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What is already know about this topic?

- Network meta-analyses (NMAs) have become successful in addressing gaps in the comparative effectiveness of the systemic treatments in moderate-to-severe psoriasis.

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- Their increasing number carries both a risk of overlap and reproducibility issues that can hamper clinical decision-making.
- Different methodological choices could have an important impact on the results of both classical and network meta-analysis.

What does this study add?

- This overview provides an assessment of the redundancy of the NMAs on the systemic treatments in psoriasis, as well as an evaluation of their methodological quality and discrepancies.
- Of the 47 included studies, only two evaluated all the available treatments, 26 received industry funding and 39 provided results of critically low confidence.
- Awareness is needed among authors and reviewers of the thoroughness of the systematic review's and meta-analysis' methods.

Abstract

Background: Network Meta-analyses (NMAs) have become successful in addressing gaps in the comparative effectiveness of systemic treatments in moderate-to-severe psoriasis. However, their increasing number carries both a risk of overlap and reproducibility issues that can hamper clinical decision-making. In this overview, we aimed to assess redundancy across these NMAs and to describe their characteristics.

Methods: We considered all systematic reviews with NMAs of randomized controlled trials that included adult patients with moderate-to-severe psoriasis and that evaluated the efficacy and/or safety of systemic treatments compared with placebo or with an active comparator. PubMed/MEDLINE, Epistemonikos, PROSPERO and the Evidence Update of the Centre of Evidence-Based Dermatology of the University of Nottingham were searched up to 25 February 2021. Our main outcome was the number per year of redundant NMAs and the extent of their overlap. We also described their features, especially, the confidence in the results of the reviews,

the studies' funding and the presence of spin (a description that overstates efficacy and/or understates harm), reporting issues and methodological characteristics.

Results: In total, 47 redundant NMAs were included. Only 2/47 (4%) included all available treatments. Both efficacy and safety were evaluated in 14/47 (30%) NMAs and both short and long-term evaluations were assessed in 5/47 (11 %). Confidence in the results was critically low for 39/47 (83%) NMAs and only 10/47 (23 %) registered a protocol. 26/47 NMAs (55%) received pharmaceutical funding. CROs were involved in 19/47 (40%) NMAs. Reporting was poor across most of the NMAs' abstracts and spin was present in all of the abstracts. Almost half of the NMA failed to consider important limitations such as heterogeneity (32%) or consistency (66%).

Discussion: In addition to a duplication of efforts, our overview showed heterogeneous methods and poor confidence in the results in a majority of the included NMAs, further distorted by reporting issues and spin. Clinicians need to interpret NMAs with caution when looking for the most reliable and comprehensive evidence.

BACKGROUND

Psoriasis is a chronic inflammatory skin disease that affects 1 to 8% of the general population.[1,2] Considering that since 2015 eight new molecules, including seven biological treatments, have been made available to treat moderate-to-severe psoriasis, physicians need complete and up-to-date synthesis of the evidence available in order to highlight their therapeutic choices. However, most biological treatments have been compared to placebo, and head-to-head comparisons of biologicals versus conventional or between them are rare.[3] Network meta-analysis (NMA) allows, after a systematic review (SR), the evaluation of several treatments in a single analysis by combining both direct and indirect evidence.[4] This method also allows an estimation of the ranking of the interventions and has become a successful tool in addressing gaps in comparative effectiveness research, especially when numerous treatments are available. However, in some topics, there is a dramatic growing number of redundant NMAs.[5-10] Such redundancy carries both a risk of overlap and reproducibility issues with differences in results that may be due to different methodological choices and to the exclusions of some of the available interventions.[11-13] This observation is also true for psoriasis. Many NMAs have been published, hence the value to assess their methodological quality as well as their comprehensiveness and agreement. The objective of our study was to assess the number per year of redundant NMAs evaluating the efficacy or safety of systemic treatments in moderate-to-severe plaque psoriasis, to describe their characteristics, and compare their differences.

MATERIAL AND METHODS

This research was based on a protocol registered prior data collection on the Open Science Framework on February the 10th 2021 (osf.io/tjrk5). Reporting was performed according to the PRISMA 2020 checklist (Supplementary Table S10).

