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Differences in biologics for treating ankylosing spondylitis: the contribution of network meta-analysis

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Abstract. – OBJECTIVE: Ankylosing Spondylitis (AS) is a chronic form of arthritis of unknown origin affecting the spine. In this study, we aimed to identify clinical and safety profiles of adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and secukinumab that are biologic agents (biologics) mainly used for the treatment of AS, and to understand differences between them.

MATERIALS AND METHODS: An extensive literature research was performed in MEDLINE and EMBASE in order to identify all network meta-analysis (NMA) and/or mixed treatment comparison (MTC) papers. NMA and/or MTC, with a ranking of the effectiveness of biologics in AS, were included in the analysis, and the adhesion to ISPOR guidelines was investigated.

RESULTS: 60 studies were identified; after applying exclusion criteria methods, 7 studies underwent further analysis. Infliximab was the drug that exhibited the highest probability for achieving clinical efficacy by ASAS20 at 12 and 24 weeks. Considering only subcutaneous biologics, Golimumab achieved the highest probability for achieving the ASAS20 response at 12 weeks.

CONCLUSIONS: Results from NMA on the use of biologics in AS indicates infliximab emerged as the drug with the highest probability of obtaining ASAS20 response both at 12 and 24 weeks of treatment.

Key Words:
Ankylosing spondylitis, Network meta-analysis, Biologic drugs, Infliximab.

Introduction

Ankylosing Spondylitis (AS) is a chronic form of arthritis of unknown origin belonging to the broader category of spondyloarthropathies that primarily affects the spine. AS mainly involves the spinal joints and frequently progresses into ankylosis of the affected joints[1], but up to half of the patients experience concomitant peripheral joint arthritis[2]. Several studies reported the relevance of HLA-B27 as a genetic marker predisposing for the development of disease and suggesting familial aggregation, although the relationship between such gene and the development of the disease remains unclear[3]. Differently from other and more common kinds of arthritis, such as rheumatoid arthritis and psoriatic arthritis, the use of biologic drugs is more often required to achieve disease control, as only a very small part of patients reaches low disease activities with non-biologic disease-modifying antirheumatic drugs (DMARDs) or non-steroidal anti-inflammatory drugs (NSAIDs)[4-10]. At now, several anti-TNF (originator and biosimilar) and no anti-TNF agents are available for treating AS, and new drugs characterized by new treatment targets are under development. Adalimumab ADA, Certolizumab pegol CPG, Etanercept ETA, Golimumab GOL, Infliximab INF, and Secukinumab SEC have been registered for use in AS, and their efficacy and safety profiles have been extensively investigated. The lack of head to head studies comparing efficacy and safety profiles between anti-TNF agents in AS makes difficult the choice of drug to administer and often based on personal experience or costs, instead of choosing treatment on efficacy and safety parameters according to the subset of disease or prognostic factors of response to therapy. Registry studies based on the use of anti-TNF agents seem to point out similar

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results for different drugs, thus generating confusion in the prescription patterns of biologic drugs for such disease. Head to head randomized controlled trials (RCTs) would require a large patient sample size in order to identify differences in terms of efficacy of biologic agents, thus leading to high costs. Nevertheless, a tailored therapy for patients affected by AS remains an unmet need. Highlighting eventual differences in such efficacy and safety profiles is essential in this sense, and in the absence of head to head studies, NMA and indirect comparisons represent the only innovative and useful tool[11-15].

Differently from common meta-analysis, where multiple studies are included in the analysis to evaluate the efficacy of a single agent *vs.* placebo or other treatments, NMA grants the possibility of the estimation of several parameters from studies that performing similar comparisons and makes possible to obtain new and relevant data by assembling and analyzing data of several studies on the same subject.

Some studies[16-21] have been published using this statistical tool in different pathologies, such as metabolic, cardiovascular, neuropsychiatric and rheumatic diseases, and its use is spreading in the scientific literature. Also, for AS, several papers reporting the NMA meta-analysis of previous RCTs were published. By this paper, we aimed to identify all published Bayesian network meta-analysis reporting the use of biologic drugs in patients affected by AS, to perform a synthesis of the evidence and to better understand the differences among them.

