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A review of network meta-analysis comparing biologics in the treatment of rheumatoid arthritis

G. GIGLIUCCI[1], U. MASSAFRA[1], B. FREDIANI[2], A. DE CATA[3], L. GALLELLI[4], D. INTEGLIA[5], G. PICARELLI[1], A. MIGLIORE[1]

[1]Operative Unit of Rheumatology, San Pietro Fatebenefratelli Hospital, Rome, Italy
[2]Institute of Rheumatology, University of Siena, Policlinico Le Scotte, Siena, Italy
[3]Department of Medical Sciences, Division of Internal Medicine and Rheumatology Unit, IRCCS Scientific Institute and Regional General Hospital "Casa Sollievo della Sofferenza", San Giovanni Rotondo, (FG), Italy
[4]Department of Health Science, University of Catanzaro and Clinical Pharmacology and Pharmacovigilance Operative Unit, Mater Domini Hospital, Catanzaro, Italy
[5]ISHEO Srl, Rome, Italy

Abstract. – OBJECTIVE: Even though in recent years significant improvements have been made in the management of patients with rheumatoid arthritis due to the introduction of biologic agents, it is still difficult to identify the most effective and safest available treatment. The choice and comparison between biological agents are a challenge, for only limited head-to-head clinical studies are available.

The aim of this manuscript is to review the published network meta-analysis (NMA) to gain a better understanding of efficacy and safety of biological agents and small molecules in the management of RA patients.

MATERIALS AND METHODS: We used MEDLINE and EMBASE to identify network meta-analyses from 2008 to June 2019 comparing efficacy and safety of licensed biological agents and tsDMARDS at the approved dosages using predefined text words related to the topic. The following scenarios have been investigated: patients not responding to csDMARD (cDMARDs – IR); csDMARD naïve patients; patients not responding to biologics (bDMARDs – IR); patients in biological monotherapy.

RESULTS: On the basis of the data present in the literature, we are able to hypothesize some trends of response in terms of efficacy in different subsets of patients, for example patients in monotherapy, bDMARds unresponsive patients, and Methotrexate-naive patients.

The differences of the results presented in many works are due to the different inclusion criteria used in the studies, the type of biologics agent used in each study (according to the available molecules in the different years of publication), as well as differences in the methodology of NMA and in the presentation of the data.

CONCLUSIONS: We suggest that the next NMA follows the indications suggested by the Professional Society for Health Economics and Outcomes Research (ISPOR) so that the results are comparable and comprehensible.

Key Words:
Rheumatoid arthritis, Network meta-analysis, Biological agents, tsDMARDs.

Introduction

Rheumatoid arthritis (RA) is a chronic progressive autoimmune inflammatory disease that leads to joint pain, stiffness, and later resulting in deformity of joints if untreated[1]. Therapeutic management of rheumatic arthritis usually involves treatment with non-steroid anti-inflammatory drugs (NSAIDs), glucocorticoids, and disease modifying anti-rheumatic drugs (DMARDs), like methotrexate (MTX), sulfasalazine (SSZ), hydroxychloroquine (HCQ), and leflunomide (LEF) where effects are limited to avoid disease progression[2]. With the arrival of these biologics, tremendous advances have been made in the treatment of RA, since they target specific mediators of inflammation[3,4]. Since biologics are more expensive than standard DMARDs therapy, they are allowed only for patients with an inadequate response with conventional therapy. A variety of biologics are available with ones for the treatment of RA: Abatacept (ABA) inhibitor of T cell activation, Adalimumab (ADA) TNFα-inhibitor (aTNF),

Corresponding Author: Gianfranco Gigliucci, MD; e-mail: gianfranco.gigliucci@hotmail.it

Anakinra (ANA) interleukin 1 (IL1) receptor antagonist, Certolizumab (CZP) aTNF, Etanercept (ETA) aTNF, Golimumab (GOL) a human monoclonal antibody, Infliximab (INF) aTNF, Rituximab (RTX) monoclonal antibody against protein CD20, Tofacitinib (TOF) and Baricitinib (BAR) JAK inhibitor, Tocilizumab (TCZ) IL6 inhibitor. The choice and comparison between biological agents are a challenge, because until now, only limited head-to-head clinical studies are available. When head-to-head trials of two interventions aren't available, indirect comparisons and network meta-analyses enable the estimation of effects, as well as the simultaneous analysis of networks involving more than two interventions[5].

In this manuscript we reviewed the most updated network meta-analysis (NMA) on the efficacy and safety of biological agents and small molecules in the management of RA patients, according to different clinical subset: cDMARDs – IR (inadequate response), DMARD naive, bDMARDs – IR, monotherapy.

Materials and Methods

We used MEDLINE and EMBASE to identify network meta-analysis when comparing efficacy and safety of licensed biological agents at therapeutic doses, such as ABA, ADA, ANA, CZP, ETA, GOL, INF, RTX, biosimilar, TOF, BAR, and TCZ from 2008 up to June 2019. Both engines were intensively searched, and search terms included a combination of the following terms: "Indirect comparison" OR "Bayesian" OR "Network meta-analysis" OR "Probabilistic meta-analysis" OR "Mixed treatment comparison" AND "Rheumatoid Arthritis" AND "Biologic" OR "antiTNF" OR "Biosimilar" OR "Abatacept" OR "Adalimumab" OR "Anakinra OR "Certolizumab" OR "Etanercept" OR "Infliximab" OR "Golimumab" OR "Rituximab" OR "Tofacitinib" OR "Baricitinib" OR "Tocilizumab". A first screening was performed by a single reviewer to identify and exclude from further analysis on all duplicates. Consequently, the remaining papers were analyzed independently by three reviewers (AM, GG, UM). The second screening was performed by each reviewer by title. Then, all three reviewers analysed the remaining abstracts and papers that published partial abstracts and non-English written articles were excluded. In a further step, remaining abstracts were analysed in full text. Discrepancies in the results gathered at each step by different reviewers were resolved on face to face discussion.

All included meta-analyses were then analyzed for main characteristics: included studies, treatment arms, methodology of statistical analysis, presentation of results. The results obtained from the included studies were then summarized and critically discussed. Our included search materials were studies with biologics, such as ABA, ADA, ANA, CZP, ETA, INF, biosimilar, GOL, TCZ, RTX, TOF, and BAR in comparison to placebo and DMARDs (including triple therapy HCQ+MTX+SSZ).

Clinical efficacy was assessed through clinimetric parameters, such as DAS28, HAQ, remission status and signs of radiological disease progression. The efficacy results have been reported according to different scenarios which are related to the characteristics of the population examined: patients with AR DMARDs IR, patients with RA naive to MTX, patients with RA in monotherapy, patients with AR BIO IR. The safety profile was evaluated separately by evaluating withdrawals related to adverse events (AEs) and the appearance of serious adverse events (SAEs).

Results

We identified 168 studies, 32 of these (19%) were excluded because of duplicates produced by the search methodology; 85 (50.6%) were excluded after title screening, 3 (1.8%) after abstract analysis, and 9 (5.4%) because they were only either abstract or were not in English. Finally, 2 studies (1.2%) were excluded after the full text analysis because they were not adhering to network meta-analysis guidelines. Therefore, 37 studies (22%) were included for further analysis (Figure 1, Table I). All biologics are superior in terms of efficacy with respect to placebo in all analysed scenarios.

Five meta-analyses[6-10] consider RA trials with a mixed patient population, since they include patients not responding to csDMARD therapy with csDMARD naïve patients or not responding to therapy with biologics.

DMARDs IR Patients

27 studies investigated clinical effectiveness of biologics in RA patients who are DMARD or MTX unresponsive in combination therapy; the main characteristics and results are described in Table II. ANA was compared with other biologics in 8 studies and it was found to be less effective with respect to the other biologics[9,11-17]. The combination of bDMARDs plus DMARDs was superior compared

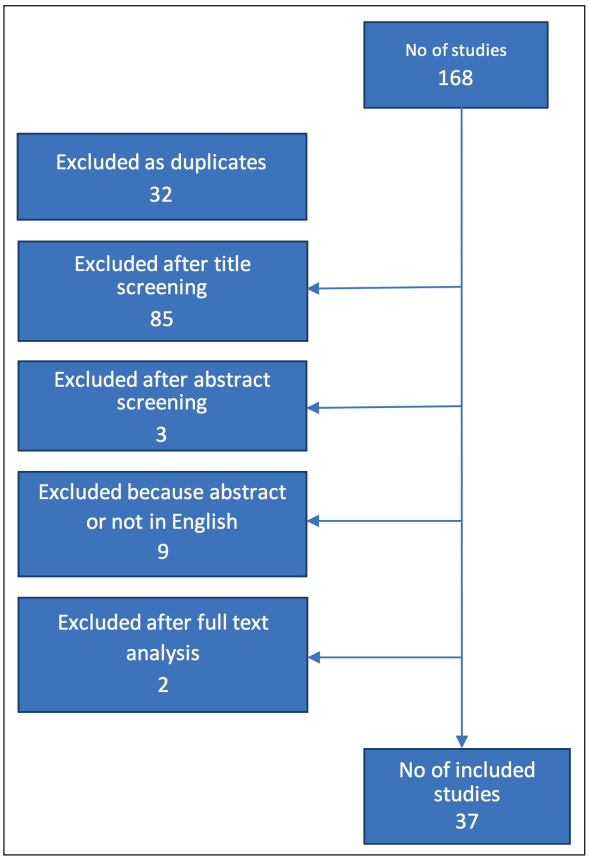

Figure 1. Flow chart of the review process.

to DMARDs. Ten manuscripts[6-8,12,13,18-22] reported a greater trend of efficacy of CZP compared to other biological therapies although in different outcomes. Singh et al[11] comparing ABA, ADA, ANA, ETA, INF, and RTX reported in terms on Number Needed to Treat (NNT) *vs.* placebo reporting the following NNT: 3 for ETA, 4 for ADA, 4 for RTX, 5 for ABA, and 5 for INF. For ANA, benefit from NNT was not significant.