Eligibility criteria

We considered all SR with NMA of randomized controlled trials (RCTs) that included adults with moderate-to-severe psoriasis and that evaluated the efficacy or safety of systemic treatments compared with placebo or with an active comparator. Systemic treatments included non-biologic systemic treatments (acitretin, cyclosporine, fumaric acid, methotrexate), small molecules (apremilast, tofacitinib, BMS-986165) and biologic treatments (anti-TNF-alpha: etanercept, infliximab, adalimumab, certolizumab; anti-IL12/23: ustekinumab; anti-IL17: secukinumab,

ixekizumab, brodalumab, bimekizumab; anti-IL 23: guselkumab, tildrakizumab, risankizumab, mirikizumab).

Study identification

We aimed to identify all relevant SR with NMA, regardless of language. We searched PubMed/MEDLINE, Epistemonikos, PROSPERO, as well as the Evidence update of the Centre of Evidence-Based Dermatology of the University of Nottingham from inception up to 25 February 2021. We checked the reference lists of the included and excluded publications to identify additional NMAs. Detailed search strategy is provided in the Supplementary Table S1.

The selection process was conducted by two authors (RG, LLC) independently through Covidence (http://covidence.org). After exclusion of the duplicates, these two authors screened each title and abstract to exclude irrelevant studies and then examined the remaining full-texts for eligibility. The two authors discussed any disagreement to reach consensus and, if necessary, were helped by a third author (ES). Two authors (RG, LLC, ES, FN, GC, JPR, SA, TB) independently extracted the data using a standardized form previously piloted. References and reason for exclusion are detailed in Supplementary Table S3.

Overview outcomes

Our main outcome was to determine the total number of redundant NMAs per year and to describe the overlaps between them. To be considered overlapping, the NMAs had to come from the same topic by addressing the same disease with the same indication of treatment.[7] We assessed overlaps between NMAs for the studied population, the included treatments, the considered outcomes and the timing of evaluation, defined either as short-term (between 2 and 28 weeks after randomization) or long-term (after 28 weeks), and the methodological choices used for the NMA. A treatment was considered available for inclusion if at least one phase-II or above trial evaluating that treatment had been published before the date of last search of the considered NMA.

Our secondary outcomes aimed to describe and compare the general characteristics of the included NMA. Hence, we:

- assessed the confidence in the results of the reviews according to AMSTAR-2 and the studies' funding and its effect on the reporting of efficacy in the abstract. AMSTAR-2, is a 16 items instrument designed to critically appraise SR of RCTs or non-randomized studies of healthcare

intervention with or without meta-analysis.[14] Two authors independently assessed the methodological quality as 'high', 'moderate', 'low' or 'critically low' according AMSTAR-2 rules (Supplementary Table S11).

- checked for the presence of spin and reporting issues in the abstract according to the classification of Yavchitz *et al.*, and the 2013 PRISMA-checklist for abstracts (Supplementary Table S12 and Figure S5).[15,16] The detection and description of spin in the abstracts was done by two authors independently following the classification from Yavchitz *et al.*, blinded to the funding status of each article. To fit to NMA specificities the items 10, 11 and 12 related to the 'misleading interpretation' category were summarized as one item: "Selective reporting of or overemphasis on the ranking of interventions without considering its uncertainty".
- evaluated the agreement between the conclusions of the NMAs published at similar periods by comparing the treatments reported as having the best short-term efficacy.

Data extraction

The main characteristics of the NMAs were extracted, such as the name of the first author, date of publication, primary studies' inclusion and exclusion criteria, studied population, included interventions in the network and considered outcomes with their timeframe of evaluation. Were also extracted the information regarding the registration of a protocol, the use of reporting guidelines, the number of studies included in the SR and the NMA and the methodological choices used for the NMA. Additionally, were extracted the list of previously cited NMAs on the same topic, authors' affiliation, studies funding, declaration of efficacy in the abstracts, conflicts of interest among authors, and assistance of a contract research organization (CRO).[17]

Statistical analyses

Descriptive analyses were conducted and categorical variables were presented as percentages. Median were presented with their interquartile range. The effect of funding was analyzed according to the following categories: academic funding, industry funding, none, not reported. As an exploratory analysis, the assessments of significant difference were based on the χ^2 or Fisher's exact test for categorical data as appropriate. Statistical significance threshold was set at 0.05.