Materials and Methods

To identify all published papers reporting on the use of Bayesian network meta-analysis on efficacy and safety profiles of biologic drugs administered in patients affected by AS, an extensive literature research was performed in MEDLINE and EMBASE in the period from January 1st, 2010 to December 31th, 2019. Both engines were intensively searched, and search terms included a combination of the following terms: ("Indirect comparison" OR "Bayesian" OR "Network metanalysis" OR "Probabilistic metanalysis" OR "Mixed treatment comparison") AND "Ankylosing Spondylitis" AND ("Biologic" OR "anti TNF" OR "Biosimilar" OR " Adalimumab" OR "Certolizumab" OR "Etanercept" OR "Infliximab" OR "Golimumab" OR "Secukinumab"). Results of research and any further selection of articles were performed using EndNote X7. A first screening was performed by a single reviewer for identifying and excluding from further analysis all duplicates. Consequently, the remaining papers were analyzed independently by three reviewers. A second screening was performed by each reviewer by title. Then, all three reviewers analyzed the remaining abstracts, and papers that only published abstracts without full text and articles published in a language different from English were excluded. In a further step, the remaining abstracts were analyzed in full text. Network meta-analysis that reported the results of a MTC with ranking of biologic drugs in the probability of obtaining a certain endpoint, were included in the analysis, and the adhesion to ISPOR guidelines was evaluated[22]. Discrepancies in results obtained at each step by different reviewers were resolved by face to face discussion.

All included meta-analysis were then analyzed for main characteristics, such as characteristics of included studies for NMA, characteristics of patients and of treatment arms of studies analyzed, methodology of analysis and presentation of results in the light of appropriateness of methodology for NMA[23]. Results obtained by included studies were then summarized and critically discussed.

Results

60 studies were identified by the search strategy. Twenty-one studies were found to be duplicates produced by the search methodology. Twenty-seven studies were then excluded by title screening, with accordance among reviewers. Similarly, 3 studies were excluded after abstract analysis. None of the remaining studies were excluded for being abstracts only or for being written in a language different from English. Again, accordance was achieved for excluding 2 studies after full-text analysis. In the end, 7 studies were included for further analysis[24-27] (Figure 1). The main characteristics of the included studies are reported in Table I.

The first published MTC regarding the use of biologic drugs in patients affected by AS was performed by Migliore et al[24] in 2012. This meta-analysis focused on the use of licensed doses for the three anti-TNF available in 2012 for the therapy of AS, ADA, ETA and INF. The primary

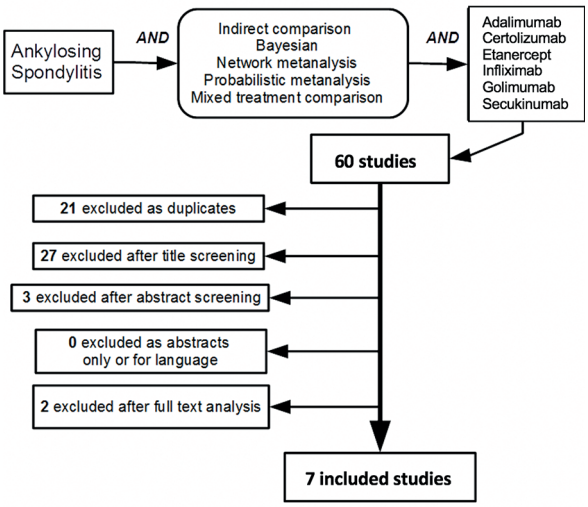

Figure 1. Flow Diagram for the selection of studies.

and only outcome measure considered for MTC was ASAS20, with a length of follow-up of 24 weeks. All included studies reported the use of anti-TNF agents in patients naive to biologic treatments. This study included in its analysis 3 RCTs, 1 for each biologic agent, with similar characteristics in terms of demographic and disease characteristics. Also, the length of follow-up was similar among all three studies included in the analysis. Migliore et al[24] evaluated ASAS20 gathering data from such studies and in the final ranking, INF at a dose of 5 mg/kg every 8 weeks resulted as the drug with the highest probability (75%) of inducing ASAS20 response at 24 weeks, followed by ETA and ADA with a percentage of 15% and 13% respectively.

