META-ANALYSIS

DOI: http://dx.doi.org/10.15403/jgld-3804

Comparative Efficacy and Tolerability of Janus Kinase Inhibitor Therapies for Moderate to Severe Crohn's Disease: A Network Meta-analysis

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Received: 02.06.2021
Accepted: 08.08.2021

ABSTRACT

Background & Aims: A number of Janus kinase (JAK) inhibitors (tofacitinib, filgotinib, upadacitinib) have been tested for moderate and severe Crohn's disease (CD) in randomized control trials (RCTs). However, data on their comparative efficacy and tolerability is lacking. We aimed to study their performance comparatively, by means of network meta-analysis (NWM).

Methods: We searched the Pubmed/Medline, EMBASE, and Cochrane Library databases for relevant RCTs through March 2021 and data was extracted. A bayesian NWM was performed to investigate the efficacy and tolerability of the above JAK inhibitors and to explore their rank order in treating moderate and severe CD patients. The cumulative ranking probability for each intervention at the end of treatment period, was evaluated by means of surfaces under cumulative ranking (SUCRA) values.

Results: Four RCTs were entered into this NWM. They included 811 patients totally, randomized to 11 interventions, i.e. placebo, tofacitinib (1mg BID, 5mg BID, 10mg BID, 15mg BID), filgotinib 200 OD and upadacitinib (3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID and 24mg OD). Two upadacitinib doses (6 mg BID and 24 mg BID) and filgotinib 200 OD, performed best as judged by the relevant forest plots, league matrixes, rankograms, SUCRA values (96.7%, 84,6 %and 78,7%, respectively) and the clustered ranking plots for efficacy and tolerability.

Conclusions: Upadacitinib 6 mg BID, upadacitinib 24 mg BID and filgotinib 200 OD performed better as induction therapies in comparison to control therapies. Consequently, these regimens may play a therapeutic role in CD and therefore they merit further evaluation with well-designed RCTs.

Key words: Crohn's disease - JAK inhibitors - efficacy – tolerability - network meta-analysis.

Abbreviations: BID: twice daily; CD: Crohn's disease; CDAI: Crohn's disease activity index; CI: confidence interval; CrI: credible interval; IBD: inflammatory bowel disease; IL: interleukin; JAK: Janus kinase; NWM: network meta-analysis; OD: once daily; OR: odds ratio; RCT: randomized controlled trial; RoB: risk of bias; SUCRA: surfaces under cumulative ranking; TNF: tumor necrosis factor; UC: ulcerative colitis.

INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory bowel disease (IBD), characterized by relapses and progressive intestinal lesions which may result in complications such as abscesses, fistulae and strictures [1, 2]. Over recent decades, biologic therapies, i.e. against tumor necrosis factor-alpha (TNF-a), leucocyte integrins and interleukin (IL) pathways, have become significant therapies in our armamentarium for moderate-to-severe CD and ulcerative colitis (UC) [3]. However, there are some limitations accompanying these therapies as a percentage of patients do not respond and, in some, there is a loss of response over time [4, 5]. In addition, currently available biologic treatments are administered intravenously or subcutaneously, which potentially represents a burden for patients and might compromise their compliance to treatment [6]. Furthermore, despite the introduction of lower-cost biosimilars, the cost of biologic treatments remains an important challenge for healthcare budgets [7]. Finally, there are some safety issues which are related with both traditional and biologic treatments [8-10]. For all the above reasons, novel treatment options easily administered, effective, well-tolerated and safe are required.

Janus kinase (JAK) inhibitors are orally administered, non-immunogenic small molecule drugs. Four intracellular tyrosine kinase (TYK) proteins, i.e. JAK1, JAK2, JAK3 and TYK2, are included in the JAK group and their activation is responsible for initiating the intracellular signaling associated with different cytokine receptors. JAK phosphorylation subsequently activates the intracytoplasmic signal transducer and activator of transcription (STAT) pathways to control downstream target gene expression of inflammatory mediators [11,12]. Consequently, research has been focused on the clinical application of JAK inhibitors in immune-mediated inflammatory diseases and among other indications, considerable attention is currently being paid to the clinical use of JAK inhibitors in IBD. Three JAK inhibitors (tofacitinib, upadacitinib and filgotinib) are now under consideration for use in IBD and of those tofacitinib has been approved for oral use in moderate-to-severe UC [13]. In parallel, there are RCTs comparing these JAK inhibitors to placebo for moderate-to-severe CD. However, knowledge of their comparative efficacy and tolerability is lacking.