Deviation from the protocol

Description of the methodological characteristics of the included NMAs were added to provide additional details of the included studies. We also assessed the agreement between the studies' conclusions regarding the treatments reported as having the best short-term efficacy in the abstracts

RESULTS

Included studies

Of the 1176 citations of potentially eligible studies, 47 were included (Figure 1).

Redundant NMAs and overlaps

We included 47 NMAs assessing systemic treatments in moderate to severe psoriasis.[18-64] The publication rate grew from one published per year in 2006 to a maximum of 12 per year in 2020 (Figure 2). Main characteristics of the included NMAs are summarized in Table 1 and detailed in Supplementary Table S8.

All NMAs included adult patients with moderate-to-severe plaque psoriasis and three also included children and young adults.[32,41,58] Most NMAs only included some of the available treatments. A majority of 39/47 (83%) of the NMAs evaluated exclusively the licensed dosage of the included interventions. Biological treatments were evaluated in all NMAs but all available biological treatments were considered in 6/47(12.8%) NMAs. Included interventions in each NMA are summarized in Figure 3. Disregarding other interventions, biological treatments were the only treatment category evaluated in 28/47 (59.6%) NMAs. Five (10.6%) NMAs evaluated all treatment categories. All available non-biological treatments were included in 14/47 (29.8%) and 2/47 (4.3%) included all available small molecules. In the end, two NMAs included all available biological treatments, non-biological treatments, and small molecules.[31,48]

The majority of the NMAs evaluated the short-term efficacy of the included interventions. Efficacy outcomes alone were evaluated in 32/47 (68.1%) NMAs and 39/47 (79.6%) NMAs only evaluated short-term outcomes (Supplementary Figure S1). Both efficacy and safety outcomes were evaluated in 14/47 (29.8%) NMAs. The outcome quality of life was evaluated in 12/47 (25.5%) NMAs (Supplementary Figure S2). Both short and long-term outcomes were studied in 5/47 (10.6%) NMAs.

Overlaps in the methodological choices for the NMA

Regarding the methodological characteristics, most NMAs used a Bayesian approach for their analysis and the majority of the results were obtained using a random-effect model. Methodological characteristics of the NMAs' are summarized in Table 2.

The definitions of the nodes in the NMAs differed between NMAs, which led to different network shapes. Most NMAs, 37/47 (78.1%), performed a dose-level analysis, 9/47 (19.1%) performed a drug-level analysis, and 6/47 (12.8%) a class-level analysis. Four performed both a drug and class-level analysis, and one performed both a dose-level and class-level analysis.

Similarity between studies and population baseline characteristics were evaluated and addressed in 17/47 (36.2%) NMAs. Statistical heterogeneity in the classical MA was evaluated in 32/47 (68.1%) studies and 15 of those also evaluated the heterogeneity in the NMA.

Updates and citation of previous NMAs

Among the 47 NMAs, four (8.5%) were updates of previous NMAs and stated as such in their manuscript. Almost all studies (89.1%) cited previously published NMAs but the median percentage of NMAs cited in relation to the number of NMAs already published was 19% (IQR = 7.8%-36.9%) (Supplementary Figure S3).

Assessment of the methodological quality

In all, 21/47 reviews (44.7%) stated using reporting guidelines. Among the 11 (23.4%) NMAs who stated following a written protocol, 10 were registered and accessible on PROSPERO and one was not retrieved. The confidence in the results, using AMSTAR-2, was critically low for 39/47 (83.0%) NMAs, low for 6/47 (12.8%), and moderate for 2/47 (4.3%). Some of the failed critical domains were the absence of registered protocol for 39 NMAs, the absence of adequate literature search for 37 NMAs or the absence of evaluation of the risk of bias of the included studies for 16 NMAs (Supplementary Figure S4).

Funding and conflicts of interest

Among the 47 included NMA, 12 (25.5%) received academic funding, 26 (55.2%) pharmaceutical funding, 6 (12.8%) NMAs reported an absence of funding and 3 (6.4%) did not report whether

they were funded or not (Supplementary Table S4). Authors' conflicts of interest were declared in 43/47 (87.8%) NMAs and 33/43 (76.7%) had at least one author with declared conflicts of interests with pharmaceuticals companies. CRO were involved in 19/47 (40.4%) of the NMAs, 18 of those funded by pharmaceutical companies. We found employees of pharmaceutical companies among the authors of 24/47 (51.0%) NMAs and employees of CROs in 16/47 (34.0%) NMAs.