Five studies[14,15,23-25] investigated aTNF as a class. Regarding jak inhibitors, five NMA[15-17,26,27] studied the efficacy and the safety of TOF and two NMA[10] studied BAR.

Buckley et al[15] compared the efficacy of old and new biologics. The new bDMARDs demonstrated greater ACR20/50/70 responses than MTX alone. ACR20/50/70 responses with combined aTNF, ABA, TCZ, and TOF were comparable to placebo. In pairwise comparison, for ACR20 ABA, combined aTNF, TCZ, and ANA showed a probability to have a greater clinical response than TOF, respectively of 67%, 86%, 66% and 27%.

Only two NMA[25,27] analyzed triple therapy or other csDMARDs combination; Hazlewood et al[27] showed that Triple therapy (MTX+HCQ+SSZ), MTX+HCQ, MTX+leflunomide (LEF), was found superior to oral MTX and Flieschman et al[25] found that the achievement of ACR70 was more likely in patients treated with combined aTNF-MTX compared with triple therapy in the fixed-effects model, but not the random-effects model in which no differences were observed.

Three NMA[16,25,27] evaluated the effect of DMARD on radiographic progression of disease in IR patients; Hazlewood et al[27] reported that no treatment was found to be statistically superior to MTX; Singh et al[16] found that B-dMARDs+MTX were more effective than B-DMARDs+C-DMARDs; Fleischman et al[25] found that combined aTNF-MTX was likely superior to the triple therapy only in the fixed-effects model.

Singh et al[16] updated the 2009 publication for a total of 79 RCTs and they used more sophisticated evidence synthesis (according to the evolution of statistical evaluation), like for example the use of NMA methodology. This work analyzed efficacy in terms of ACR50, HAQ, remission, and radiographic progression of combined aTNF (ADA, CZP, ETA, GOL, INF), combined non aTNF (ABA, TCZ, RTX), ANA and small molecule TOF, *vs.* comparator (MTX, DMARD, placebo (PL), or a combination. NMA estimates for ACR50 combined aTNF+MTX/DMARD, combined non-aTNF+MTX/DMARD and ANA+MTX/DMARD were similar with more efficacy than the comparator with an NNT for an additional beneficial outcome (NNTB) of 4 (3 to 5) for combined aTNF and 5 (3 to 7) for the combined non aTNF. Moreover, biologics in combination with MTX were more effective in achieving ACR50 than biologics in combination with DMARDs. Similar results were found for HAQ, remission, and radiographic progression.

Four manuscripts investigated biosimilars[6,9,25,28]. Simpson et al[9] showed the best profile in terms of ACR response of ETA SB4 in comparison with other biological treatments, while Baji et al[6] showed no significant difference between the efficacy of INF biosimilar and other biologics but these studies analyzed a mixed population (not only DMARDs IR). Bae et al[28] studied the efficacy of INF biological and of two INF biosimilars (SB2, CT-P13) in terms of ACR20/50/70 and they ranked the percentage to be the best treatment: ACR20Biosimilar INF+MTX 79%, INF+MTX 70% and PBO+MTX 18%. The ACR50 and ACR70 response rates showed a similar distribution pattern to the ACR20.

Table I. Studies on clinical efficacy and safety of biologics in RA.

Author	Biologics studied	Method	Efficacy Outcome	Follow-up time	Evaluation		No. of studies	Patient Population
					Safety	Economical		
Lee et al[37]	ADA, ETA, INF, MTX	Bucher method	ACR 20/50/70	52-55 wks	Yes	No	3	csDMARDs failure
Singh et al[11]	ABA, ADA, ANA, ETA, INF, RXB, placebo, MTX, csDMARDs	Mixed effect logistic regression, Random effect model	ACR 50	Not reported	Yes	Yes	31	Not reported
Bergman et al[51]	ABA, ADA, ETA, INF, RXB, MTX, placebo	Bayesian MTC, Fixed effect model	ACR 20/50/70	24-30 wks	No	No	18	csDMARDs failure
Devine et al[18]	ABA, ADA, ETA, INF, GOL, RXB, TCZ, MTX placebo	Bayesian ITC	ACR 50, HAQ	6-12 mts	No	No	30	csDMARDs failure
Launois et al[12]	ADA, ANA, ETA, INF, GOL, CZP, TCZ, placebo	Bayesian random effect model, No inferiority Study	ACR 20/50/70	6-8 mts	No	No	19	csDMARDs failure
Schmitz et al[19]	ADA, CZP, ETA, INF, GOL, MTX, placebo	Bayesian MTC	ACR 20/50, HAQ	24 wks	No	No	16	MTX Failure
Gallego-Galisteo et al[20]	ABA, ADA, CZP, ETA, GOL, INF, TCZ, placebo	Bucher method with ETA as reference drug	ACR 20/50/70	24 wks	No	No	10	csDMARDs failure
Turkstra et al[13]	ABA, ADA, ANA, CZP, ETA, INF, TOC, GOL, RTX, Placebo, MTX	MTC indirect comparison	ACR 20/50/70	24 wks	No	No	27	csDMARDs failure
Guyot et al[52]	ABA, ETA, INF, ADA, CZP, RTZ, TCZ, Placebo+ MTX	NMA, Fixed and randomized effect models	HAQ, ACR 50	24-52 wks	No	No	16	MTX failure
Salliot et al[23]	ABA, RXB, TCZ, MTX, placebo	Mantel-Haenszel, Bucher, 24 wks	αTNF combined, Song	ACR 20/50	No	No	19	MTX naïve, MTX failure
Orme et al[21]	ABA, ADA, CZP, ETA, GOL, INF, RXB, TCZ, csDMARDs.	Bayesian, fixed randomized effect model	ACR 20/50/70	12-30 wks	No	No	37	csDMARDs failure, Combination, Monotherapy
Aaltonen et al[34]	ADA, CZP, ETA, INF, GOL, MTX + placebo, MTX	Meta-analysis RCT	ACR 20/50/70	3-12 mts	Yes	No	41	MTX naïve, Non naïve, Combination, Monotherapy
Guyot et al[22]	ABA, ADA, CZP, ETA, GOL, MTX, placebo	Bayesian NMA	ACR 20/50/70, HAQ	24-28 wks	No	No	11	MTX Failure

Continued

Table I (continued). Studies on clinical efficacy and safety of biologics in RA.

Author	Biologics studied	Method	Efficacy Outcome	Follow-up time	Evaluation		No. of studies	Patient Population
					Safety	Economical		
Desai et al[38]	ABA, ADA, ANA, CER, ETA, GOL, INF, RTX, TZB, csDMARDs, placebo	Bayesian MTC	Treatment discontinuation (withdrawals)	12 up to 104 wks	Yes	No	44	Active RA
Hochberg et al[24]	ABA, Combined TNF-i group (ADA, ETA, CZP, GOL, INF), placebo+ csDMARDs, placebo+ biologic agent	Bayesian, random effect model	ACR 20/50/70 DAS 28 remission	24-48 wks	Yes	No	19	csDMARDs Failure
Baji et al[6]	ABA, ADA, CZP, ETA, GOL, INF, RXB, TCZ, Biosimilar INF, placebo +MTX, placebo+ csDMARDs	Bayesian MTC	ACR 20/50	24 wks	Yes	No	36	MTX Naïve, csDMARDs Failure
Jansen et al[14]	ABA, ANA, TCZ, and combined TNF (ADA, CZP, ETA, GOL, INF), MTX, placebo	Bayesian, RCT, Fixed and random effect models	Pain, Physical component summary, PCS, PGA, SF 36, HAQ-DI.	24 wks	No	No	22	Monotherapy, csDMARDs failure
Kim et al[31]	ABA, GOL, RXB, TCZ, placebo	Bayesian NMA	ACR 20/50/70 HAQ		No	No	6	TNF-α inhibitor failure
Buckley et al[15]	ABA, Combined antiTNF (ADA, ANA, CZP, ETA, GOL, INF), TCZ, TOF, placebo, placebo + MTX	Bayesian NMA, Fixed random effect models	ACR 20/50/70	24 wks	No	No	28	csDMARDs Failure, Monotherapy, Combination
Tvete et al[7]	ABA, ADA, ANA, TOF, ETA, CZP, RTX, GOL, TCZ, INF, placebo, placebo+csDMARDs, csDMARDs	Bayesian, MTC regression analysis approach	ACR 50		No	No	54	Monotherapy, Combination
Migliore et al[29]	ADA, ETA, TCZ, csDMARDs, placebo	Bayesian MTC, Fixed effect model	ACR 20/50/70	16-24 wks	No	No	10	Monotherapy
Lee et al[26]	TOF with and without MTX, ADA+MTX, placebo, MTX	Bayesian NMA, Random effect model	ACR 20	3-24 mts	Yes	No	10	csDMARDs, MTX Failure, Monotherapy

Continued

Table I (continued). Studies on clinical efficacy and safety of biologics in RA.