The comparative efficacy and tolerability of RCTs, concerning multiple treatments competing for a similar therapeutic result, can be achieved by utilizing a useful evidence synthesis tool, i.e. a network meta-analysis (NWM) [14-16]. Network meta-analysis incorporates both direct and indirect evidence, thus providing information concerning the relative effects of treatments included in relevant RCTs. The comparative efficacy and tolerability of JAK inhibitors for moderate-to-severe CD has not been explored. In this study, therefore, we aimed to examine the above, by means of NWM of published RCTs.

METHODS

To identify studies and extract data in this NWM, we have followed the steps (i.e. identification, screening, eligibility, inclusion) described in our previous publications [17]. Thus, the PubMed/MEDLINE and Embase databases were searched until March 2021 to identify human studies written in English using the following search text and/or Medical Topic Heading (MeSH) terms: („janus kinase inhibitors"[All Fields] OR „janus kinase inhibitors"[MeSH Terms] OR (*„janus"[All Fields] AND „kinase"[All Fields] AND „inhibitors"[All Fields]) OR „janus kinase inhibitors"[All Fields]) AND (IBD[All Fields] OR („crohn disease"[MeSH Terms] OR („crohn"[All Fields] AND „disease"[All Fields]) OR „crohn disease"[All Fields] OR („crohn's"[All Fields] AND „disease"[All Fields]) OR „crohn's disease"[All Fields]*)). In addition, a manual search of all review articles, published editorials and retrieved original studies, was made. Two authors (T.R and K.E) independently extracted data from each study. Any disagreement was settled with further discussion until consensus was reached. This NWM was performed according to the PRISMA statement for interventions [18], whereas the rating of the quality of treatment effect estimates was achieved by using the GRADE (i.e. Grading of Recommendations Assessment, Development and Evaluation) working group modality [19]. Furthermore, we appraised the confidence in estimates derived from this NWM, as described in our previous publications [20, 21].

We defined the inclusion and exclusion criteria before starting the study investigation. Thus, appropriate studies were included provided that the following criteria were met a) published as complete articles or abstracts with data that could be extracted; b) written in English, and c) RCTs with JAK inhibitors in one arm. Studies not meeting the above criteria were excluded. In this NWM, the induction of clinical remission, i.e. Crohn's disease activity index (CDAI) < 150, was defined as the end point for efficacy. For RCTs reporting on maintenance of induced remission, outcomes were assessed at the last point of follow-up.

For pair-based meta-analyses and heterogeneity estimation (Cochran's Q test and the I^2 metric), we followed the methodology described previously [17]. In addition to heterogeneity, we assessed inconsistency, i.e. the agreement between direct and indirect evidence and the transitivity assumption, as these are critical when conducting an NWM [22, 23]. We constructed comparison-adjusted funnel plots and checked their symmetry to assess whether small-scale trials influence the efficacy results. Surfaces under cumulative ranking (SUCRA) values were used in intervention network charts to examine the cumulative ranking probability for each intervention concerning the efficacy achieved by this intervention compared to an ideal intervention showing the best efficacy without doubt, i.e. SUCRA = 1 or 100% when expressed as a percentage [14-16]. Except for efficacy, tolerability was taken into account and all the competing treatments therefore were compared and ranked hierarchically according to their performance on two outcomes, i.e. efficacy and tolerability. We achieved this by constructing a two-dimensional clustered ranking plot with the relevant dendrogram, presenting jointly the relative ranking of treatments (based on SUCRA values) for efficacy and tolerability. Using this hierarchical method, we were able to detect clusters of treatments with similar performance on both outcomes [14-16]. Data were processed using software suitable for bayesian network meta-analysis, namely Stata 13.2 (StataCorp, College Station, TX) [14, 15] and NetMetaX [16]. In all included RCTs, the intention to treat results (ITT) were taken into account.