Treatments ranking, reporting in the abstracts and spin evaluation

In all, 23/47 (48.9%) NMAs reported a statistical method to assess the ranking of the included interventions. Among the 47 NMAs, 16 (34.0%) used the SUCRA, 3 (6.4%) used the probability of being best, 5 (10.6%) used the ranking probabilities and 4 (8.5%) used the mean rank.

Regarding the reporting evaluation of the NMAs' abstracts, we found that 70% of them scored 3 or less out of the 11 items PRISMA-checklist (Supplementary Table S6). Besides, the number of treatments as well as the molecules cited as best varied between the NMAs. For the short-term efficacy, 17 NMAs stated one treatment as being best, 16 cited two or three treatments as being best and 9 cited more than three treatments. For industry-funded NMAs, the funding company's treatment was systematically cited among the best treatments. Even though industry-funded NMAs tended to be more likely to cite only one treatment as best, there was no statistically significant association between the funding status and the number of treatments cited as best in the abstracts ($p = 0.084$) (Supplementary Table S5). Furthermore, even NMAs published in the same year had several discrepancies regarding the treatments reported as having the best short-term efficacy (Figure 4). In 2020 for example, ustekinumab was cited among the best treatments by Mahil et *al.* but not my Armstrong et *al.* nor by Sbidian et *al.*

Finally, at least one type of spin was found in all NMAs' abstract with a median number of spin was 3 (IQR: 2-4) (Supplementary Table S9). A spin found in 30/47 (63.8%) abstracts was the selective reporting of or overemphasis on efficacy outcomes. Effect of the type of funding (Supplementary Table S7), on the number of spins per NMAs was not significant ($p = 0.67$).

DISCUSSION

Our overview included 47 NMAs evaluating the efficacy and safety of systemic treatments in moderate-to-severe psoriasis with an acceleration of publication from 1 NMA published in 2006 to 12 published in 2020. Besides the redundancy of the included NMAs our overview showed for a majority of them their incompleteness and a low methodological quality of the SR as well as the network meta-analyses. Furthermore, aside from reporting issues, there were some discrepancies between the NMAs' conclusions regarding the number of treatments declared as best in each abstract. Some declared one treatment as being the best, other a cluster of treatments and the molecules cited as best varied between studies. These differences were found even between NMAs published the same year, with a systematic declaration of efficacy for the supporting pharmaceutical company's treatment when industry funding was present.

From a clinical perspective, all interventions with therapeutic indication in moderate-to-severe psoriasis should always be included in the SR and, if possible, in the network of evidence.[65,66] For some clinicians, it can be relevant to only consider the biological treatments. However, all available treatments should be considered, even if not of direct interest, as it increases the amount of data for the comparisons of interest and thus provides more precise estimates. In our overview, most NMAs only included some of the available treatments. Only 6 included all available biological treatments and only 2 evaluated all available systemic treatments. Moreover, both efficacy and safety have to be assessed. Nevertheless, efficacy was the only outcome of focus for two-third of the NMAs, when safety was evaluated in only one-third. Both short and long-term endpoints were studied in only 10% of the NMAs.

Beyond the redundancy, confidence in the results was low or critically low for 96% of the NMAs according to AMSTAR-2. Among the critical domains that hindered the confidence in the results of most of the NMAs, 39 NMAs did not register a protocol, 16 did not assess the risk of bias of the included studies. Additionally, NMA requires that some assumptions are verified, for example transitivity, to ensure the validity of the results.[67] Our results show that at least two-third of the included NMAs did not explicitly report checking for those assumptions.