Author	Biologics studied	Method	Efficacy Outcome	Follow-up time	Evaluation		No. of studies	Patient Population
					Safety	Economical		
Lee et al[32]	ABA, RXB, TCZ, TOF all +MTX, placebo+MTX	Bayesian NMA, Random effect model	ACR 20/50/70		Yes	No	4	TNFi failure
Hazlewood et al[27]	csDMARDs, Triple Therapy, MTX combined with ABA, ADA, CZP, ETA, GOL, INF, RTX, TCZ, TOF, placebo	Bayesian NMA, Random effect model	ACR 50, Radiographic progression	12-16 wks	Yes	No	197	Naïve, MTX failure
Singh et al[16]	ABA, ADA, ANA, CZP, ETA, GOL, INF, RXB, TCZ, TOF, csDMARDs, placebo	Network meta-analysis (NMA) using a Bayesian mixed treatment comparison (MTC) approach, and traditional meta-analysis	ACR 50, HAQ, DAS28 remission, Radiographic progression	6-12 mts or more	Yes	No	79	MTX or csDMARDs failure
Singh et al[30]	ABA, ADA, ANA, CZP, ETA, GOL, INF, RXB, TCZ, TOF, csDMARDs, placebo	Network meta-analysis (NMA) using a Bayesian mixed treatment comparison (MTC) approach, and traditional meta-analysis	ACR 50, HAQ, DAS28 remission, Radiographic progression	6-12 mts or more	Yes	No	41	MTX or csDMARDs failure (biologic monotherapy)
Migliore et al[35]	ADA, ETA, INF, GOL, RTX, ABA, MTX	Bayesian MTC, Fixed effect model	ACR 20/50/70	24-108 wks	Yes	No	10	Early RA, Naive
Alfonso-Cristancho et al[8]	ABA, ADA, CZP, ETA, GOL, INF, RXB, TCZ, csDMARDs, placebo	RCT	ACR 20/50/70	26 wks	No	No	68	csDMARDs failure, TNF failure or both, monotherapy
Bergrath et al[17]	Alone or in combination with MTX/csDMARDs: ABA, ADA, ANA, CZP, ETA GOL, INF, TCZ, TOF, BAR; placebo	Bayesian NMA, Fixed and Random effect model	ACR 20/50/70	24 wks	Yes	No	45	csDMARDs failure, Monotherapy and combination
Singh et al[33]	ABA, ADA, ANA, CZP, ETA, GOL, INF, RXB, TOF	Bayesian NMA	ACR 50, HAQ, DAS28 remission	6-12 mts or more	Yes	No	12	Biological failure
Singh et al[36]	ABA, ADA, ANA, CZP, ETA, GOL, INF, RXB, TOF	Bayesian NMA	ACR 50, HAQ, DAS28 remission, Radiographic progression	6-12 mts or more	Yes	No	19	MTX naive

Continued

Table I (continued). Studies on clinical efficacy and safety of biologics in RA.

Author	Biologics studied	Method	Efficacy Outcome	Follow-up time	Evaluation		No. of studies	Patient Population
					Safety	Economical		
Fleischmann et al[25]	Combined antiTNF (ADA, CZP, ETA, GOL, INF, INF biosimilar) + MTX or Triple Therapy (MTX + HCQ+SSZ)	Bayesian NMA, Fixed and Random effect model	ACR 70, Radiographic progression PRO	3, 6, 12, 24 mts.	Yes	No	52	MTX failure or naive, TNFi+MTX. Triple therapy (MTX+HCQ+SSZ)
Maneiro et al[39]	INF, ETA, ADA, CZP, GOL, ABA, RXB, TCZ, TOF, placebo, csDMARDs	NMA e random-effects method	Risks for malignancies accompanying bDMARDs and TOF	≥ 22 wks	Yes	No	113	Not specified
Park et al[40]	Combined antiTNF (ADA, CZP, ETA, GOL, INF), ABA, RTX, TCZ, TOF, placebo	Bayesian NMA	Treatment discontinuation	12-104 wks	Yes	No	34+6e	csDMARDs failure, Biologics failure
Simpson et al[9]	ABA, ADA, ANA, CZP, ETA, ETA SB4, GOL, INF, INF CT-P13, INF SB2, TCZ, csDMARDs, combined csDMARDs	Bayesian NMA	ACR20, ACR50, ACR70, EULAR response	22-30 wks	No	No	46	MTX naïve, csDMARDs experienced
Bae et al[28]	Biosimilar INF+MTX, INF+MTX, placebo+ MTX	Bayesian NMA random-effects model	ACR20, ACR50, ACR70	22-54 wks	Yes	No	7	MTX failure
Lee et al[10]	ADA, BAR (alone or + csDMARDs), placebo+ csDMARDs	Bayesian NMA random-effects model	ACR20	12 wks	Yes	No	7	csDMARDs failure, csDMARDs naïve, Biologics failure, Monotherapy

Abbreviations. ABA: Abatacept; ACR: American College of Rheumatology; ADA: Adalimumab; AE: Adverse events; ANA: Anakinra; BAR: Barcitinib; csDMARDs: conventional synthetic disease: modifying antirheumatic drugs; CZP: Certolizumab; DAS: Disease activity score; ETA: Etanercept; GOL-Golimumab; HAQ: Health assessment Questionnaire; HCQ: Hydroxychloroquine; INF: Infliximab; IR: Inadequate response; LDGC: Low dose Glucocorticoid; MTC: Mixed treatment comparison; MTX: Methotrexate; NMA: Network meta-analysis; PCS: Physical component summary; PGA: Patient's global assessment; PRO: Patient reported outcomes; RA: Rheumatoid Arthritis; RCT: Randomised clinical Trials; RXB: Rituximab; SF36: Medical Outcomes Study Short Form 36 Health Survey; SSZ: Sulfasalazine; TCZ: Tozilizumab; TOF: Tofacitinib; TNFi: Tumor Necrosis Factor inhibitor.

Table II. Studies on DMARD or MTX failure patients.

Author	Biologics	Results
Lee et al[37]	ADA, ETA, INF, MTX	The RRs for achieving ACR20, ACR50, and ACR70 responses in the ETA group were significantly lower when compared with ADA group. The RR for achieving an ACR20 response in the ETA group was lower when compared to INF group.
Singh et al[11]	ABA, ADA, ANA, ETA, INF, RXB, placebo, MTX, csDMARDs	Each individual biologic was significantly more likely than placebo to achieve an ACR50 except for ANA that was less effective than ADA and ETA for achieving ACR50. Statistical significance was noted for ADA and ETA. The numbers needed to treat for benefit were 3 for ETA, 4 for ADA and RTX, 5 for ABA and INF. For ANA, the number needed to treat for a benefit was not significant.
Bergman et al[51]	ABA, ADA, ETA, INF, RXB, MTX, placebo	TCZ was comparable in terms of ACR20/50, but exhibited higher ACR70 than combined aTNF, ADA and RTX.
Devine et al[18]	ADA, CZP, ETA, INF, GOL, RXB, TCZ, MTX placebo	Ranking based on median log a t 6 months were CZP 2.6, TGZ 1.7, RXB, 1.6, INF 1.6, ETA 1.4, ADA 1.4, GOL 1.4, ABA 1.2, ANA 1.0 and MTX 0.8. At 12 months CZP 2.0, ADA 1.4, INF 1.4, ETA 0.9 ABA 0.6, and MTX 0.8.
Launois et al[12]	ADA, ANA, ETA, INF, GOL, CZP, TCZ, placebo	According to the random-effects model, efficacy results show relatively high OR on the ACR20 criterion for all treatments except ANA. CZP exhibits the highest OR value (11.82), significantly than INF (3.31), ADA (3.72), and ANA (2.40) but not significantly different from ETA (8.07), GOL (3.62), and TCZ (4.13). Regarding the ACR50, CZP exhibits a high OR (10.81), comparable ETA (11.45) and markedly but not significantly higher than that of every other treatment. ACR70 CZP exhibits the highest OR (15.8), which is not significantly different from other treatments.
Schmitz et al[19]	ADA, CER, ETA, INF ABA, GOL, MTX, placebo	The RR for CZP achieving ACR20 and ACR50 response shows better efficacy over ADA, INF and GOL. ETA was found superior to INF and GOL. For ACR50 response, ETA was found nearly equal in efficacy to CZP, and ADA showed superiority over INF. For HAQ, among the aTNF, ETA achieved the highest improvement vs. placebo. In comparison among biologics, all aTNF agents showed greater efficacy than INF. CZP and ETA were found to be superior to ADA. ETA showed improved efficacy over GOL.
Gallego-Galisteo et al[20]	ABA, ADA, CZP, ETA, GOL, INF, TCZ, placebo	CZP was found to be most effective in terms of ACR20. For ACR50, higher efficacy was found with ADA, ETA and TCZ. INF was found to be least effective in terms of ACR20/50/70.
Turkstra et al[13]	ABA, ADA, ANA, CZP, ETA, INF, TCZ, GOL, RTX, MTX	For ACR 20 response, ANA and GOL did not exhibited any advantage compared to control arm. For, ACR 20/50, a statistical significance was found for CZP compared to other drugs and ETA vs. ADA and ETA.
Guyot et al[52]	ABA, ETA, INF, ADA, CER, RTZ, TCZ, placebo + MTX	For ACR50 and HAQ, ABA and other biologics are comparable. Regarding DAS28, ABA was found less effective than TCZ and ABA.
Salliot et al[23]	ABA, RXB, TCZ, aTNF combined, MTX, placebo	Combined aTNF may be more likely than combined non-aTNF biologicals and ABA to achieve ACR50 response. No difference for ACR50were noticed among combined aTNF and TCZ. ABA was found to be less effective than TCZ in terms of ACR50.
Orme et al[21]	ABA, ADA, CER, ETA, GOL, INF, RXB, TCZ, DMARDs	Probability of best treatment was: for ACR 20 CER 64.2%, ETA 35.1; for ACR 50, CER 35.6% ETA 55.6%, GOL 3.6%. for ACR70, CER 28.5%, ETA 64.7% GOL 2.7% TCZ 3.6%. Probability of best treatment in monotherapy was: for ACR20 -TCZ 69.2%, ETA 23.6%, ADA6.9%; for ACR50, TCZ 69.2%, ETA 23.6%, ADA 6.9%; for ACR20 TCZ 69.2%, ETA 23.6%, ADA 6.9%.
Aaltonen et al[34]	ADA, CZP, ETA, INF, GO, MTX + placebo, MTX	In ACR 50 at 6 months GOL was found inferior compared to ADA, CZP and ETA from the control group. GOL was found to be inferior for obtaining ACR 20 at 6 months compared to CZP combination therapy.
Guyot et al[22]	ABA, ADA, CZP, ETA, GOL, MTX, placebo	Best expected HAQ was found with CER followed by GOL, ADA, ABA, ETA and INF. At 6 months, better ACR20 response was attained by CZP.