RESULTS

Characteristics of Studies

The process of study selection is shown in Fig. 1. Thus, out of 977 titles yielded by the initial search, 4 RCTs were eligible for meta-analysis [24-27]. The characteristics of these RCTs are shown in Table I. They were phase II, double-blind, randomized, placebo-controlled trials, in patients with moderate-to-severe CD and included 811patients totally, randomized to 11 treatments, i.e. placebo, tofacitinib 1mg BID, tofacitinib 5mg BID, tofacitinib 10mg BID, tofacitinib 15mg BID, upadacitinib 3 mg BID, upadacitinib 6 mg BID, upadacitinib 12 mg BID, upadacitinib 24 mg BID, upadacitinib 24 mg OD and filgotinib 200 OD. The RCT by Sandborn et al. [24], included 4 arms, i.e. placebo, tofacitinib 1 mg BID, 5 mg BID and 15 mg BID. The RCT by Panés et al. [25], included 4 arms, i.e. placebo, tofacitinib 5 mg BID, tofacitinib 10 mg BID and tofacitinib 15 mg BID. The RCT by Vermeire et al. [26], included 2 arms, i.e, placebo and filgotinib 200 mg OD. Finally, the RCT by Sandborn et al. [27], included 6 arms, i.e. placebo, upadacitinib 3mg BID, upadacitinib 6mg BID, upadacitinib

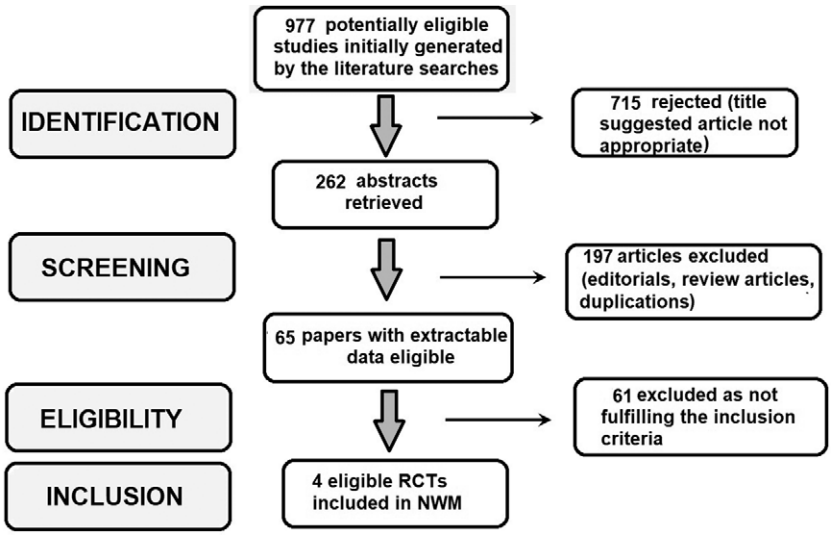

Fig. 1. Flow chart of studies included in the network meta-analysis.

12mg BID, upadacitinib 24mg OD and upadacitinib 24mg BID. Concerning quality assessment, the bar graph of Fig. 2A depicts the summary of the risk of bias (RoB), characterized as high, unclear and low RoB, concerning 5 items, i.e. random sequence generation (selection bias), allocation concealment (selection bias), incomplete outcome data (attrition bias), blinding of participants and personnel (performance bias) and publication format.

Network Meta-analysis

Efficacy network map

The network map of all 11 therapeutic interventions is shown in Fig. 3, with all 55 possible comparisons, i.e. 25 direct and 30 indirect. In this map the node size reflects the number of patients allocated to each treatment, whereas the edge thickness is in proportion to the precision, i.e. the inverse of variance of each direct comparison [16].