The incompleteness of the NMAs and the methodological differences identified might explain, to some extent, the differences in the results. As Mills *et al.* showed, excluding some studies from NMAs can have an important impact on the results.[12] On the same note, Palpacuer *et al.* demonstrated using the "vibration of effect" framework, *i.e.* the extent to which an effect may

change under multiple distinct analyses, that different inclusion and exclusion criteria can lead to opposite results.[13]

Adding to those previous points, several abstracts were impaired with poor reporting and included a various numbers of spins. The second most frequent type of spin was related to the treatments' ranking. In 24/47 NMAs, the included treatments were ranked in decreasing size of relative treatment effect without taking into consideration the uncertainty of the estimates or the overlap between confidence intervals. When adequate ranking methods were used, some authors still failed to take into consideration the uncertainty when interpreting the ranking of the interventions.[67] As for the reporting, some NMAs reported a single treatment as being the best while other reported several.

Pharmaceutical companies supported more than half of the included NMAs. When short-term efficacy was discussed in the abstract, the funding pharmaceutical company's treatment was systematically mentioned as the best or one of the best. This observation, added to the lack of registered protocol across the NMAs and the malleability of the methodological choices, asks whether the industry-funded NMAs are prone to publication bias by only submitting NMAs where the treatment of the pharmaceutical company shows the best result possible.

This proliferation of redundant NMAs is troubling. Journals ought to be aware of this issue and not prioritize publications of redundant reviews. Authors of a new NMA should plan their study with a registered protocol to clearly lay out what is unique and contributory about theirs, as well as to allow other authors to identify ongoing NMAs and avoid unnecessary duplication. Academic and clinical authors should be wary of collaborating with industry when starting new NMAs.

To our knowledge, there is only one similar overview, published in 2020 and funded by LEO Pharma. In this article, Wright *et al*. addressed the same issue as this overview.[68] Our overview included 47 NMA compared to the 25 they included. Wright *et al.* concluded that analyses published within a similar time-period were similar in their results and conclusions despite different methodological choices and funding sources, but nonetheless highlighted that consideration should be given to the NMAs that include all relevant trials and interventions and rely on valid methodology. Our conclusion differed from theirs as we included more NMAs and focused our attention on the reporting of the efficacy of the interventions in the abstracts rather than the actual ranking reported in the articles. Contrarily to Wright *et al.*, our review also

assessed the methodological quality of the studies using AMSTAR-2 as well as the reporting of the results and the presence of spin.

Our overview had limitations. The date of last search of this overview was February the 25th 2021, and it is likely that additional NMAs have been published between then and time of publication. However, we believe that conducting an updated search would certainly change the number of redundant NMAs identified but would not change our overall conclusion. Furthermore, as there is currently no validated tool to assess the methodological quality of the NMAs, we chose to use AMSTAR-2, which is used for SR with classical MA. This was also true for Yavchitz *et al*. description of spin, which led us to adapt their classification for the need of this overview. Another limitation was the impossibility to assess outcome reporting bias since few NMAs registered a protocol.

CONCLUSION

Proliferation in the number of NMAs has led to the increase in the number of redundant and overlapping studies. Our overview found important differences in methodological choices. Most NMAs included a fraction of the available treatments and ignored safety outcomes. Some authors seemed to focus on the conduct of NMAs, but disregarded mandatory steps of systematic review prior to the quantitative synthesis such as protocol registration or appropriate search strategy. Consequently, many NMAs provided results of low confidence, further distorted by reporting issues and spin. As the studies' conclusions diverged, clinicians need to interpret them with caution when looking for the most reliable and comprehensive evidence. Improving the quality of publications using this method requires joint efforts to disseminate these good practices. These efforts concern the authors, the experts in the methods used and the reviewers of scientific journals. In combination, an international effort led by scientific societies should aim to raise awareness among authors and reviewers to the thoroughness of systematic review and meta-analysis methods.

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Figure Legends

Figure 1. Flow diagram of the studies included in the overview.

Figure 2. Cumulative number of published NMAs over time.

Figure 3. Interventions included in the NMA for each study.

