6 RCT	No significant statistical difference in terms of efficacy.
Rodgers et al[11], 2011	ADA, IFX, ETA	Bayesian. York model	12W	ACR20, ACR50, ACR70, PsARC, PASI, HAQ	Yes	QALY, ICER	44 RCT (efficacy: 6; safety; Cost-effectiveness: 6)	INX showed highest probability of Response. ETA favored in terms of ICER and QALY.
Migliore et al[12], 2012	ADA, ETA, IFX	Bayesian, MTC fixed effect model	24W	ACR20	No	No	4 RCT	Greatest ACR20 response achieved with ETA (71%) followed byIFX (24.7%) and ADA (4.3%).
Thorlund et al[13], 2012	ADA, ETA GOL, IFX	Indirect comparison. Randomized effect models	24W	PsARC, HAQ, PASI	No	No	7 RCT	Highest PSARC RR achieved with golimumab, Largest PASI MD achieved with infliximab, Larget MD HAQ improvement with etanercept and infliximab.
Kirson et al[14], 2013	ADA, ETA, IFX	Indirect comparison using matching adjustment	24W	ACR20, ACR50, ACR70, PsARC, HAQ, PASI50, PASI75, PASI 90	No	CPR (Cost per responder)	3 RCT	ADA exhibited more cost effectiveness; IFX showed higher cost per responder.
Fenix-Caballero et al[15], 2013	ADA, ETA, GOL, IFX	Indirect treatment comparison based on Bucher method	24W	ACR20, ACR50, ACR70, PsARC, HAQ, PASI	Yes	No	4 RCT	no significant statistical difference in ACR50.
Cawson et al[16], 2014	ADA, ETA, GOL, IFX	Bayesian network meta-analysis	NA	PsARC, HAQ	No	ICER, QALY	12 RCT	ETA found to be cost-effective.
Betts et al[17], 2016	ADA, APR	Bayesian (Fixed effect model) Markov Chain Montecarlo (MCMC)	16W	ACR20	No	NNT, CPR	3 RCT	ADA was associated with highest response rate (54%) followed by APR (31%) and MTX (28%).
Ungprasert et al[18], 2015	ADA, APR, CZP, ETA, GOL, IFX, SEC, USK	Bayesian randomized effect model	12-24W	ACR20	No	No	12 RCT	Pooled older inhibitors SEC achieved better ACR20 compared with new ones such as APR, CZP and USK.
Ungprasert et al[19], 2016	ABA, APR, SEC, USK	Indirect comparison treatment	24W	ACR20	No	No	5 RCT	No significant difference with no TNF inhibitors and biological agents in achieving ACR20.
Kawalec et al[20], 2018	ABA, APR, SEC, USK	Randomized effect model and adjustment for multi-arm studies	16-24W	ACR20, ACR50, PASI75	Yes	No	8 RCT	No significant differences among non-anti-TNF-α biologics. SEC 300 mg was ranked the highest for the ACR20 and the safest in terms of any AEs. USK 90 mg presented the lowest overall risk of SAEs.

Table continued

Table I. ***(Continued).*** Main characteristics and results of the included studies.