A second report was published in 2013 by Shu et al[25]. They included in the analysis 14 studies reporting the use of 4 biologic agents, ADA, ETA, INF and GOL in patients affected by AS and naive to biologic treatments. Studies included in this analysis also reported the use of not licensed doses, and for this reason, the number of included studies is larger. The length of follow-up was similar among studies, varying from 10 to 14 weeks. Once again, INF at a licensed dosage of 5 mg/kg resulted as the drug with the highest probability of inducing ASAS20 response at 12 weeks in terms of odds ratio (OR) (6.53), followed by GOL 100 mg (6.09), ETA 50 mg (5.98), GOL 50 mg (5.94), ADA (5.92) and ETA 25 mg (5.05).

In the following year, another NMA was published by Baji et al[26]. In this paper, data coming from 13 different RCTs were included, 8 studies having a follow-up of 12 weeks, and 5 studies having a follow-up of 24 weeks. In the researches with a follow-up of 12 weeks, 5 reported the use of ETA, 2 the use of ADA and 1 the use of INF. Among studies with a follow-up of 24 weeks, 1 reported the use of ADA, ETA, GOL, INF, and biosimilar INF, respectively. This was the first study including data on a biosimilar biologic drug, the biosimilar of INF, CT-P13, thus leading to a larger number of included investigations. In this study, the probability of inducing ASAS20 response was evaluated at 12 and 24 weeks. Also, safety outcomes were evaluated. All patients included in the studies analyzed were naive to biologic treatments. At 12 weeks, INF proved to be the drug with the highest probability of inducing ASAS20 response (OR 6.74), followed by biosimilar INF (OR 6.39), GOL (OR 5.7), ADA (OR 4.81) and ETA (OR 4.35). At week 24, INF showed the highest OR compared to placebo (7.2), followed by INF biosimilar (6.25), ADA (4.81), ETA (4.76), and GOL (4.53).

In the fourth study, performed by Migliore et al[27] in 2014, only subcutaneous anti-TNF agents were considered, and the ASAS20 remained as the primary endpoint of evaluation. A total of 5 studies reporting the use of ADA, ETA, GOL, and CPG were taken into account for evaluation, and the follow-up time was set at 12 weeks. 2 studies reported the use of ETA and 1 study reported the use of each of the remaining biologic agents. GOL resulted as the biologic agents with the highest probability of achieving ASAS20 response at 12 weeks out of all the subcutaneous biologic agents. The rank was: GOL 41.28%; ADA 29.91%; ETA 28.74%; CPG 0.07%.

In 2016, Betts et al[28] published a NMA of 15 studies that reported effectiveness in terms of number needed to treat (NNT) for ASAS 20 and ASAS 40 of anti-TNF (ADA, ETA, INF, CPG, GOL) and non-anti-TNF (SEC) molecules. Follow up times were 12-14-16 weeks. Patients treated with INF had the lowest NNT for ASAS 20 (2.3), followed by ADA (2.8) and ETA (2.9). INF also had the lowest NNT for ASAS40 (2.6) followed by ADA (2.8) and SEC (3.5). Regarding costs, ADA had the lowest 12-week cost per additional ASAS20 responder, followed by INF and GOL, as well as ADA had the lowest cost also per additional ASAS40, followed by INF and ETA. This study was conducted from a US payer perspective.

Table I. Main characteristics of the included studies.