Continued

Table II (continued). Studies on DMARD or MTX failure patients.

Author	Biologics	Results
Hochberg et al[24]	ABA, Combined aTNF (ADA, ETA, CZP, GOL, INF), placebo+DMARDs, placebo+biologic	ABA had similar efficacy at 6 months and higher likehood of achieving ACR70 and DAS28 remission at 12 months *vs.* combined aTNF.
Baji et al[6]	ABA, ADA, CER, ETA, GOL, INF, RXB, TCZ, Biosimilar infliximab, MTX+placebo, csDMARDs+placebo	For ACR20, CZP exhibited highest OR, compared to placebo (OR 7.69), followed by ABA OR 3.7, TCZ, OR 3.69, and INF-biosimilar OR 3.47. For CR 50, CZP showed the highest OR compared to placebo OR 8.46, followed by TCZ, OR 5.57, and INF-biosimilar OR 4.06. The results of pairwise comparison did not show significant differences between the efficacy of INF biosimilar and the other biologicals.
Jansen et al[14]	ABA, ANA, TCZ, and combined aTNF (ADA, CZP, ETA, GOL, INF), MTX, placebo	In combination therapy with MTX, combined aTNF, ABA and TCZ exhibited comparable reductions in pain and PGA, while ANA exhibited the smallest value. Regarding HAQ, greatest improvement expected with combined aTNF and TCZ. Comparable improvements were found on SF36 with ABA, combined aTNF and TCZ.
Buckley et al[15]	ABA, combined aTNF (ADA, ANA, CZP, ETA, GOL, INF) TCZ, TOF, placebo, placebo + MTX	For combined therapy with MTX, all classes of novel DMARDs demonstrated greater ACR20/50/70 responses than MTX alone. ACR20/50/70 responses with aTNF, ABA, TCZ, and TOF were comparable.
Tvete et al[7]	CZP, ABA, ADA, ETA, TCZ, GOL, INF, RXB, ANA, placebo, placebo+csDMARDs	In combination with MTX to achieve ACR50 the rank was: CZP, followed by TCZ, ANA, RXB, GOL, INF, ABA, ADA, ETA.
Lee et al[26]	TOF with and without MTX, ADA+MTX, MTX, placebo	TOF + MTX had the highest probability of being the best treatment for achieving the ACR20 response rate followed by ADA + MTX, TOF in monotherapy, MTX, and placebo.
Hazlewood et al[27]	csDMARDs, Triple Therapy, MTX combined with ABA, ADA, CZP, ETA, GOL, INF, RTX, TCZ, TOF, placebo	Triple therapy (MTX+HCQ+SSZ), MTX+(HCQ), MTX+ LEF, MTX plus IM gold, MTX plus most biologics, and MTX plus TOF were found superior to oral MTX for ACR50 response. The probability of ACR50 response was 61% with triple therapy and ranged widely (27-70%) with other treatments. No treatment was found to be statistically superior to oral MTX for inhibiting radiographic progression.
Singh et al[16]	ABA, ADA, ANA, CZP, ETA, GOL, INF, RXB, TCZ, TOF, csDMARDs, placebo	For ACR50 aTNF+MTX/DMARD, non-aTNF +MTX/DMARD and ANA+MTX/DMARD were similar with more efficacy than comparator with a NNTB of 4 (3 to 5) for aTNF and 5 (3 to 7) for non aTNF. Biologic + MTX was more effective in achieving ACR50 than biologic + DMARDs. Similar results were found for HAQ, remission and radiographic progression.
Alfonso-Cristancho et al[8]	ABA, ADA, CER, ETA, GOL, INF, RXB, TCZ, csDMARDs, placebo	TCZ + MTX was significantly better than placebo and MTX alone for ACR 20/50/70 response at 26 weeks. At 52 weeks, compared to MTX alone, TCZ + MTX was significantly better for ACR20/50 response. TCZ + MTX was significantly better than ETA alone for ACR 20, ACR 50, and ACR 70 responses at 26 weeks and ACR 20 and ACR 50 responses at week 52. Compared to ADA monotherapy, TCZ + MTX was significantly better for ACR 20 and ACR 50 response at 26 weeks. TCZ +MTX was significantly better for the other following comparisons: ABA + MTX for ACR 50 at 26 weeks; ADA + MTX for ACR 50 at 52 weeks; ETA + MTX for ACR 50 at 26 weeks and ACR 20 at 52 weeks; INF + MTX for ACR 50 at 26 weeks, and TCZ alone for ACR 50 at 26 weeks. Only CZP + MTX for ACR 20 at 52 weeks follow-up appeared superior to TCZ.

Continued

Table II (continued). Studies on DMARD or MTX failure patients.

Author	Biologics	Results
Bergrath et al[17]	Alone or in combination with MTX/csDMARDs, ABA, ADA, ANA, CZP, ETA GOL, INF, TCZ, TOF, BAR; placebo	TOF + MTX showed a more effective response than placebo + MTX, comparable to all other MTX combination therapies in terms of ACR20 and ACR50 at 24 weeks and in terms of ACR70 more effective than placebo + MTX and CZP + MTX.
Fleischmann et al[25]	Combined aTNF (ADA, CZP, ETA, GOL, INF, INF biosimilar.) + MTX or Triple Therapy (MTX + HCQ+SSZ)	Achievement of ACR70 and the likelihood of no radiographic progression at 2 years was more likely in patients treated with combined aTNF-MTX compared with triple therapy in the fixed-effects model, but not in the random--effects model.
Simpson et al[9]	ABA, ADA, ANA, CZP, ETA, ETA, SB4, GOL, INF, INF CT-P13, INF SB2, TCZ, csDMARD, combined csDMARDs	The ranks for ACR and EULAR responses were: bsDMARD ETN SB4 + MTX, following by TCZ monotherapy, TOC + MTX and boDMARD ETN + MTX. No clear differences were found between the boDMARDs and their bsDMARDs.
Bae et al[28]	Biosimilar INF+MTX, INF+ MTX, placebo+MTX	For attaining ACR20, biosimilar + MTX had the highest probability of achieving ACR20 response rate (SUCRA = 0.7964), followed by infliximab + MTX (SUCRA = 0.7018) and MTX alone (SUCRA = 0.0018). The ACR50 and ACR70 response rates showed a similar distribution pattern to the ACR20 response rate.
Lee et al[10]	ADA, BAR (alone or + csDMARDs), placebo+ csDMARDs	The ranking probability based on SUCRA for attaining ACR20 is: BAR+csDMARDs 0.7930, BAR 0.7034, ADA+MTX 0.3687, Placebo+DMARD 0.0045

Abbreviations. ABA: Abatacept; ACR: American College of Rheumatology; ADA: Adalimumab; AE: Adverse events; ANA: Anakinra; BAR: Barcitinib; csDMARDs: conventional synthetic disease: modifying antirheumatic drugs; CZP: Certolizumab; DAS: Disease activity score; ETA: Etanercept; GOL-Golimumab; HAQ: Health assessment Questionnaire; HCQ: Hydroxychloroquine; INF: Infliximab; IR: Inadequate response; LDGC: Low dose Glucocorticoid; MTC: Mixed treatment comparison; MTX: Methotrexate; NMA: Network meta-analysis; PCS: Physical component summary; PGA: Patient's global assessment; PRO: Patient reported outcomes; RA: Rheumatoid Arthritis; RCT: Randomised clinical Trials; RXB: Rituximab; SF36: Medical Outcomes Study Short Form 36 Health Survey; SSZ: Sulfasalazine; TCZ: Tozilizumab; TOF: Tofacitinib; TNFi: Tumor Necrosis Factor inhibitor.