Author, Year/ Journal	Compared Biologics	Method	Length of follow up	Evaluation			N. of studies	Results
			Clinical efficacy parameters		Safety	Economic		
Wu et al[21], 2018	SEC, USK, CLA, IXE	Random effects model, Bayesian network meta-analyses	16-24W	ACR20, ACR50	Yes	No	6 RCT	SEC (300 mg monthly) had the highest efficacy in terms of probability to achieve ACR20 and ACR50 (96-91%), followed by IXE (64-66%), USK (54-55%), CLA (42-45%). CLA (200mg monthly), USK (45mg 12 weekly) and SEC (150mg monthly) had the lowest probability of having AEs, serious AEs and intolerability respectively.
Strand et al[22], 2018	APR, USK, SEC, ADA, ETA, IFX, CZP, GOL	Bayesian network meta-analysis, fixed effect model	24W	ACR20, ACR50, ACR70, PASI75, PASI90	Yes	CPR (Cost per responder)	13 RCT	For ACR20 response the probability to be the best treatment resulted: GOL 61.6%, ADA 61.2%, IFX 56.2%, SEC 55,2%, followed by the others. In terms of ACR50: IFX 57.1%, ETA 46.6%, ADA 42.8%, GOL 39.8% followe by the others. In terms of ACR70: ADA 40.8%, INF 34.2%, GOL 27.4%, SEC 27%, followed by the others. For PASI75 resulted:INF 77.1%, GOL 74.1%, ADA 72.7%, SEC 60.4% followed by the others. In terms of PASI90: IFX 61.0%, GOL 57.2%, ADA 55.5%, SEC 42.3%, folloewd by the others. Also, an analysis regarding NNT was performed.
McInnes et al[23], 2018	ADA, CZP, ETA, GOL, INF, SEC, USK, APR	Bayesian NMA, both random-effect and fixed-effect models	12-16W	ACR20, ACR50, ACR70, PASI50, PASI75, PASI90, PsARC	No	No	21 RCT	For ACR INF, GOL, ADA and SEC showed better results, as well as for PASI (ADA excluded). For PsARC SEC shower a better profile
Song et al[24], 2019	TOF, APR	Bayesian random-effects network meta-analysis	12-16W	ACR20, ACR50, ACR70	Yes	No	8 RCT	TOF 10 had the highest probability of being the best treatment in terms of ACR20 (78%), followed by APR 30 mg (67%), TOF 5 mg (59%), APR 20 mg (44%). No significant differences in the incidence of serious adverse events.
Lu et al[25], 2019	TOF, APR, GUS, USK, SEC, IXE, BRO, CLA, ABA, ADA, ETA, IFX, CZP, GOL	Pairwise meta-analyses, Random-effects model	12-16-<24W	ACR20, PASI75	Yes	No	29 RCT	In terms of ACR 20 the rank is: IFX (96%), GOL (92%), ETA (88%), ADA (80%), GUS (75%), SEC (70%) followed by the rest. In terms of PASI75 the rank is: INF (97%), GUS (83%), ADA (77%), IXE (77%), USK (69%), SEC (62%), followed by the rest. For safety all molecules have a good profile, with best results of ADA, ABA, SEC, USK, BRO (GOL for SAEs).
Ruyssen-Witrand et al[26], 2020	TOF, APR, USK, SEC, IXE, ABA, ADA, ETA, IFX, CZP, GOL	Bayesian NMA, random-effects and fixed-effects models	12-16W	ACR20, ACR50, ACR70, PASI50, PASI75, PASI90, PASI 100, PsARC	Yes	No	25 RCT	For ACR, INF was most effective, followed by GOL and ETA. which were statistically superior to most other treatments. IXE 80 was statistically superior to ABA, APR, USK. For PsARC GOL, IFX, ETA were superior to most other agents. For PASI, IFX was numerically most effective. For safety few differences between treatments were found.
Gladman et al[27], 2020	ABA, ADA, APR, CZP, ETA, GOL, IFX, SEC, IXE, TOF, USK	Bayesian NMA, both random-effect and fixed-effect models	12-24W	ACR20, HAQ, PASI75, DSS, LAI	Yes	No	24 RCT	TOF had similar efficacy compared with most bDMARDs and APR in improving joint symptoms (based on ACR20), and with some bDMARDs in improving skin symptoms (based on PASI). Based on HAQ improvement TOF was similar to that observed for most bDMARDs and APR. Improvements in DSS and LEI were comparable between treatments
Qiu et al[28], 2020	IFX, APR, TOF, USK, GOL, ABA, SEC, CZP, BRO, ADA, ETA, CLA, IXE	Pairwise meta-analysis, Random-effect model	12-24W	ACR20, PASI75	Yes	No	30 RCT	IFX, APR, USK, ABA, SEC, BRO, ETA and CLA showed significant increases in ACR20 and PASI75 compared to placebo. In mixed comparisons, ETN and IFX were more effective than GOL (OR 3.33 and 1.24 respectively), while for PASI75 IFX was superior to CZP (OR 10.08). ETN and IFX have the most favorable SUCRA for achieving ACR20 and PASI75 response

Abbreviations: ACR – American College of Rheumatology, ABA – Abatacept, ADA – Adalimumab, APR – Apremilast, BRO – Brodalumab, CLA – Clazakizumab, CZP – Certolizumab, ETA – Etanercept, GOL – Golimumab, GUS – Guselkumab, IFX – Infliximab, IXE – Ixekizumab, SEC – Secukinumab, TOF – Tofacitinib, USK – Ustekinumab, HAQ – Health Assessment Questionnaire, ICER – Incremental cost-effective ratio, MD – Mean difference, NMA – Network Meta-analysis , NNT – Numbers needed to treat, PASI – Psoriasis Area and Severity Index, PsARC – Psoriatic Arthritis Response Criteria, QALY – Quality life adjusted years, RR – Relative risks. ICER – incremental cost-effectiveness ratio, CPR – Cost per responder, RCT – Randomized Controlled Trials, AEs – Adverse events.