Efficacy network forest and funnel plots

The pair-wise comparisons [ORs (95% CI)] of all 25 direct treatment comparisons is depicted in the forest plot of Fig. 4. Out of these, 8 yielded significant results, i.e. upadacitinib 6 mg BID vs placebo (OR=6.38, 95%CI: 2.32-17.55), upadacitinib 6 mg BID vs upadacitinib 12 mg BID (OR=6.14, 95%CI: 2.22-16.92), upadacitinib 6 mg BID vs upadacitinib 3 mg BID (OR=5.40, 95%CI: 2.02-14.46), upadacitinib 6 mg BID vs upadacitinib 24 mg OD (OR=4.05; 95%CI: 1.50-10.92), upadacitinib 24 mg BID vs placebo (OR=3.71, 95%CI: 1.40-9.82), upadacitinib 24 mg BID vs upadacitinib 12 mg BID (OR=3.57; 95%CI: 1.35-9.47), upadacitinib 24 mg BID vs upadacitinib 3 mg BID (OR=3.14; 95%CI: 1.22-8.08) and filgotinib 200 mg OD vs placebo (OR=3, 95%CI: 1.37-6.58). There was no significant heterogeneity (Q=14.37, I2=23.47%, p=0.21).The respective comparison-adjusted funnel plot is shown in Fig. 2B. It appears symmetrical, implying the

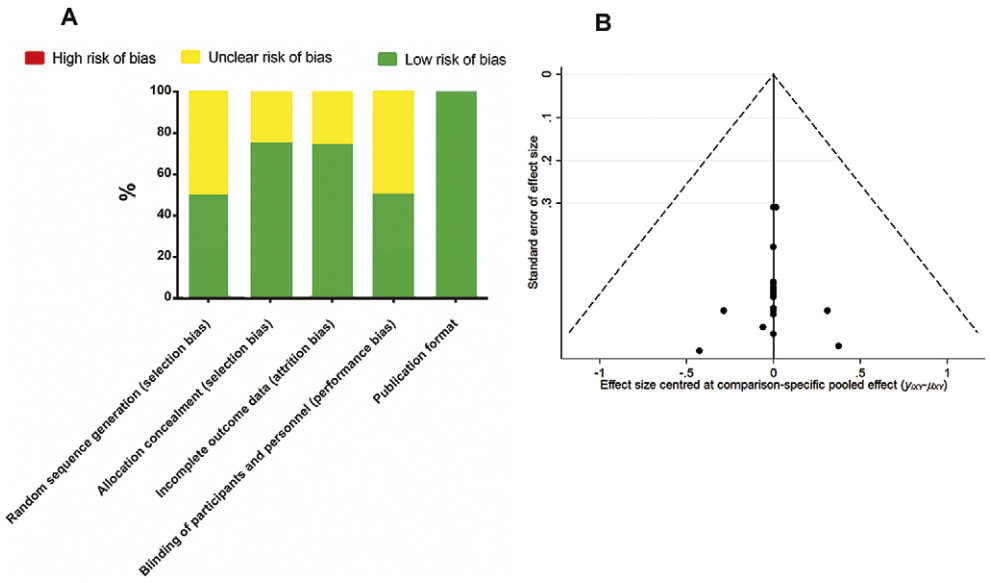

Fig. 2. A. Risk of bias graph depicting each risk of bias item presented as percentage across all included studies. B. Comparison-adjusted funnel plot.

Table I. Main characteristics of the studies included in the network meta-analysis