Fleischmann et al[25] analyzed INF bio similar but in a combined group with aTNF and they did not show details about the biosimilar molecules. About BAR, Lee et al[10] realized a ranking in term of probability to be the best treatment to achieve ACR20 with the following results: BAR+csDMARDs, BAR in monotherapy, ADA+MTX, Placebo+DMARD.

Use of B-DMARDs in Monotherapy

The use of B-DMARDs in monotherapy has been investigated in eleven studies (Table III), reporting that the combination therapy of aTNF+MTX was more effective than both MTX monotherapy and aTNF monotherapy. Between non aTNF agents five manuscripts[8,14,15,21,29] reported that TCZ could represent the best treatment. The same authors reported that response with TCZ+MTX were similar to those with TCZ monotherapy. Four authors reported data on TOF[15,17,26,30] and two on BAR[10].

Effect of bDMARDs in IR-aTNF

The effect of bDMARDs in IR-aTNF has been investigated in seven NMA[8,10,23,25,31-33]. The results are reported in Table IV. Three authors report that for ACR responses switching to non-TNF biologics shows higher probability than cycling of alternative aTNF[23,31,32]. Singh et al[33] compared combined aTNF (ADA, CZP, ETA, GOL, INF), combined non-aTNF (TCZ, ABA, RTX) and small molecules TOF finding no statistical or clinical differences. Lee et al[10] reported that BAR in association with csDMARDs or alone, is more effective than ADA+MTX to achieve ACR20.

Clinical Effectiveness in MTX Naïve

Seven studies[9,10,25,27,33-35] investigated clinical effectiveness in MTX Naïve patients. The results are reported in Table V. Migliore et al[35] reported that all biologics proved to be more effective than MTX plus placebo for all ACR responses. The highest probability expressed in ranking for attaining ACR70 was exhibited by ADA (33.28%), while ETA exhibited highest probability for attaining ACR20 (62.95%) and ACR50 (37.1%).

Hazlewood et al[27] compared the triple therapy (MTX+SSZ+HCQ) and most regimens combining MTX+cDMARDs and biological DMARDs or TOF with MTX. All combination of MTX plus bDMARDs and TOF were statistically superior to oral MTX alone. Triple therapy was the only conventional synthetic DMARD combination with statistically significant higher odds of ACR50 response than oral MTX. In pairwise comparisons, it showed statistically no significant difference between triple therapy and MTX plus any bDMARD. About the inhibition of radiographic progression, MTX combined with ADA, ETA, CZP, or INF was statistically superior to oral MTX and no differences were found between triple therapy and oral MTX. Fleischmann et al[25] compared aTNF (ADA, CZP, ETA, GOL, INF, and biosimilar-INF) with MTX *vs.* triple therapy. Achievement of ACR70 at 2 years was more likely in patients treated with combined aTNF-MTX *vs.* triple therapy in the fixed-effects model but not in the random-effects model. Similar results were found with respect to the radiographic progression. No differences were reported considering ORs for ACR50, ACR20 and DAS28-ESR remission, DAS28-ESR/CRP. Equally no differences were found for changes in joint space narrowing, in joint erosion or in mTSS at 2 years. Singh et al[36] compared combined aTNF (ADA, ETA, GOL, INF) *vs.* combined non-aTNF biologics (ABA and RTX). For ACR50, aTNF biologics and non-aTNF biologics subgroups showed a RR of 1.44 and 1.27, and NNTB = 6 and = 8 respectively. For RA remission rates NNTB = 7 and NNTB = 6 respectively. Simpson et al[9] compared ABA, ADA, CZP, ETA and its biosimilar SB4, GOL, INF and its biosimilars INF CT-P13 and INF SB2, and TCZ in MTX naïve patients, in terms of ACR response, finding that MTX – methyil prednisolone was most likely to achieve the best response. BAR showed a good rank in terms of efficacy[10].

Results on Safety of Biologics

19 studies[6,10,11,16,17,24-28,30,32-34,36-40] evaluated the safety of bDMARDs in RCTs (Table VI).

Six meta-analyses indicated a best safety profile of ETA[6,11,16,34,37,38], but also ADA and RTX showed good results. Specifically, Singh et al[16] showed the NNT for harm, which appeared to be progressively lower starting from ADA, ANA, and INF to become non-significant for ETA, ABA, and RTX. TOF in two meta-analyzes[17,26] shows a better profile than ADA, TCZ, RTX, ABA MTX, and placebo. Park et al[40] showed that combination therapy with cDMARDs ABA and combined aTNF had a better profile of safety than TOF. Fleischmann et al[25] and Hazlewood et al[27] showed a discrete safety profile of triple therapy similar to aTNF in association with MTX. Two investigations[6,28] showed a better profile of safety of INF originator than INF biosimilar but without statistical significance. Lee et al[10] showed a better rank in terms of safety regarding BAR in monotherapy.

Table III. Studies on monotherapy.

Author	Biologics	Results
Orme et al[21]	ADA, ETA, TCZ, placebo	ADA, ETA, TCZ were significantly better than placebo for attaining ACR 20/50/70. The probabilities to be the best treatment (random model) to achieve ACR 20/50/70 are TCZ 69%, ETA 24% and ADA 7%.
Aaltonen et al[34]	ADA, CZP, ETA, INF, GO, MTX + placebo, MTX	aTNF vs. MTX showed no statistical significance at any time point using ACR 20/50/70. The combination of aTNF+MTX was superior in efficacy in all time points.
Jansen et al[14]	TCZ, combined aTNF (ADA, CZP, ETA, GOL, INF), MTX, placebo	TCZ showed greater improvements in pain and PGA were observed than with aTNF monotherapy. TCZ was at least as efficacious as aTNF in HAQ-DI improvements. There is a 93% and 96% probability that aTNF + MTX results in a greater reduction in pain and PGA than aTNF as monotherapy. These differences are expected to be greater than the MCID. For HAQ-DI there is a 92% chance that aTNF + MTX is more efficacious than aTNF as monotherapy. For TCZ the improvement in pain, PGA, and HAQ-DI with and without MTX was comparable at 24 weeks.
Buckley et al[15]	ABA, combined aTNF (ADA, ANA, CZB, ETA, GOL, INF), TCZ, TOF, placebo	Both combined aTNF and TCZ showed greater ACR20 response than placebo. TCZ relative to combined aTNF monotherapy show difference not statistically significant, but TCZ as monotherapy shows a 91% of probability to result in a greater ACR20 response than combined aTNF. For ACR50 and ACR70 responses, similar findings were observed. TCZ displayed higher ACR responses also than TOF. ACR20/50/70 responses with TCZ + MTX were similar to those with TCZ monotherapy, whereas greater responses were observed with combined aTNF + MTX than with combined aTNF monotherapy. Relative efficacy estimates for the indirect comparison of TOF + MTX with TOF monotherapy were very uncertain
Tvete et al[7]	CZB, ABA, ADA, ETA, TCZ, placebo, placebo+DMARDs	Ranking to achieve ACR 50 is CZB, ETA, TCZ, ABA and ADA.
Migliore et al[29]	ADA, ETA, TCZ, DMARDs, placebo	Ranking of probability for attaining ACR 20/50/70 was TCZ followed by ETA and ADA.
Lee et al[26]	TOF 5mg, with and without MTX, ADA+MTX, placebo, MTX	For achieving the ACR20 TOF had the probability of 40%, better than MTX and placebo but worse than TOF + MTX and ADA+MTX.
Singh et al[30]	ABA, ADA, ANA, CZP, ETA, GOL, INF, RXB, TCZ, TOF, DMARDs, placebo	For ACR50 combined aTNF showed a statistically significant improvement with RR of 1.43 vs. cDMARDs; but combined non-aTNF was not significant (RR: 1.57). Both respective RRs from NMA did showed a clinically meaningful and statistically significant result. For RA remission. NMA estimates showed a statistically significant and clinically meaningful difference vs. active comparator for combined aTNF (OR 2.11) and combined non-aTNF (OR 4.59).
Alfonso-Cristancho et al[8]	ABA, ADA, CZP, ETA, INF, GOL, RIT, TCZ, DMARDs, placebo	TCZ was significantly better than ETA and ADA for ACR 50 at 26 weeks, and ETA for ACR 20/50 at 52 weeks.
Bergrath et al[17]	ABA, CZP, ETA, TCZ, TOF, placebo	TOF showed comparable ACR20/50/70 against other monotherapies.
Lee et al[10]	ADA, BAR (alone or + csDMARDs), placebo + csDMARDs	The ranking probability based on SUCRA for attaining ACR20 is: BAR+ csDMARDs 0.7930, BAR 0.7034, ADA+MTX 0.3687, Placebo+ DMARD 0.0045