vealed that ETA was shown to be less effective in terms of ACR70 when compared to IFX (ARR 17%,), ADA (ARR 14%,) and GOL (ARR 10%). Cawson et al[16] conducted network meta-analysis and economic evaluation of ADA, ETA, GOL and IFX for treating PsA in the UK. He adopted the methodology of Rodgers et al[11] 2011 and recommended methods by NICE. Results revealed that all four TNF-α inhibitors were effective in attaining PsARC, and ETA and IFX were more effective than placebo for improving HAQ scores. In terms of ICER and QALY, ETA was found to be more effective and economical compared to GOL and ADA. When considered NICE willingness to pay, ETA was the preferred option (£20000-£30000 per QALY). Bets et al in 2015[17], estimated ACR20 response rates, NNT and incremental cost per responder associated with methotrexate, APR and ADA among methotrexate naïve patients, who were treated for PsA. The median NNT was then calculated for each treatment as the reciprocal of the difference in the estimated ACR20 response rates between the treatment arms. In terms of the treatment cost for 16 weeks, ADA ($10,010.44) was followed by APR ($6843.75) and methotrexate ($436.09). Relative to placebo, ADA was found to require the lowest NNT to achieve an ACR20 response (NNT: 2.63), compared with APR (6.69) and methotrexate (8.31). Relative to placebo, methotrexate had the lowest cost per ACR20 responder ($3622), followed by ADA ($26,316), and APR ($45,808). Furthermore, ADA also provides a lower NNT relative to methotrexate compared to APR (3.92 *vs.* 34.72) and has lower incremental costs per responder ($37,517 *vs.* $222,488).

Ungprasert et al[18] in 2015 studied the comparative efficacy of older TNF-α inhibitors with APR, CZP and USK. Clinical trial results of older TNF-α inhibitors were pooled and an indirect comparison was made. It was found that patients who received older TNF-α inhibitors had a statistically higher chance of achieving ACR20 compared with APR 30 mg (RR 2.42), USK 45 mg (RR 2.38,), USK 90 mg (RR 2.08,) and CZP (RR 2.20). The possibility of achieving ACR20 response with older TNF-α inhibitors was not different from SEC 150 mg and SEC 300 mg.

In 2016, Ungprasert et al[19] published another study result comparing the efficacy of non-TNF-α biological agents (SEC, USK, APR and Abatacept - ABA) in patients TNF-α inhibitors IR using indirect comparison technique. No significant differences in comparison were noticed among them. In 2018, Kawalec et al[20] assessed the comparative effectiveness and safety of novel biologic therapies in PsA, (ABA, APR, SEC and USK). The overall PsA population and anti-TNF-α naive, anti-TNF-α failure, or anti-TNF-α experienced subpopulations were considered. No significant differences were found among non-anti-TNF-α biologics in the treatment of PsA in the comparisons of the highest efficacy and safety, but SEC 300 mg was ranked the highest for the ACR20 response rate and the safest drug in terms of any AEs, while USK 90 mg presented the lowest overall risk of SAEs.

Wu et al[21] in 2017 evaluated in pairwise meta-analysis efficacy of biologics targeting IL-12/23 and IL-17 in PsA. SEC 300 mg was superior to USK 45 mg (OR 2.71).

In 2018 Strand et al[22] published a study comparing indirectly efficacy of TNF-α inhibitors e non-TNF-α biological agents (SEC, USK, APR) both in joint (ACR20/50/70) and skin outcome (PASI 75/90). TNFi had the better joint outcome, with GOL with the best ACR 20 responses, IFX the best ACR50 responses and ADA the best ACR70 responses, with a similar response in biologic-naïve patients and NNTs for the three TNF-I compared with other mechanisms of actions.

For ACR20 response rate, ADA showed a NNT 2.3 (1.8, 3.2), APR 6.1 (4.4, 9.5), CZP 3 (2.2, 4.6), ETA 3 (2.1, 5.4), GOL 2.2 (1.7, 3.4), IFX 2.6 (1.8, 4.3), SEC 150 mg 2.6 (2.3, 4), SEC 300 mg 2.6 (1.9, 4.1), USK 45 mg 5.4 (3.7, 9.2) USK 90 mg 4.4 (3.2, 6.7).