Author/ Year	Journal	Biologic drugs compared	Number of studies included	Primary outcome	Secondary outcome	Safety outcome	Structural outcome	Economic evaluation	Length of follow-up (weeks)	Biologic drugs failure/naive	Fixed/ random effect models
Migliore et al 2012[24]	Journal Medical Economics	ADA, ETA, INF	3	ASAS20	None	No	No	No	24	TNF Naive	Fixed
Shu et al 2013[25]	Clinical Experimental Rheumatology	ADA, ETA, GOL, INF	14	ASAS20	None	No	No	No	10-14	TNF Naive	Random
Baji et al 2014[26]	European Journal Health Economics	ADA, ETA, GOL, INF, B-INF	13	ASAS20	None	SAEs	No	No	12-24	TNF Naive	Random
Migliore et al 2015[27]	Clinical Drug investigation	ADA, CPG, ETA, GOL	5	ASAS20	None	No	No	No	24	TNF Naive	Fixed
Betts et al 2016[28]	Rheumatology and Therapy	ADA, ETA, INF, CPG, GOL, SEC	15	ASAS20/40	None	No	No	Yes	12-14-16	TNF Naive (not for CPG and SEC)	Random
Chen et al 2016[29]	Medicine	ADA, ETA, GOL, INF, SEC, TCZ	14	ASAS20	ASAS40, ASAS5/6, ASAS partial remission and 50% improvement in baseline Bath AS disease activity index	No	No	No	12-14	Not specified	Random
Wang et al 2018[30]	The Journal of Rheumatology	ADA, CPG, ETA, GOL, INF, B-INF	20	BASDAI, BASFI, CRP	None	No	No	No	12-24	Not specified	Random

In the same year, Chen et al[29] reported data from 14 studies in patients affected by AS treated with an anti-TNF agent, anti-IL-23 or anti-IL-17, and placebo. This NMA reported results in terms of efficacy considering ASAS20 as primary outcome, and ASAS40, ASAS5/6, ASAS partial remission and 50% improvement in baseline Bath Ankylosing Spondylitis Disease Activity (BASDAI 50) as secondary outcomes at week 12 or 14. INF had the highest probability of being ranked the best for achieving ASAS20, followed by SEC.

For the other outcomes, no regimen was significantly superior to others; however, INF resulted the best treatment for ASAS40 and ASAS5/6. All anti-TNF agents demonstrated to be more efficacious than placebo. No statistically significant differences were found comparing a biologic agent against another directly.

Wang et al[30] in 2018 reported results of 20 studies regarding patients with AS in treatment with ADA, CPG, ETA, GOL, INF, and INF biosimilar. Results at 12 and 24 weeks showed that anti-TNF was significantly better than placebo in reducing BASDAI and Bath Ankylosing Spondylitis Functional Index (BASFI) at 12 weeks and 24 weeks. In the analysis that included the open-label study, INF was significantly better in reducing BASDAI than ADA (relative effect size –1.1 MD 95% CrI –2 to –0.1), CPG (relative effect size –1.2 MD 95% CrI –2.3 to –0.02), ETN (relative effect size –1.2 MD 95% CrI –1.8 to –0.4), and GOL (relative effect size –1.1 MD 95% CrI –2 to –0.1). INF was also significantly better in reducing BASFI than CPG (relative effect size –1.0 MD 95% CrI –1.7 to –0.03). Biosimilar INF had a similar result in reducing BASDAI than INF. In the analysis that excluded the open-label trial, INF was not more efficacious than other anti-TNF in decreasing BASDAI but when adjusted for baseline BASDAI and baseline C reactive protein (CRP), INF remained superior to CPG, ADA, and ETN in reducing BASDAI. When adjusted for baseline BASFI and baseline CRP, INF was superior to CPG and ETN in BASFI reduction. At 24 weeks, the advantage of INF seen at 12 weeks was not present, but INF showed a numerically higher reduction in terms of BASFI, BASDAI, and CRP.

We report in Table II a column with specific details, if present, about bias related to consistency or homogeneity in the different NMAs.