Abbreviations. ABA: Abatacept; ACR: American College of Rheumatology; ADA: Adalimumab; AE: Adverse events; ANA: Anakinra; BAR: Barcitinib; csDMARDs: conventional synthetic disease: modifying antirheumatic drugs; CZP: Certolizumab; DAS: Disease activity score; ETA: Etanercept; GOL-Golimumab; HAQ: Health assessment Questionnaire; HCQ: Hydroxychloroquine; INF: Infliximab; IR: Inadequate response; LDGC: Low dose Glucocorticoid; MTC: Mixed treatment comparison; MTX: Methotrexate; NMA: Network meta-analysis; PCS: Physical component summary; PGA: Patient's global assessment; PRO: Patient reported outcomes; RA: Rheumatoid Arthritis; RCT: Randomised clinical Trials; RXB: Rituximab; SF36: Medical Outcomes Study Short Form 36 Health Survey; SSZ: Sulfasalazine; TCZ: Tozilizumab; TOF: Tofacitinib; TNFi: Tumor Necrosis Factor inhibitor.

Table IV. Studies on biological failure patients.

Author	Biologics	Results
Salliot et al[23]	ABA, GOL, RXB, TCZ, placebo	RXB demonstrated a higher probability of achieving an ACR50 than TCZ but no significant differences were found comparing RXB to TCZ, RXB to GOL, ABA to RXB, ABA to TCZ, GOL to TCZ, RXB or ABA
Kim et al[31]	ABA, GOL, RXB, TCZ, placebo	Switching to non-aTNF biologics was more effective than cycling aTNF inhibitors. Non-aTNF biologics were associated with higher ACR: in ACR20, TCZ has the better probability at 94%, followed by RXB 4%, ABA 2%, GOL 0,1%; in ACR 50 TCZ shows a probability of 61% followed by ABA 19%, RXB 17%, GOL 3%; in ACR 70 the probabilities to be the best treatment are RXB 47%, TCZ 34%, ABA 18% and GOL 1%. In the HAQ comparison, ABA shows the best results followed by TCZ, RXB and GOL.
Lee et al[32]	ABA, RXB, TCZ, TOF (all +MTX), placebo+MTX	In term of rank TCZ was the second line non-aTNF biologic that exhibited highest clinical efficacy for attaining ACR20 response followed by RXB, ABA, TCZ, and TOF.
Alfonso-Cristancho et al[8]	ABA, ADA, CZP, ETA, INF, GOL, RIT, TCZ, DMARDs, placebo	About monotherapy TCZ was significantly better than ETA and ADA for ACR 50 response at 26 weeks, and ETA for ACR 20/50 response at 52 weeks.
Singh et al[33]	ABA, ADA, ANA, CZP, ETA, GOL, INF, RXB, TOF	Compared to cDMARDs, biologic+MTX was associated with a clinically meaningful and statistically significant improvement in ACR50, HAQ, and RA remission rates in direct comparisons, with a NNTB = 7 for ACR50, NNTB = 5 for HAQ and NNTB = 17 for remission rates. No statistically or clinically differences were found using the NMA type of biologics between aTNF, non-aTNF biologics and TOF.
Fleischmann et al[25]	Combined antiTNF (ADA, CZP, ETA, GOL, INF, INF biosimilar.) + MTX or Triple Therapy (MTX + HCQ+SSZ)	For ACR70 at 6 months, the OR in the random-effects model was 0.77 and OR values <1 indicate a better performance for combined aTNF-MTX vs. triple therapy. Achievement of ACR70 at 2 years was more likely in patients treated with aTNF-MTX compared with triple therapy in the fixed-effects model but not in the random-effects model. Similar results were found about the radiographic progression. No differences were indicated based on ORs for ACR50, ACR20 and DAS28-ESR remission, DAS28-ESR/CRP.
Lee et al[10]	ADA, BAR (alone or + csDMARDs), placebo+ csDMARDs	The ranking probability based on SUCRA for attaining ACR20 is: BAR+csDMARDs 0.7930, BAR 0.7034, ADA+MTX 0.3687, Placebo+DMARD 0.0045

Abbreviations. ABA: Abatacept; ACR: American College of Rheumatology; ADA: Adalimumab; AE: Adverse events; ANA: Anakinra; BAR: Barcitinib; csDMARDs: conventional synthetic disease: modifying antirheumatic drugs; CZP: Certolizumab; DAS: Disease activity score; ETA: Etanercept; GOL-Golimumab; HAQ: Health assessment Questionnaire; HCQ: Hydroxychloroquine; INF: Infliximab; IR: Inadequate response; LDGC: Low dose Glucocorticoid; MTC: Mixed treatment comparison; MTX: Methotrexate; NMA: Network meta-analysis; PCS: Physical component summary; PGA: Patient's global assessment; PRO: Patient reported outcomes; RA: Rheumatoid Arthritis; RCT: Randomised clinical Trials; RXB: Rituximab; SF36: Medical Outcomes Study Short Form 36 Health Survey; SSZ: Sulfasalazine; TCZ: Tozilizumab; TOF: Tofacitinib; TNFi: Tumor Necrosis Factor inhibitor.

Table V. Studies on MTX naïve patients.

Author	Biologics	Results
Aaltonen et al[34]	ADA, CZP, ETA, INF, GO, MTX + placebo, MTX	At six months patients naıve to MTX are statistically significantly less likely to reach either ACR20/50/ compared to patients who had already been previously treated with MTX.
Hazlewood et al[27]	cDMARDs, Triple Therapy, MTX + ABA, ADA, CZP, ETA, GOL, INF, RTX, TCZ, TOF, placebo	ACR50: no statistically significant difference between triple therapy and MTX plus any biologics. About the inhibition of radiographic progression, MTX combined with ADA, ETA, CZP, or INF was statistically superior to oral MTX and no differences were found between triple therapy and oral MTX.
Migliore et al[35]	ADA, ETA, INF, GOL, RTX, MTX+placebo	ADA showed highest probability for attaining ACR70 while ETA had highest probability of attaining ACR20 and ACR50 (ranking).
Singh et al[36]	ABA, ADA, ANA, CZP, ETA, GOL, INF, RXB, TOF	For ACR50, combined aTNF biologic and combined non-aTNF biologic showed a risk RR of 1.44 and 1.27, and NNTB = 6 and = 8 respectively. For RA remission rates NNTB = 7 and NNTB = 6 respectively.
Fleischmann et al[25]	Combined antiTNF (ADA, CZP, ETA, GOL, INF, INF biosimilar) + MTX or Triple Therapy (MTX + HCQ+SSZ)	For ACR70 at 6 months, the OR in the random-effects model was 0.77 and OR values <1 indicate a better performance for combined aTNF-MTX vs. triple therapy. Achievement of ACR70 at 2 years was more likely in patients treated with aTNF-MTX compared with triple therapy in the fixed-effects model but not in the random-effects model. Similar results were found about the radiographic progression. No differences were indicated based on ORs for ACR50, ACR20 and DAS28-ESR remission, DAS28-ESR/CRP.
Simpson et al[9]	ABA, ADA, ANA, CZP, ETA, ETA SB4, GOL, INF, INF CT-P13, INF SB2, TCZ, csDMARD, combined csDMARDs	MTX plus MP was most likely to achieve the best ACR response. There was insufficient evidence that combination boDMARDs was superior to two or more csDMARDs.
Lee et al[10]	ADA, BAR (alone or + csDMARDs), placebo+ csDMARDs	The ranking probability based on SUCRA for attaining ACR20 is: BAR+ csDMARDs 0.7930, BAR 0.7034, ADA+MTX 0.3687, Placebo+ DMARD 0.0045

Abbreviations. ABA: Abatacept; ACR: American College of Rheumatology; ADA: Adalimumab; AE: Adverse events; ANA: Anakinra; BAR: Barcitinib; csDMARDs: conventional synthetic disease: modifying antirheumatic drugs; CZP: Certolizumab; DAS: Disease activity score; ETA: Etanercept; GOL-Golimumab; HAQ: Health assessment Questionnaire; HCQ: Hydroxychloroquine; INF: Infliximab; IR: Inadequate response; LDGC: Low dose Glucocorticoid; MTC: Mixed treatment comparison; MTX: Methotrexate; NMA: Network meta-analysis; PCS: Physical component summary; PGA: Patient's global assessment; PRO: Patient reported outcomes; RA: Rheumatoid Arthritis; RCT: Randomised clinical Trials; RXB: Rituximab; SF36: Medical Outcomes Study Short Form 36 Health Survey; SSZ: Sulfasalazine; TCZ: Tozilizumab; TOF: Tofacitinib; TNFi: Tumor Necrosis Factor inhibitor.