For ACR50 response rate ADA showed a NNT 2.8 (1.8, 4.9), APR 11.8 (7, 23.5), CZP 4.8 (2.9,8.9), ETA 2.5 (1.6, 5.1), GOL 3.1 (1.7, 6.6), IFX 2 (1.3, 3.9), SEC 150 mg 3.7 (2.5, 6), SEC 300 mg 3.7 (2.3, 7.2), USK 45 mg 7.7 (4.4, 15.8) USK 90 mg 6.1 (3.7, 11.7).

For ACR70 response ADA showed a NNT 2.6 (1.3, 7.4), APR 40.3 (15.8, 222.7), CZP 7 (3, 17.8), ETA 15.2 (3.3, 318.5), GOL 4 (1.4, 14.6), IFX 3.2 (1.3, 10.3), SEC 150 mg 4 (2, 9), SEC 300 mg 4.1 (1.9, 11.1), USK 45 mg 13 (5.2, 39.7) USK 90 mg 10.4 (4.4, 27.8).

Infliximab showed the best NNT both for PASI75 response (NNT 1.4 – CrI 1.2-1.9) and PASI90 response (NNT 1.7 - CrI 1.3-2.5). Skin disease shows better PASI75 and PASI90 responses rates in patients treated with IFX at week 24, with similar rankings on PASI75 and PASI90 among biologic-naïve patients between all the TNF-I except etanercept.

McInnes[23] compared psoriatic arthritis outcomes (ACR, PASI and PsARC) between SEC,

TNF-I, USK and APR. In this study, SEC 150 and 300 mg showed ACR20 response rates superior to APR 20 or 30 mg and USK 45 mg. ADA, GOL and IFX 5 mg/kg show similar or slightly superior ACR20 response rates when compared with SEC, but not statistically significant. In the biologic naïve population IFX and GOL showed statistical superiority over all treatments in the network, except for SEC and ADA. In the biologic experienced population, all treatments except USK showed superiority to placebo, and CZP showed superiority over both doses of USK. In term of skin disease, SEC demonstrates a response rate for PASI 50/75/90 superior to APR, CZP, ADA and ETA. IFX showed statistical superiority to all treatments except SEC, GOL and USK.

No treatment shows superiority compared with active treatment in PsARC response rates in biologic naïve patients.

In 2019, Song and Lee[24] analysed the efficacy of TOF and APR in patients with active psoriatic arthritis with pairwise comparisons. APR 30 mg bid had the better probability of achieving ACR20, followed by placebo.

Lu et al[25] in 2019 evaluate the efficacy and safety of bDMARDs and tsDMARDs in PsA during the first 12-16 weeks. They identify nine distinct clusters of treatment evaluating ACR20 response rates and PASI75 response rates. IFX, GOL, ETA, GUS, ADA and SEC 300 mg ranked high for both efficacy parameters; IXE and USK 90 mg have high PASI75 response rates and moderate ACR20, SEC 150 mg, USK 45 mg and CZP have moderate efficacy in both outcomes, APR and TOF had similar efficacy.

In 2020 Ruyssen-Witrand et al[26] evaluate the efficacy of bDMARDs including data on IXE. In bDMARDs naïve population IFX was the most effective agents, followed by GOL and ETA, although GOL and ETA were not superior to IXE. IXE was superior to APR and USK. The best performance in PsARC response rate was for GOL, IFX and ETA.

In 2020 Gladman et al[27] evaluate the efficacy of TOF, bDMARDs and APR for the treatment of psoriatic arthritis. In this NMA TOF showed similar efficacy compared with bDMARDs and APR both in improving joint symptoms (ACR20) and skin symptoms.

Qiu et al[28] evaluated 14 molecules for the treatment of PsA. In this NMA IFX, APR, USK, ABA, SEC, Brodalumab (BRD), ETA and Clazakizumab (CLA) showed significant increases in ACR20 and PASI75 compared to placebo. In mixed comparisons, ETN and IFX were more effective than GOL (OR 3.33 and 1.24 respectively), while for PASI75 IFX was superior to CZP (OR 10.08), so ETN and IFX have the most favorable SUCRA for achieving ACR20 and PASI75 response.