Study / year/ Ref. (No)	Countries involved	Publication type/ Journal	Clinical remission definition; timing of outcome	Total No of patients involved	Study protocol
Sandborn et al/ 2014 / (22) (A3921043 study)	48 centers in 12 countries (Belgium, Czech Republic, France, Hungary, Italy, Netherlands, Poland, Slovakia, South Africa, Spain, United Kingdom, USA)	Full paper (Clinical Gastroenterology and Hepatology)	CDAI<150, at week 4	139	A Phase II Study of Tofacitinib, in Patients with Crohn's Disease. Adult patients with moderate-to-severe active Crohn's disease were assigned randomly to groups given 1 mg,5 mg, 15 mg tofacitinib or placebo for 4 weeks, at 48 centers in 12 countries. The end points were the proportion of clinical responders at week 4 (decrease from baseline in the Crohn's Disease Activity Index score of >70 points [Response-70]) and clinical remission (Crohn's Disease Activity Index score of <150 points) at week 4.
Panes et al / 2017/ (23) (NCT01393626 and NCT01393899 studies)	Spain, USA, Germany, Belgium, Netherlands, Canada.	Full paper (Gut)	CDAI<150, at week 8	280	A phase IIb randomized placebo-controlled trial. Adult patients with moderate-to-severe CD were randomized to receive induction treatment with placebo, tofacitinib 5 or 10 mg twice daily for 8 weeks. Those achieving clinical response-100 or remission were re-randomized to maintenance treatment with placebo, tofacitinib 5 or 10 mg twice daily for 26 weeks. Primary endpoints were clinical remission at the end of the induction study, and clinical response-100 or remission at the end of the maintenance study.
Vermeire et al/ 2916/ (24) (FITZROY study)	52 centers in nine European countries (Belgium, Germany, Poland, France, Czech Republic, Romania. Russia, Hungary, Bulgaria)	Full paper (Lancet)	CDAI<150, at week 10	172	A phase II, double-blind, randomized, placebo-controlled trial, in patients with moderate-to-severe Crohn's disease treated with filgotinib (the FITZROY study). For eligibility reads, a single central reader was assigned. Patients were randomly assigned (3:1) to receive filgotinib 200 mg once a day or placebo for 10 weeks. Patients were stratified according to previous anti-tumour necrosis factor alpha exposure, C-reactive protein concentration at screening (≤10 mg/L or >10 mg/L), and oral corticosteroid use at baseline, using an interactive web based response system. The primary endpoint was clinical remission, defined as CDAI less than 150 at week 10. After week 10, patients were assigned based on responder status to filgotinib 100 mg once a day, filgotinib 200 mg once a day, or placebo for an observational period lasting a further 10 weeks.
Sanborn et al/ 2021/ (24) (CELEST study)	15 centers in nine countries (USA, Canada, France, Belgium, Netherlands, Germany, UK, Italy, Spain)	Full paper (Gastroentero-logy)	CDAI<150, at week 12 or 16.	220	A double-blind, phase II trial in adults with moderate to severe CD and inadequate response or intolerance to immunosuppressants or tumor necrosis factor antagonists. Patients were randomly assigned (1:1:1: 1:1:1) to groups given placebo or 3 mg, 6 mg, 12 mg, or 24 mg upadacitinib twice daily, or 24 mg once daily, and evaluated by ileocolonoscopy at weeks 12 or 16 of the induction period. Patients who completed week 16 were re-randomized to a 36- week period of maintenance therapy with upadacitinib. The primary endpoints were clinical remission at week 16 and endoscopic remission at week 12 or 16.

absence of publication bias. All 55 possible comparisons (25 direct and 30 indirect) in this NWM are shown in the forest plot of Fig. 5A. Of these comparisons [ORs, 95% Credible Intervals (CrI)], 13 yielded significant results. In this network forest plot there was no significant heterogeneity and also the evaluation of inconsistency yielded insignificant overall results, meaning that the comparative effect sizes that were obtained by direct and indirect comparisons were consistent (Supplementary Table 1). When taking placebo as reference treatment, the results showed that, among 10 treatments tested against it, only three, i.e. upadacitinib 6 mg BID, upadacitinib 24 mg BID and filgotinib 200 mg OD yielded significant results (Fig. 5B). The remaining seven comparisons yielded insignificant results. None of the tofacitinid tested doses were superior to placebo.

Efficacy league matrixes, rankograms and SUCRA values

The comparative efficacies [ORs (95% CrI)] of the 11 treatments are shown in the league matrix of Fig. 6A. The respective rankogram is shown in Fig. 6B in close relationship with SUCRA values shown in Table II. These results showed that upadacitinib 6 mg BID (SUCRA 96.7%), upadacitinib 24 mg BID (SUCRA 84.6%) and filgotinib 200 OD (SUCRA 78.7%) performed better in comparison to rest of the treatments.