Table VI. Studies on clinical safety of biologics in RA.

Author	Biologics	Results
Lee et al[37]	ADA, ETA, INF, MTX	aTNF in combination with MTX are comparable to MTX in terms of withdrawal due to side effects. ETA showed less withdrawal due to side effects when compared to ADA while no differences were found between ETA INF and ADA INF.
Singh et al[11]	ABA, ADA, ANA, ETA, INF, RXB, placebo, MTX, DMARDs	ANA, ADA and INF exhibited higher withdrawal rates than placebo while ABA and RXB reported not significantly difference with placebo and ETA exhibited lower rate of withdrawal due to adverse effects. Biologics exhibited higher withdrawal rates due to AE among patients DMARDs IR, biologics IR or both, but not on DMARDs naive patients.
Aaltonen et al[34]	ADA, CZP, ETA, INF, GOL, MTX + placebo, MTX	Combined aTNFs did not statistically significantly differ from the control. INF, ADA, and CZP showed an increased risk to discontinue, while ETA had a decreased risk. INF, ETA and GOL increased the likelihood of an injection or infusion reaction while ADA and CZP did not statistically significantly differ from the controls. aTNF monotherapy *vs.* MTX were comparable. aTNF in monotherapy and placebo showed a trend of increased risk of AE from aTNF-blockers.
Desai et al[38]	ABA, ADA, ANA, CER, ETA, GOL, INF, RTX, TZB, DMARDs, placebo	Biologics were more likely to withdraw due to adverse effect. ABA exhibited lower withdrawal rates when compared to CER, INF and TCZ. ETA was favoured when compared to ADA, ANA, CZP, INF and TC. RXB exhibited significant lower withdrawal rates when compared against CZP, INF and TCZ.
Hochberg et al[24]	ABA, Combined aTNF (ADA, ETA, CZP, GOL, INF), placebo +DMARDs, placebo +biologics	Lowest withdrawal rate due to any reason or adverse event was found less with ABA compared to combined aTNF group at 6 and 12 months
Baji et al[6]	ABA, ADA, CZP, ETA, GOL, INF, RXB, TCZ, Biosimilar INF, placebo+DMARDs	Lowest OR was obtained from ETA 0.84, followed by ADA 0.85 and ABA 0.91. AE rate was better with CZP than placebo (OR 2.02) while no significant difference was found between the other biologics and placebo. About pairwise comparison no differences was found among biologics.
Lee et al[26]	TOF with and without MTX, ADA+MTX, placebo, MTX	Withdrawn due to AEs was lower in the placebo group than in the TOF plus MTX, but without statistical difference. This study showed the following to be the best treatment: 87% for TOF, 65% for MTX, 39% for ADA +MTX, 32% for placebo, 28% and 21% for TOF + MTX.
Lee et al[32]	ABA, RXB, TCZ, TOF, all +MTX, placebo+MTX	Better profile of safety for TOF 5 mg and placebo than the other treatments but the number of patients who withdrew due to AEs did not differ significantly among the treatment options.
Hazlewood et al[27]	cDMARDs, Triple Therapy, MTX combined with ABA, ADA, CZP, ETA, GOL, INF, RTX, TCZ, TOF, placebo	In MTX naive patients, MTX plus azathioprine had a statistically significant increase in withdrawals due to AE compared with oral MTX. IM/SC MTX plus ciclosporin, INF, or TCZ showed a higher rate of withdrawals due to AE than oral MTX. No statistically significant differences were found in comparisons between different bDMARDs plus MTX. MTX plus SSZ plus HCQ was associated with a statistically lower rate of withdrawals due to AE than MTX plus INF. In MTX-IR patients, MTX plus ciclosporin and MTX plus TCZ gained statistical significance on withdrawal rates due to AE compared to oral MTX. In pairwise comparison MTX plus ABA was associated with statistically significant lower rate of withdrawals due to AE than bDMARDs plus MTX, and MTX when combined with SSZ and HCQ.
Singh et al[16]	ABA, ADA, ANA, CZP, ETA, GOL, INF, RXB, TCZ, TOF, DMARDs, placebo	Results were inconclusive for combined aTNF +DMARD and combined non-aTNF. Higher withdrawal rates resulted for INF, and lower rates for ETA. The odds of SAEs were higher in patients comparing biologic combination therapy vs. comparator but in individual comparisons, compared to other biologic + MTX, GOL + MTX and CZP + MTX were associated with higher odds of SAEs while ABA +MTX were associated with lower odds.
Singh et al[30]	ABA, ADA, ANA, CZP, ETA, GOL, INF, RXB, TCZ, TOF, DMARDs, placebo	In monotherapy, combined aTNF, and combined non aTNF, ANA and TOF showed inconclusive results for withdrawals due to AEs and SAEs.

Continued

Table VI (continued). Studies on clinical safety of biologics in RA.

Author	Biologics	Results
Bergrath et al[17]	Alone or in combination with MTX/cDMARDs: ABA, ADA, ANA, CZP, ETA GOL, INF, TCZ, TOF, BAR; placebo	In monotherapy TOF related withdrawals due to AE were favourable in comparison with ADA, comparable to other monotherapies, and less likely to occur when compared to placebo, CZP and TCZ TOF + DMARDs were less favourable than placebo + DMARDs and ABA + DMARDs with respect to withdrawals due to AE. TOF + MTX was less favourable than placebo + MTX, ETA + MTX, ABA + MTX, and GOL+ MTX.
Singh et al[33]	ABA, ADA, ANA, CZP, ETA, GOL, INF, RXB, TOF	No statistical significant difference were noticed on withdrawal rates due to AE.
Singh et al[36]	ABA, ADA, ANA, CZP, ETA, GOL, INF, RXB, TOF	No statistical significant difference were noticed on withdrawal rates due to AE.
Fleischmann et al[25]	Combined aTNF (ADA, CZP, ETA, GOL, INF, INF biosimilar) + MTX or Triple Therapy (MTX + HCQ+SSZ),	In MTX-IR patients lower odds of infection was observed on triple therapy. For overall AEs, discontinuation due to AEs, serious AEs and malignancy no differences were found between triple therapy aTNF-MTX. In MTX naïve patients, the ORs showed no difference in the odds of discontinuation rates due to AEs, overall AEs, serious infections and elevated level of aspartate aminotransferase between aTNF-MTX and triple therapy.
Maneiro et al[39]	INF, ETA, ADA, CZP, GOL, ABA, RXB, TCZ, TOF, placebo, csDMARDs.	Treatment of RA with b-DMARDs or TOF does not increase the risk for malignancies.
Park et al[40]	Combined aTNF (ADA, CZP, ETA, GOL, INF), ABA, RTX, TCZ, TOF, placebo	No significant differences in discontinuation rates between TOF and biologics in the DMARD-IR patients were found. In the biologics-IR group, aTNF and RTX showed significantly lower total discontinuation rates than TOF.
Bae et al[28]	Biosimilar INF+MTX, INF+MTX, placebo+MTX	The safety based on the number of serious AE (SAEs) did not differ significantly among the three interventions. SUCRA rank (probability to be the best treatment): Placebo + MTX 0.6915, Infliximab + MTX 0.5268, Biosimilar + MTX 0.2817
Lee et al[10]	ADA, BAR (alone or + csDMARDs), placebo + csDMARDs	The ranking probability based on SUCRA for safety in terms of number of TEAEs is: BAR 0.6795, Placebo+ DMARD 0.6395, ADA+MTX 0.4174, BAR+DMARD 0.2962.

Abbreviations. ABA: Abatacept; ACR: American College of Rheumatology; ADA: Adalimumab; AE: Adverse events; ANA: Anakinra; BAR: Barcitinib; csDMARDs: conventional synthetic disease: modifying antirheumatic drugs; CZP: Certolizumab; DAS: Disease activity score; ETA: Etanercept; GOL-Golimumab; HAQ: Health assessment Questionnaire; HCQ: Hydroxychloroquine; INF: Infliximab; IR: Inadequate response; LDGC: Low dose Glucocorticoid; MTC: Mixed treatment comparison; MTX: Methotrexate; NMA: Network meta-analysis; PCS: Physical component summary; PGA: Patient's global assessment; PRO: Patient reported outcomes; RA: Rheumatoid Arthritis; RCT: Randomised clinical Trials; RXB: Rituximab; SF36: Medical Outcomes Study Short Form 36 Health Survey; SSZ: Sulfasalazine; TCZ: Tozilizumab; TOF: Tofacitinib; TNFi: Tumor Necrosis Factor inhibitor.

Discussion

Even though significant improvements had been made for the treatment of RA, proper selection of a drug still remains challenging. Clinicians and decision makers would like to identify the most effective treatment among a range of alternatives. RCTs often do not include all available comparator interventions of interest. Traditional pairwise meta-analysis provides only a limited view of the existing evidence without addressing the relative merits of all available options. To overcome this gap the network meta-analysis has been built to synthesize and to compare all available evidence within a consistent framework, fully preserving the randomization within each trial[41-43]. This method considers all trials simultaneously and enables integration of direct evidence from head-to-head trials (when they exist) with indirect evidence (through a common comparator)[44-46].