Discussion

According to our information, this is the first review on network meta-analysis on biologics used for the treatment of PsA patients who were not responding to cDMARDs therapy. Since biologics are expensive, it is important to assess comparative studies of biologics on both clinical and cost-effectiveness outcome. Even if several studies were conducted on clinical efficacy comparing single biologic with DMARD, no head-to-head RCTs comparing between approved biologics have been performed. Moreover, two generations of biologics, old anti-TNF-α and new non-anti-TNF-α biologics are available. The need to carry out at least an indirect comparison leads to perform NMA. Six NMA had been performed for indirect comparison of approved biologics for clinical endpoints and economic evaluation. However, they differ for data sources (trial network, individual trial characteristics, follow-up, compared drugs, critical appraisal); methods (assumptions, heterogeneity and/or inconsistency, methodological concerns) and results in presentation (comparison of direct and indirect effects, uncertainty, rankings, implications of findings).

This is due to a lack of standardized guidance in conducting NMA even if seven Institutions provided guidelines on conducting NMA. [AHRQ (Agency for Healthcare Research and Quality), CADTH (Canadian Agency for Drugs and Technologies in Health), EUnetHTA5 (European network for Health Technology Assessment), HAS5 (Haute Autorite de Sante´), ISPOR (International Society for Pharmacoeconomics and Outcomes Research), NICE (National Institute for Health and Clinical Excellence), PBAC (Pharmaceutical Benefits Advisory Committee)][21,29-34]. Consequently, the results of NMAs included in this review on PSA are not completely concordant.

In the comparison of efficacy, biologic therapies appeared superior in comparison to placebo. 5 included studies reported no statistical difference in terms of efficacy between biologic therapies [8,10,15,19,20]. Only two studies reported a better profile in terms of efficacy of IFX [11,13]. Rodgers et al[11] reported IFX as associated with the high-

est probability of response on PsARC, ACR and PASI outcomes, but in patients who achieve a PsARC response to treatment, the highest mean reduction in HAQ was found with INX and ETA. These results were similar to what reported by Thorlund et al[13], who included also GOL, finding the highest RR in PsARC response.

Only four authors calculated the probability of best treatments among the compared treatments and reported their corresponding ranking[10,11,16,19]. As reported above, Rodgers et al[11] reported IFX as the best treatment in terms of achieving PsARC, ACR and PASI response. By contrast, Migliore et al[12] reported ETA as the treatment with the best probability to achieve ACR20 response compared to IFX and ADA. Both these studies analysed the old classic biologics treatment for PsA but they differ regarding the follow-up period analysed (12 weeks Rodgers et al[11], 24 weeks Migliore et al[12]) and the studies included.

Only two studies evaluated the NNT parameter: Betts et al[17] and Strand et al[22]. Betts et al[17] compared NNT (calculated as the reciprocal of the difference in the estimated ACR20 response rates) between APR, MTX, and ADA in methotrexate naïve PsA population[17]. ADA resulted as the best option, but the authors don't report comparative data about other outcomes like ACR 50, ACR 70 and HAQ; neither this study compared other current bDMARDs such as CZP, ETA, GOL, INF, USK and SEC. The authors did not find studies on methotrexate naïve pure patients for these molecules. The analysis only on methotrexate naive patient population represents an important limit.

According to Strand et al[22], to achieve ACR20 response, the best molecule is GOL with 2.2, while for ACR 50 patients needed to achieve the outcome, for ACR the best molecule is IFX, with 2 patients needed to achieve the outcome, while for ACR 70 response the best molecule is ADA, with 2.6 patients needed to achieve the outcome. The information reported by Strand et al[22] is particularly useful for a decision-maker because it immediately provides the number of how many patients need to be treated to achieve the desired outcome. The results shown are different between the two works (Betts and Strand)[17,22] probably due to the different studies included in the analyses and for the different molecules analysed (the two studies were published in different years).

More recently, Kawalec et al[20] considered also new therapies for the treatment of PsA, and even if they didn't find a significant statistical difference between biologic therapies, SEC showed the best probability to achieve ACR20 stratifying patients in three sub-populations: naïve, anti-TNF-α inhibitors experienced, and anti-TNF-α failure.