Green: included intervention, Red: not included intervention, Grey: not yet available, withdrawn or loss of therapeutic indication. NMAs are ranked in chronological order by date of last literature search. Interventions are ranked in chronological order, from the oldest to the most recent first published trial. The NMAs for which the date of last search was not reported ('?') were ranked in relation to the other NMAs by chronological order of publication. The date written after each treatment corresponds to the date of publication of the first trial evaluating that treatment. DLS : date of last search, MTX: methotrexate, ACI: acitretin, FUM: fumaric acid esters, ALE: alefacept, CIC: ciclosporin, ETA: etanercept, EFA: eflizumab, INF: infliximab, ADA: adalimumab, UST: ustekinumab, IXE: ixekizumab, BRO: brodalumab, CERTO: certolizumab, APR: apremilast, TOF: tofacitinib, SEC: secukinumab, GUS: guselkumab, TIL: tildrakizumab, RIS: risankizumab, BIME: bimekizumab, TYK2: tyrosine kinase 2 inhibitor, MIRI: mirikizumab

Figure 4. Treatments cited as best in the abstract in relation to the included treatments for each NMA.

Each "X" represents the included treatments, squares filled in green represent the treatments cited as best, red squares represent the treatment of the funding pharmaceutical company.

ACI: acitretin, FUM: fumaric acid esters, ALE: alefacept, BRIA: briakinumab, ITO: itolizumab, CIC: ciclosporin, ETA: etanercept, EFA: eflizumab, INF: infliximab, ADA: adalimumab, UST: ustekinumab, IXE: ixekizumab, BRO: brodalumab, CERTO: certolizumab, APR: apremilast, TOF: tofacitinib, SEC: secukinumab, GUS: guselkumab, TIL: tildrakizumab, RIS: risankizumab, BIME: bimekizumab, TYK2: tyrosine kinase 2 inhibitor, MIRI: mirikizumab

Table 1: Included NMAs characteristics

Included NMA	Number of studies in SR	Number of studies in NMA	Included interventions	Number of included interventions	Studied outcomes	Timeframe of evaluation	Source of funding	CRO¤
Woolacott 2006	39	16	Some biologic, some conventional	6	Efficacy	Short-term	Academic	No
Reich 2008	15	15	Some biologic	4	Efficacy and quality of life	Short-term	Industry	Yes
Bansback 2009	22	22	All biologic, some conventional	7	Efficacy	Short-term	Industry	No
Reich 2012	20	20	Some biologic	5	Efficacy	Short-term	Industry	Yes
Lin 2012	17	17	All biologic	5	Efficacy	Short-term	Academic	No
Baker 2012	31	20	All biologic	7	Efficacy and quality of life	Short-term	Industry	No
Galvan Banqueri 2013	14	14	Some biologic	4	Efficacy	Short-term	NR	No
Igarashi 2013	NR	NR	Some biologic	5	Efficacy	Short-term	Industry	Yes
Schmitt 2014	48	48	Some biologic, some conventional	8	Efficacy	Short-term	None	No
Gupta 2014	21	21	Some biologic, some conventional	6	Efficacy	Short-term	None	Yes
Signorovitch 2015	15	15	Some biologic	4	Efficacy	Short-term	Industry	Yes
Messori 2015	13	13	Some biologic	3	SAEs, Infection	Short-term	None	No
Fan 2015	6	6	Some biologic	2	Efficacy	Short-term	Industry	No
Sbidian 2017	109	74	All biologic, all conventional, all small molecules	19	Efficacy, safety and quality of life	Short-term	Academic	No
Jabbar Lopez 2017	41	41	Some biologic, some conventional	7	Efficacy, safety and quality of life	Short-term	Academic	No
Gomez Garcia 2017	27	27	Some biologic	5	Efficacy and safety	Short-term	Academic	No
AlSawah 2017	24	24	Some biologic	5	Efficacy	Short-term	Industry	No
Loos 2018	34	34	Some biologic, some small molecules	8	Efficacy	Short-term	Academic	No
Cameron 2018	45	45	Some biologic, some small molecules	10	Efficacy, safety and quality of life	Short-term	Industry	Yes
Sawyer 2018	67	54	Some biologic, some conventional, some small molecules	10	Efficacy	Short-term	Industry	Yes
Imafuku 2018	4	4	Some biologic	4	Efficacy	Short-term	Industry	Yes
Geng 2018	33	33	Some biologic, some conventional	7	Efficacy	NR	NR	No
Warren 2018	6	6	Some biologic	4	Efficacy and quality of life	Short-term	Industry	No
Lv 2018	75	75	Some biologic, some conventional, alefacept, efalizumab	NR	Efficacy, safety and quality of life	NR	Academic	No
Armstrong 2018	20	20	Some biologic, some	7	Efficacy	Short-term	Industry	Yes