Discussion

In this systematic review, we aimed to identify, analyze and report NMA investigating the use of biologic agents in patients affected by AS. Differently from frequentist meta-analysis, probabilistic meta-analysis allows the indirect comparison of various treatments for a single disease respect to a single or multiple endpoints. In this review, we summarized data about the use of anti-TNF agents approved for the treatment of AS at their licensed doses. We tried to summarize results obtained in previous NMA and to check for concordance of results, in terms of clinical outcomes, mainly at 12 and 24 weeks. Globally all anti-TNF agents demonstrated to be more efficacious than placebo. No statistically significant differences were found comparing directly approved biologic agent against another; however, a trend could be outlined. Interestingly, INF proved to be the treatment characterized by the highest probability of inducing ASAS20 response in patients affected by AS to biologic treatments at 12 and 24 weeks in all studies where its use was analyzed. INF also resulted the best choice in terms of efficacy in a single study investigating other parameters of efficacy, such as BASFI, BASDAI, CRP at 12 weeks; with a good profile also for ADA regarding the reduction of CRP[30]. When only subcutaneous anti-TNF were taken into consideration[27], GOL proved to be the drug with the highest probability of achieving ASAS20 response; this data was confirmed by Baji et al[28], who proved GOL to be the drug with the highest probability of inducing ASAS20 response after infusional drugs, such as INF and biosimilar INF. Regarding INF biosimilar, Wang et al[30] showed that at 12 weeks biosimilar INF-dyyb had MD similar to INF in reducing BASDAI, consistent with the result of the head-to-head trial between the 2 drugs, but at 24 weeks, the advantage of INF seen at 12 weeks was not present[30]. Also, SEC showed a good profile in terms of efficacy regarding ASAS 20 and ASAS 40[28,29]. These results were interesting, but SEC is studied in a few NMA (two reported works)[28,29].

It is interesting to report the concordance among all included studies in terms of results, although studies were performed in different years and included a growing number of studies and/or biologic agents.

Results of NMAs may represent a useful tool for decision-makers when approaching the difficult choice of what drug to administer in a certain

Table II. Results reported from MTC metanalyses included in the study about primary outcomes/ASAS response.

Author/ Year	Primary outcome	Biologic Drug	Reported bias about consistency and homogeneity	Ranking	Results
Migliore et al 2012[24]	ASAS20	INF, ETA, ADA	No test performed to check the consistency or homogeneity	INF: 1st (75%*); ETA: 2nd (15%*); ADA: 3rd (13%*)	All anti-TNF agents demonstrated to be more efficacious than placebo. INF shows a 72% probability of being the best treatment, while ADA and ETA show 13% and 15%, respectively. No differences comparing directly an anti-TNF-α agent against another.
Shu et al 2013[25]	ASAS20	INF, GOL, ETA, ADA	No test performed to check the consistency or homogeneity	INF: 1st (6.53#); GOL 100: 2nd (6.09#); ETA 50: 3rd (5.98#); GOL 50:4th (5.94#); ADA: 5nd (5.92#); ETA 25: 7th (5.05#)	All treatments demonstrated to be more effective than placebo. Ranking analysis suggested that INF 5 mg/kg at 0, 2, 6 weeks may be the best efficacious therapy compared with placebo followed by GOL 100, ETA 50, GOL 50, ADA and ETA 25. All of these between-treatment comparisons detected no significant analysis.
Baji et al 2014[26]	ASAS20	INF, INF biosimilar, GOL, ADA, ETA	No test performed to check the consistency or homogeneity	INF: 1st (6.74#); INF bio: 2nd (6.39#); GOL: 3rd (5.7#); ADA: 4th (4.81#); ETA: 5th (4.35#)	At week 12, regarding ASAS 20 resposne all biologicals were found to be significantly superior to placebo. Compared to placebo, INF showed the highest OR 6.74, followed by INF biosimilar OR 6.39, GOL OR 5.7, ADA OR 4.81, ETA OR 4.35.
Baji et al 2014[26]	ASAS20	INF, INF biosimilar, GOL, ADA, ETA	No test performed to check the consistency or homogeneity	INF: 1st (7.2#); INF bio: 2nd (6.25#); ADA: 3rd (4.81#); ETA: 4th (4.76#); GOL: 5th (4.53#)	At week 24, all biologicals were found to be significantly superior to placebo. INF showed the highest OR compared to placebo OR 7.2, followed by INF biosimilar OR 6.25, ADA OR 4.81, ETA OR 4.76 and GOL OR 4.53.
Migliore et al 2015[27]	ASAS20	GOL, ADA, ETA, CPG	No test performed to check the consistency. or homogeneity	GOL: 1st (41.28%*); ADA: 2nd (29.91%*); ETA: 3rd (28.74%*) CPG: 4th (0.07%*)	All subcutaneous anti-TNF-alpha agents are more effective in inducing an ASAS20 response than placebo. At 12 weeks, GOL resulted the drug that more probably represents the best choice with a percentage of 41.28%, followed by ADA 29.91%, ETA 28.74% and CPG 0.07%. No differences were observed when comparing directly anti-TNF-alpha agent against another.
Betts et al 2016[28]	ASAS20/ ASAS40	INF, ADA, ETA, GOL, SEC, CPG	No test performed to check the consistency or homogeneity	INF: 1st (2.3°; 71,7%*); ADA: 2nd (2.8°; 63.6%*); ETA: 3rd (2.9°; 62%*); GOL: 4th (3.1°; 60.3%*); SEC: 4th (3.1°; 60.2%*) CPG: 5th (4.4°; 50.5%*)	At 12 weeks INF had the lowest NNT 2.3, followed by ADA 2.8, ETA 2.9, GOL and SEC 3.1 and CPG 4.4. In terms of percentage to be the best treatment the ranking is the same: INF 71.7%, ADA 63.6%, ETA 62%, GOL 60.3%, SEC 60.2%, CPG 50.5%. For ASAS 40, INF had the highest probability to be the best treatment with a NNT of 2.6 and a parcentage of 51,5%, followed by ADA 2.8/49.2%, SEC 3.5/42,4%, ETA 3.6/41.4%, GOL 4.0/38.6%, and CPG 4.7/34.8%.