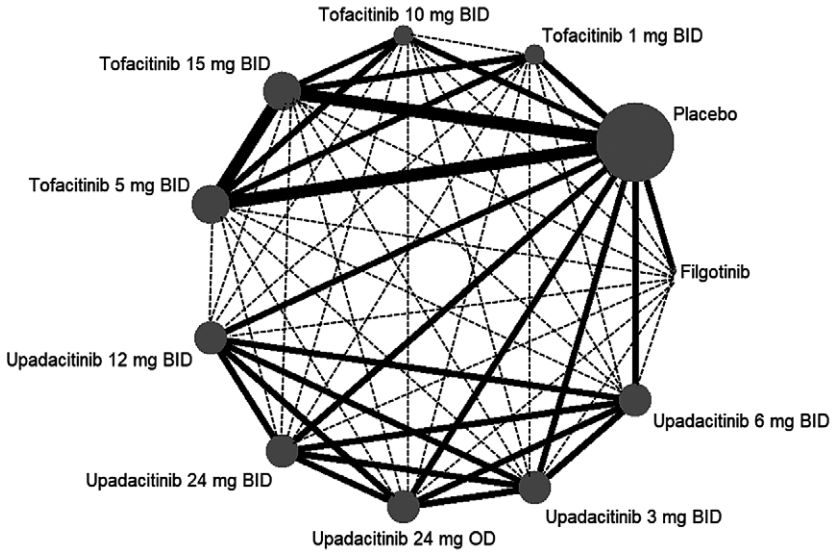

Fig. 3. Network map of all 55 comparisons [25 direct (solid lines)] and 30 indirect (interrupted lines)]. The node size reflects the number of patients allocated to each regimen, whereas edge thickness is in proportion to the precision, i.e. the inverse of variance of each direct comparison.

Tolerability and Hierarchical Cluster Analysis

The included RCTs in the NWM did not evaluate tolerability. owever, they reported withdrawals due to side effects and from this data tolerability could be inferred for the treatments tested. Hence an additional tolerability NWM was performed (Fig. 7). Taking into account SUCRAs for both efficacy and tolerability (Table II) we constructed the relevant clustered ranking plot for the treatments included in this NWM (Fig. 8A) with the respective dendrogram depicting the treatment similarities (Fig. 8B). Both these figures show that the 11 treatments formed 4 clusters with similar performance. One of those clusters, i.e. upadacitinib 6 mg, upadacitinib 24 mg BID and filgotinib 200 mg, showed the best combined performance concerning efficacy-tolerability and achieved the best similarity in the relevant dendrogram.

DISCUSSION

Janus kinase inhibitors have been approved for a variety of diseases, such as autoimmune diseases, rheumatoid arthritis