The majority of the studies had been carried out with older anti-TNF-α inhibitors such as ADA, ETA or IFX. Four papers investigated the newly approved agents such as APR, CZP, GOL, USK, SEC[17-20]. The studies carried out by Ungpracept et al[18] seem to indicate that there is much probability to achieve ACR20 with older TNF-α inhibitor drugs (pooled anti-TNF-α) and SEC when compared to the other new ones. The statistical method was to pool old biologic (anti-TNF-α) data for comparison with the newest. This leads to a relevant bias since this method is not able to detect differences between each one of the old anti-TNF-α agents giving the incorrect assumption that each agent of the same old bDMARDs class has the same efficacy. In 2016 in another study Ungpracept et al[18] found no difference in terms of efficacy between no anti-TNF-α inhibitors (APR, SEC, USK) in patients with anti-TNF-α inhibitors experience but they don't express a ranking of the treatments. As quoted above these data were confirmed by Kawalec et al[20] but in this case, they remarked as SEC showed the best probability to achieve ACR20 reporting a ranking between treatments in different sub-populations.

Recent meta-analyses[21-26] evaluate comparisons between anti-TNF-α and new bDMARDs and tsDMARDs. TNF-i still has higher efficacy and lower incremental costs. Among the new mechanisms of action SEC 300 appears to be the most effective, although the data on IXE are still conflicting[25,26]. In one meta-analysis it appears to be moderately effective on the joint and high effective on the skin, while in another meta-analysis on the induction phase (first 12-24 weeks) as effective as anti-TNFs.

6 authors reported cost-effectiveness on the framework of the related country, mainly from UK, USA, and Germany[8,9,11,13,16,17]. The economic evaluation based on statistical methods for studies are not the same and varied among randomised effect model, fixed effect model and Bucher method that may deliver divergent results[35-37]. In 4 studies ETA seems to have a trend of better results in terms of cost-effectiveness[8,9,11,16] and 1 study reported ADA as the best therapies in terms of cost[14] in an analysis from the framework of US and Germany. Betts et al[17] reported a best cost effectiveness profile of ADA against APR but not methotrexate, but this study has the limit to analyse only these three molecules.

About safety profile 5 studies showed results on this item[8,10,14,15,20], reporting any AE and/or SAEs and/or withdrawal due to AEs. 3 studies reported no difference in terms of safety profile[10,14,15] but Cabbalero et al[15] showed a higher number of injection-site reactions with ETA. Woolacott et al[8] presented ETA as the treatment well tolerated in short and long-term use, but they analysed only old molecules [ETA, ADA, IFX], while in the most recent study, Kawalec et al[20] considered also new molecules approved in the treatment of PsA. They presented as the safest drugs SEC 300 mg in terms of any AEs, and USK 90 in terms of the overall risk of SAEs, both in the overall population included in this NMA.

Since understanding NMA is challenging for non-technical end-users, such as clinicians and decision-makers, it is crucial to use presentation formats that can enhance understanding and accessibility of NMAs results and meaning[38]. Recently Shannon et al[39] pointed out the need to tailor information to different audiences who may be unfamiliar with NMAs, determining not just 'what' to report but 'how' best to report it. Only ISPOR guidelines provided specific recommendations on how to present information to end-users of NMAs.

NMA is a recent analytic tool that can offer some advantages over a conventional frequentistic meta-analysis. However, some concerns can arise if authors do not follow the basic standards applicable to any meta-analysis (e.g., comprehensive search, duplicate assessment of eligibility, risk of bias, and data abstraction). The limitations of included trials such as the risk of bias, consistency, and indirectness can lead to bias in the NMA result. Also, specific limitations of NMA including intransitivity, incoherence, or lack of rankings, need to be evaluated for the creditability and quality of NMA evidence.

In summary, there is insufficient statistical evidence to demonstrate clear differences in effectiveness and safety between available biologic agents for PsA. Effect estimates are sensitive to the analytic approach, and this uncertainty should be considered by clinicians.

Conclusions

Network meta-analysis is a step forward than frequentist meta-analysis to suggest physicians and decision-makers for the treatment of PsA patients. There are many differences such as methods and clinical parameters in the conducted studies, giving the inability to elaborate a definitive conclusion. New molecules approved for the treatment of PsA showed similar efficacy, but further comparative studies methodologically well-conducted are necessary to confirm this hypothesis. It is also necessary to follow strictly international recommendations such as ISPOR guidelines to conduct NMA to uniform data sources, methods and results presentation. In this way, NMA can be able to help physicians and decision-makers for making appropriate decisions for the best possible treatment options available.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

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