(Continued)

disease in order to obtain a given endpoint. Especially in the case of biologic drugs for AS, where all drugs seem to have similar efficacy characteristics due to the lack of head to head trials.

In the case of AS, between all available biologic drugs, INF results as the drug with the highest probability of achieving ASAS20, and this should be taken into account when starting

Table II *(Continued)*. Results reported from MTC metanalyses included in the study about primary outcomes/ASAS response.

Author/ Year	Primary outcome	Biologic Drug	Reported bias about consistency and homogeneity	Ranking	Results
Chen et al 2016[29]	ASAS20/ (ASAS 40/ ASAS5/6/ ASAS partial remission/ BASDAI50 outcome)	INF, ETA, SEC, GOL, ADA	Inconsistent loops would be identified if they yielded a 95% Crl excluding 0. Second, they secondary used no desplitting technique to assess whether direct and indirect evidences are in agreement. A large p-value indicates no significant inconsistency was found.	ASAS20: INF: 1st (3.23^); SEC: 2nd (2.35^); ADA: (2.80^); GOL50: (2.73^); GOL100: (2.75^); ETA50: (1.99^); ETA25: (2.09^)	With regard to ASAS20, ADA, ETA 25 mg BIW or 50 mg QW, GOL 100 mg or 50 mg, and INF were associated with better therapeutic effect when compared with placebo. INF had the highest probability of being ranked the best for achieving ASAS20, followed by SEC. INF had the highest probability of being ranked the best for secondary outcomes, ASAS40 and ASAS5/6
Wang et al 2018[30]	BASFI BASDAI CRP	INF, INF biosimilar, ETA, GOL, ADA, CPG	Due to the small number of head-to-head trials, the authors assumed consistency in the analysis, which reduces confidence in the estimation.	BASDAI: INF bio: 1st -2.67§ (-1.94€); INF: 2nd -2.66§ (-1.95€) ADA: 3rd -1.55§ (-1,54€); GOL: 3rd -1.55§ (-1.47€) ETA: 4th -1.51§ (-1.76€); CPG: 5th -1.45§ (-1.45€) BASFI: INF: 1st -1.99§ (-1.53€); INF bio: 2nd -1.81§ (-1.34€); GOL: 3rd -1.57§ (-1.57€); ADA: 4th -1.44§ (-1.46€); ETA: 5th -1.43§ (-1.54€); CPG: 6th -1.05§ (-1.05€)	All anti-TNF were significantly more efficacious than placebo in reducing BASDAI and BASFI scores. All Anti-TNF except CPG and INF-bio were superior to placebo in decreasing CRP. At 12 weeks in the analysis that included the open-label study INF was significantly more efficacious in reducing BASDAI than ADA, CPG, ETA, and GOL. INF was also significantly better in reducing BASFI than CPG, no significant differences among anti-TNF comparing changes in CRP. In the analysis that excluded the open-label trial INF was not more efficacious than other anti-TNF in decreasing BASDAI but when adjusted for baseline BASDAI and baseline CRP, INF remained superior to CPG, ADA, and ETN in reducing BASDAI. When adjusted for baseline BASFI and baseline CRP, INF was superior to CPG and ETN in BASFI reduction. At 24 weeks, no statistically significant difference in the reduction of BASDAI, BASFI, or CRP. However INF-bio had numerically a higher reduction in BASDAI and BASFI compared to other anti-TNF, and ADA had a numerically higher reduction in CRP compared to other anti-TNF