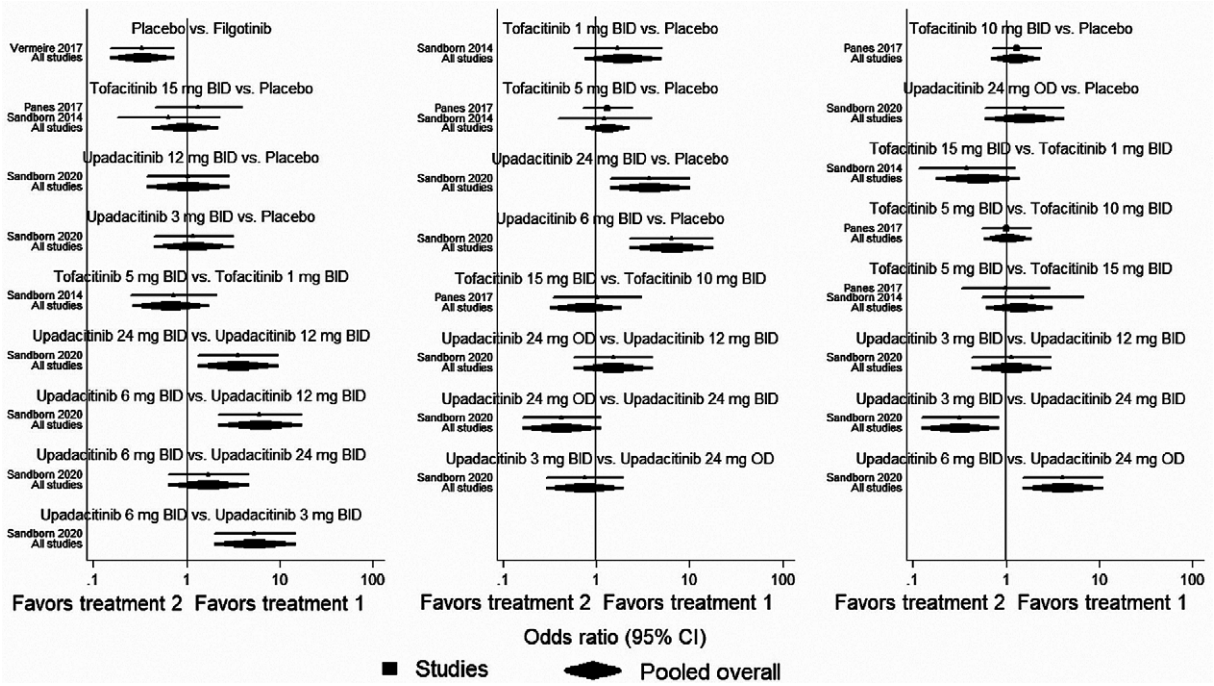

Fig. 4. Network forest plot illustrating the 25 direct pair comparisons [OR, 95% confidence intervals (CI)] of the 11 treatments included in the randomized controlled trials.