			small molecules			and long-term		
Sawyer 2019a[43]	83	77	Some biologic, some conventional, some small molecules	15	Efficacy	Short-term	Industry	Yes
Bai 2019	28	28	Some biologic	7	Efficacy and safety	Short-term	None	No
Sawyer 2019b	98	17	Some biologic, some small molecules	8	Efficacy	Long-term	Industry	Yes
Xu 2019a[57]	54	54	Some biologic	13	Efficacy, safety and quality of life	Short-term	None	No
Xu 2019b	13	13	Some biologic	5	Efficacy and safety	Short-term	Academic	No
Sbidian 2020	140	113	All biologic, all conventional, all small molecules	19	Efficacy, safety and quality of life	Short-term and long-term	Academic	No
Armstrong 2020	160*	60	Some biologic, all conventional, some small molecules	16	Efficacy	Short-term and long-term	Industry	Yes
Warren 2020a[51]	33	33	Some biologic	11	Efficacy and quality of life	Short-term	Industry	Yes
Warren 2020b	60	28	Some biologic	9	Efficacy	Short-term	Industry	
Yasmeen 2020	88	28	Some biologic, some small molecules	11	Efficacy	Long-term	Industry	Yes
Jianzhen 2020	14	13	Some biologic	4	Efficacy, safety and quality of life	Short-term	Academic	No
DuJardin 2020	5	5	Some biologic	2	Efficacy and safety	Short-term	Industry	No
Tada 2020	41	41	Some biologic	8	Efficacy	Short-term	Industry	Yes
Torres 2020	82	42	Some biologic, some conventional	14	Efficacy	Short-term	Industry	Yes
Xu 2020	66	66	All biologic	14	Efficacy and safety	Short-term	Academic	No
Mahil 2020	62	62	Some biologic, some conventional	12	Efficacy, safety, quality of life	Short-term	Academic	No
Xue 2020	50	43	Some biologic	8	Efficacy	Short-term	Industry	Yes
Diaz Acedo 2020	5	5	Some biologic	4	Efficacy	Short-term and long-term	NR	No
Song 2020	5	5	Some biologic, some small molecules	2	Efficacy and safety	Short-term	None	No
Blauvelt 2021	31	31	Some biologic	8	Efficacy	Short-term	Industry	No
Shear 2021	52	52	Some biologic, some conventional, some small molecules	13	Safety	Short-term and long-term	Industry	Yes
Mrowietz 2021	50	50	Some biologic	11	Efficacy	Short-term	Industry	Yes

Short-term: from 2 weeks to 28 weeks. Long-term: after 28 weeks.

¤ *Contract research organization*

**160 studies included in the review but no references to those studies in the article and no narrative synthesis of their results*

Table 2: Methodological characteristics of the included NMAs, n/total (%)

NMA approach	
Bayesian	32/47 (68.1)
Frequentist	7/47 (14.9)
Bayesian and Frequentist	2/47 (4.2)
Bucher method	4/47 (8.4)
NR	2/47 (4.3)
NMA model	
Fixed effect	8/47 (17.0)
Random effect	26/47 (55.3)
Fixed and Random effect	7/47 (14.9)
NR	6/47 (12.8)
Adjustment for placebo-arm response	11/47 (23.4)
Graphical representation of the network	29/47 (61.7)
Level of base case analysis	
Dose level	37/47 (78.1)
Drug level	9/47 (19.1)
Class level	6/47 (12.8)
Results reported of the classical MA	18/47 (38.3)
Results reported for all pre specified outcome of interest	41/47 (87.2)
Results reported for all relative comparisons available	30/47 (63.8)
Adequate treatment ranking	23/47 (48.9)
SUCRA	16/47 (34.0)
Probability of being best	3/47 (6.4)
Ranking probabilities	5/47 (10.6)
Mean rank	4/47 (8.5)
Evaluation of heterogeneity	28/47 (59.6)
Study of baseline characteristics	17/47 (36.2)
Model fit	8/47 (17.0)
Statistical tests or measure (Chi², Q test, I², tau)	16/47 (34.0)
Evaluation of heterogeneity in the network	15/47 (31.9)
Presence of heterogeneity	