*Probability of being the best treatment expressed as 0-100 percentage; #Probability of being the best treatment expressed as Odds Ratio; °Probability of being the best treatment expressed as Number Needed to treat (NNT); ^Subtotal forest plot; §Probability of being the best treatment expressed as effect size in analysis with open label trial; €Probability of being the best treatment expressed as effect size in analysis without open label trial.

a biologic therapy. Notably, ASAS20 is not the only endpoint, and clinicians and decision-makers should take into account also other endpoints, as ASAS40, ASAS 5/6, BASFI, BASDAI, safety, compliance, costs, immunogenicity, loss of efficacy, and consequent need for an increase in dosages. In this sense, it is clear that different factors should be considered for a more comprehensive understanding of the correct therapeutic process. Clinical Multiple Criteria Decision Analysis (CMDA)[31] could prove a useful tool for evaluating together several parameters. CMDA allows to gather and analyze data on different parameters and to establish a ranking of various possible interventions related to a given objective. Clinical Multicriteria Decision Analysis represents the application of CMDA in the field of therapeutic choice to perform by physicians, such as the case

of various biologic interventions in AS. CMDA takes into account several criteria and related parameters, weighted by a panel of experts for a given disease. The efficacy profiles of different interventions are obtained as a score determined by the probability to reach the selected parameter multiplied by the weight of the same parameter. In this way, the information arising from the weight of the criteria and the probability of success for the particular criterion are gathered and analyzed to establish an overall ranking, that could grant clinicians and decision-makers the possibility of performing a comprehensive judgement on which drug to administer. CMDA could grant the possibility of a better understanding of the role exerted by all available treatments in the management of a disease, including costs related to therapy, thus influencing in a complete way the decisional process of which drug to administer.

For this study, we have to acknowledge several limitations. First of all, it is the small number of NMA available in the scientific literature regarding AS who strictly followed ISPOR guidelines for the design of NMA[22]. Since studies were performed in different years and with different methodologies, number of included studies varied across meta-analysis. Shu et al[25] and Chen et al[29] also included treatment arms with doses not licensed for clinical use, although it was reported in this study how the licensed doses for each biologic drug were the most effective in obtaining a response. Furthermore, it remained unclear how the evaluation from OR to a different scoring reported in one of the figure of the article of Shu et al[25] was performed. For such reason, we only reported OR, whose methodology of evaluation was clearly reported. At the same time, we have data only at a restricted follow-up time, 12 and 24 weeks, while biologic treatments for AS often last for longer periods, and we have no comparative data on the long course of therapy. In this sense, integrating data coming from NMA with observational data obtained from national and international registers on the use of biologic drugs could prove useful.

Conclusions

A previous frequentist meta-analysis reported how biologic drugs in AS seem to exert similar effects in obtaining ASAS20[32]. On the contrary, NMA points out differences in the probability to achieve the clinical endpoint, giving the possibility of creating a ranking. Analyzing results from network meta-analysis on the use of biologics in AS, INF emerged as the drug with the highest probability of obtaining ASAS20, as well as other outcomes response (1 study), both at 12 and 24 weeks of treatment. However, open questions still remain, especially on several other endpoints and on long-term treatment. Hence, further data need to be analyzed with more comprehensive and complex evaluation systems.

Conflict of Interest

The Authors declare that they have no conflict of interests.

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