The advantages of network meta-analysis include: 1) the ability to compare treatments that have never been compared in any trial; 2) improvement in precision for the estimated effect sizes; 3) comparing and ranking multiple treatments in a principled statistical analysis[47,48]. In this way, network meta-analysis provides useful evidence for judiciously selecting the best choice(s) of treatment.

However, the results in the meta-analysis are sometimes not the same and some of these differences might be explained by the different methodologies employed in the assessments, the number, and quality of articles selected, the products included in the analysis, the clinical subset of patients, and the time of publication.

In DMARDs-IR patients, it is possible to find some interesting conclusions. All manuscripts confirmed the superiority of DMARDs+bDMARDs compared to the comparator. In terms of ACR20/50, ten authors[6-8,12,13,18-22] reported a greater efficacy of CZP compared to other biological therapies, while it seems to be a trend of greater efficacy regarding the achievement of ACR50/70 between CZP, ETN, and TCZ. Regarding DAS28 or DAS remission outcome, two works showed a better efficacy profile of ABA[22,24]. There was no consistency in the results regarding HAQ as the outcome[14,19,22]. Only three NMC explored the radiological progression of the disease[16,25,27]. Notably, Hazlewood et al[27] found no difference or radiographic progression of disease comparing different treatments, but in post-hoc fixed effect model, several biologics+MTX reached statistical significance. Fleischmann et al[25] concluded that combined aTNF-MTX were numerically favoured than triple therapy on radiographic progression but not in the random-effects model. Singh et al[16] summarized that biologics+MTX was more effective than biologic+DMARDs.

In terms of efficacy about triple therapies and bDMARDs the results were not the same: Hazlewood et al[27] showed that triple therapy could be superior to MTX+intravenous ABA, INF or TCZ for ACR 50, while Fleischmann et al[25] described a better profile of combined aTNF+MTX for ACR70 when compared with triple therapy. This result would be worthy of further investigation, especially according to aspects, such as pharmaco-economy or in comparison with each single biological molecule and not with the whole class.

All the meta-analyses that analyzed ANA[7,16,26,27,29,32], except two authors, confirmed that this molecule did not appear to be the first-choice drug in the treatment of RA patients, but only in selected cases.

About biosimilars, one work showed the best profile in terms of ACR response of ETA SB4 in comparison with other biological treatments[9], while Baji et al[6] showed no significant difference between the efficacy of INF biosimilar and the other biologics but these studies analyzed a mixed population (not only DMARDs IR).

Regarding the use of bDMARDs in monotherapy, four authors[8,15,21,29], showed a greater probability of efficacy in terms of ACR20/50/70 in favour of TCZ while Tvete et al[7] reported a ranking in which CZP would seem to be better than ETA, TCZ, ABA, and ADA in terms of ACR50. These results showed different ranking because the populations were different (Tvete had included a mixed population) and the authors had not studied the same biologics (Orme et al[21] and Migliore et al[29] did not consider studies on ABA or CZP). Jansen et al[14] in their meta-analyses also showed that TCZ would have greater efficacy in terms of pain control and HAQ response compared to aTNF, but the limit of this comparison is that aTNFs had been evaluated not singularly but combined as class. Buckley et al[15] and Jansen et al[14] confirmed no difference in terms of ACR efficacy between TCZ in monotherapy and in combination with MTX. Buckley et al[15] indicated for TOF in monotherapy a lower efficacy in terms of ACR than TCZ and combined aTNF, but Bergrath et al[17] reported instead a similar efficacy between TOF, CZP, ADA, and ETA without expressing a ranking. Lee et al[26] showed that TOF monotherapy is less effective than in combination with MTX.

Four meta-analyses[25,27,35,36] investigated naïve patients at MTX reporting the greater effectiveness of bDMARDs in association with MTX, and Migliore et al[35] realized a specific ranking on the probability to be the best treatment, and in terms of efficacy ACR 20/50 the first ranked was ETA and for ACR 70 ADA (the study did not consider CZP and TCZ). In the comparison of the triple therapy with bDMARDs, Fleischmann et al[25] and Hazlewood et al[27] concluded with no differences in terms of ACR20/50 between these two treatments. Fleischmann et al[25] reported a difference only in terms of 6-month ACR70 in favour of combined aTNF. However, considering all the combined aTNFs in the absence of an estimate of the results for each drug, it represents a relevant limitation in the study. Better results were found also in terms of inhibition of radiological progression in favour of bDMARDs+MTX.

Four meta-analyses[23,31-33] focused on the subset of BIO-IR patients. Kim et al[31] and Lee et al[32] performed a ranking among aTNF-IR patients, concluding that TCZ was the highest treatment efficacy in terms of ACR20/50, with better results using non-aTNF after the failure of aTNF but Salliot et al[23] and Singh et al[33], instead, found no differences in the choice of bDMARDs between aTNF and non-aTNF, but this is due to the comparison of combined aTNF and combined non-aTNF agents as group cancelling intragroup differences. This kind of comparison is unable to catch the differences between the agents of the same class and is therefore inconclusive for both clinicians and decision makers.

About the best second-line treatments for RA among patients switching between different treatment options after aTNF failure, probably the use of a molecule with a different mechanism of action could be the better choice. For example, the majority of evidence from registered data, including the Spanish Base de Datos de Productos Biológicos de la Sociedad Española de Reumatología (BIOBADASER)[49] and Swedish Stockholm TNFα Follow up Registry (STURE)[50], suggest that overall response rates are lower and drug-retention rates decrease in patients who switch to a second aTNF.

About safety data, it confirms that the combination of MTX plus aTNF resulted not associated to an increase in side effects than MTX alone. The majority of the studies report that biologics exhibited higher withdrawal rates due to AEs among patients cDMARD -IR, BDMARD -IR or both, compared to patients naïve to DMARDs. Six meta-analyses indicated a best safety profile of ETA[6,11,16,34,37,38], but also ADA and RTX showed good results. Only Singh et al[11] have calculated the NNT in terms of safety, and it is reported to be progressively lower starting from ADA, ANA and INF to become non-significant for ETA, ABA and RTX compared with controls. The data for monotherapy with bDMARDs and small molecules were interesting. TOF in two meta-analyses[17,26] had a better profile than ADA, TCZ, RTX, ABA MTX and placebo, but these data are not confirmed in case of association with MTX and in this case placebo, ABA, ETA, and GOL appeared to have better results. Also, BAR resulted the better choice in terms of safety in one work again in monotherapy[10].

Also, Park et al[40] showed how in combination therapy with cDMARDs+ABA and combined aTNF had a better profile of safety than TOF, but this type of combined analysis is moderately relevant. About the triple therapy, Fleischmann et al[25] and Hazlewood et al[27] showed a discrete safety profile similar to aTNF in association with MTX. About comparison between biosimilars and originators, two studies[6,28] showed a better safety profile of INF originator compared to INF biosimilar but without statistically significant difference.

The results reported by the meta-analyses included in this review show a certain variability, with some discordances. Rather than univocal conclusions, it is easier to draw "trends" from results that can provide useful information in the daily clinical practice of the management of patients with AR in biological therapy. Starting from the widely refuted principle of the efficacy and the discrete safety profile of bDMARDs therapy, it is nevertheless quite evident that biological drugs are not exactly all the same. The discrepancies in the results of these meta-analyses are linked to several factors: the number of studies included, the number of drugs analyzed, the characteristics of the patient population affected by RA and the statistical methodologies used. International Society of Pharmacoeconomics and outcome research (ISPOR) guidelines[41] should be observed in order to achieve valid information to guide decision makers. The ISPOR task force provides clear guidelines on reporting, interpretation of results, validity, and decision making in the absence of direct and indirect treatment comparisons of RCTs. Only a few articles are in accordance with ISPOR guidelines, and a minority of studies show a ranking or express the "probability to be the best treatment". Moreover, the results obtained are not adequately illustrated

or clarified in the different works. The methods for presenting the results or sponsoring publications also strongly limit the conclusions of some meta-analyses. For instance, Orme at al[21] report in the text that licensed-dose ETA, ADA, and TCZ monotherapy were significantly better than placebo in improving ACR outcomes, as well as etanercept monotherapy was significantly better than sulfasalazine in improving ACR outcomes. Surprisingly the author reported the rank of the "probability of best", showing that TCZ is ranked 69.2% and ETA 23.6% for obtaining ACR 20-50-70 response, only in the table, but the author doesn't mention these results in the text of the article.

Other important limitation of some meta-analyses is to consider all aTNF combined, as well as non-aTNF combined, because this type of analysis does not allow to have results categorized by type of molecules, and the absence of an estimate of results related to each drug with different capabilities in terms of effectiveness results as a relevant limit for an appropriate decision.

Conclusions

For a higher percentage of patients, the appropriate biological first-line therapy has not been identified, therefore it becomes necessary to try to identify any predictor factors of response to a specific drug. The Gold Standard in the biological therapeutic choice in Rheumatology should be the personalization of the treatment based on the presence of predictive factors, but in lack of these, the Bayesian statistical method represents a valid alternative even if more outcomes of parameters would be needed and the statistical methodology should be used appropriately.

Conflict of Interests

The authors declare that they have no conflict of interests.

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