Yes	8/47 (17.0)
No	12/47 (25.5)
Unclear	2/47 (4.2)
NR	25/47 (53.2)
Exploration of heterogeneity	15/47 (31.9)
Meta-regression	6/47 (12.8)
Subgroup analysis	1/47 (2.1)
Sensitivity analysis	5/47 (10.6)
None or NR	33/47 (70.2)
Exploration of heterogeneity when present	4/8 (50.0)
Evaluation of consistency when possible	27/41 (65.9) *N.A for 6*
Presence of inconsistency	
Yes	9/41 (22.0)
No	14/41 (34.1)
NR	18/41 (38.3)

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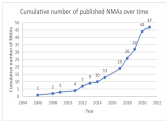

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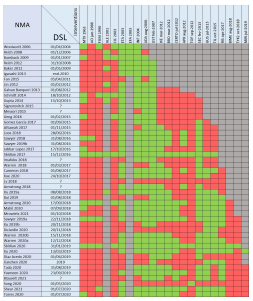

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NMA	Date of publication	ACI	CIC	FUM	MTX	ITO	EFA	ALE	BRIA	TYK2	APR	TOF	BRO	CERT	ADA	ETA	UST	GUS	INF	IXE	RIS	SEC	TIL	BIME	GOL	MIRI
WOOLACOTT 2006	2006		X	X	X		X									X			X							
REICH 2008	2008						X	X								X			X							
BANSBACK 2009	2009		X		X	X		X							X	X			X							
REICH 2012	2012						X								X	X	X		X							
LIN 2012	2012							X							X	X	X		X							
GALVAN BANQUERI 2013	2013														X	X	X		X							
IGARASHI 2013	2013						X								X	X	X		X							
SCHMITT 2014	2014		X	X	X			X							X	X	X		X							
GUPTA 2014	2014				X			X							X	X	X		X							
SIGNOROVITCH 2015	2015														X	X	X		X							
FAN 2015	2015																X		X							
SBIDIAN 2017	2017	X	X	X	X	X		X			X	X	X	X	X	X	X	X	X	X		X	X			
JABBAR LOPEZ 2017	2017				X										X	X	X		X	X		X				
GOMEZ GARCIA 2017	2017														X	X	X		X			X				
AL SAWAH 2017	2017														X	X	X			X		X				
IMAFUKU 2018	2017														X		X		X			X				
WARREN 2018	2017															X	X			X		X				
LOOS 2018	2018										X		X		X	X	X		X	X		X				
CAMERON 2018	2018										X		X		X	X	X	X	X	X		X	X			
GENG 2018	2018		X		X				X						X	X	X		X							
LV 2018	2018																X									
ARMSTRONG 2018	2018										X				X	X	X		X	X		X				
XU 2019a	2018					X	X	X	X				X		X	X	X	X	X	X		X	X			
SAWYER 2018	2019	X			X						X		X		X	X	X		X	X		X				
SAWYER 2019a	2019	X		X	X						X		X	X	X	X	X	X	X	X	X	X	X			
XU 2019b	2019														X		X	X			X		X			
BAI 2019	2019												X				X	X		X	X	X	X			
WARREN 2020b	2019												X		X	X	X	X	X	X		X	X			
WARREN 2020a	2019												X	X	X	X	X	X	X	X	X	X	X			
SBIDIAN 2020	2020	X	X	X	X					X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
ARMSTRONG 2020	2020	X	X	X	X						X		X	X	X	X	X	X	X	X	X	X	X			
JIANZHEN	2020																X	X			X		X			
DU JARDIN 2020	2020																	X					X			
TADA 2020	2020												X		X		X	X	X	X	X	X				
XU 2020	2020								X				X	X	X	X	X	X	X	X	X	X	X	X		X
MAHIL 2020	2020				X								X	X	X	X	X	X	X	X	X	X	X			
XUE 2020	2020												X		X	X	X	X	X	X		X				
DIAZ ACEDO 2020	2020												X				X			X		X				
SONG 2020	2020											X				X										
BLAUVELT 2021	2020													X	X		X	X	X	X	X	X				
TORRES 2020	2021				X				X				X	X	X	X	X	X	X	X	X	X	X		X	
MROWIETZ 2021	2021												X	X	X	X	X	X	X	X	X	X	X			

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