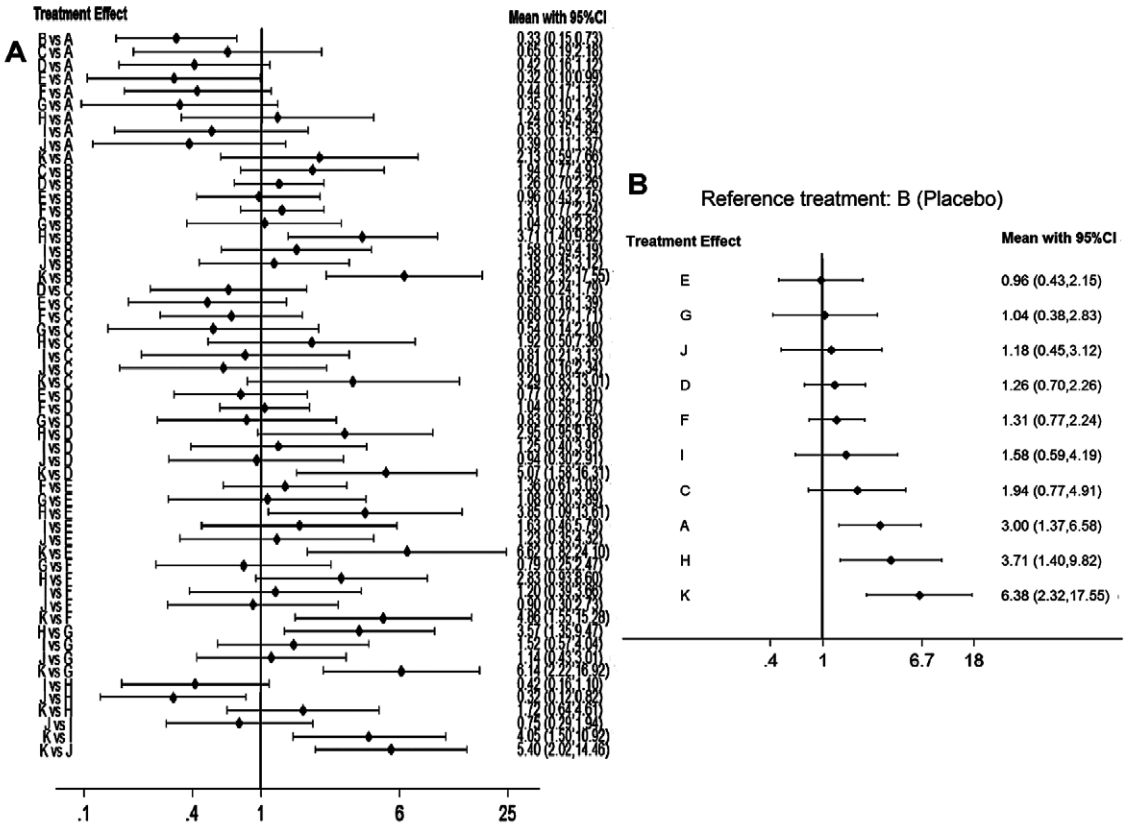

Fig. 5. A. Network forest plot [OR, 95% credible intervals (CI)] illustrating all 55 pair (direct and indirect) comparisons of regimens included in the RCTs. B. Network forest plot depicting the efficacy of the regimens compared directly with placebo. Vertical line at OR=1.0 indicates no treatment vs placebo difference. Labels: A= Filgotinib, B=Placebo, C=Tofaticinib 1mg BID, D=Tofaticinib 10mg BID, E= Tofaticinib 15mg BID, F= Tofaticinib 5mg BID, G= Upacitinib 12 mg BID, H= Upacitinib 24 mg BID, I= Upacitinib 24 mg OD, J= Upacitinib 3mg BID, K= Upacitinib 6 mg BID.

and psoriasis [28, 29]. In IBD approval was given in 2018 to tofacitinib for the treatment of moderate-to-severe UC [30, 31], whereas for CD there are only published RCTs. In this NMA, we examined the comparative efficacy and tolerability of three JAK inhibitors, i.e. tofacitinib, filcotinib, upadacitinib, in inducing clinical remission in patients with moderate-to-severe CD, as assessed by the results of relevant RCTs. All four RCTs included in this NWM, were phase II trials. The results showed that, concerning efficacy, among 11 treatments, i.e. placebo, tofacitinib (1mg BID, 5mg BID, 10mg BID, 15mg BID), upadacitinib (3 mg BID, 6 mg BID, 12 mg BID, 24 mg BID, 24 mg OD) and filgotinib 200 OD, the cluster of three treatments, i.e. upadacitinib 6 mg BID, upadacitinib 24 mg BID and filgotinib 200 OD, performed best as judged by the pair-wise and network forest plots, SUCRA values and the relevant league matrixes and rankograms. Tofacitinib did not prove effective in this NWM and in fact, in its RCTs, placebo response was high, raising concerns for future research.

In addition to efficacy, we also performed a tolerability NWM calculating SUCRA values for each treatment and creating the relevant rankograms. Both efficacy and tolerability profiles were then taken into account in the created clustered ranking plot and dendrogram. Through this methodology we were able to assess treatment efficacy-tolerability profile and we found that the cluster of three treatments, i.e. upadacitinib 6 mg BID, upadacitinib 24 mg BID and filgotinib 200 OD, remained the best performer. All this might signal that these three treatments merit further evaluation concerning efficacy and tolerability in well-designed phase III RCTs in patients with moderate-to-severe CD. Towards this notion, plans are already going ahead for upadacitinib [27, 32].

In two of the included RCTs [25 ,27], after the induction period, the authors re-randomized patients and provided data concerning maintenance assessment of efficacy and safety. Thus, Panés et al. [25], reported that clinical response was maintained at 26 weeks in 46.5% of CD patients treated with tofacitinib compared to 35.7% of patients treated with placebo. In addition, clinical remission was maintained in 39.5% of patients treated with tofacitinib compared to 28.5% of patients treated with placebo. In this study, the proportion of patients maintaining clinical response or remission, with either tofacitinib 5 mg BID or 10 mg BID, was not significantly different compared to placebo. Sandborn et al. [27], in their RCT evaluated upadacitinib as maintenance treatment in patients with moderate-to-severe CD and found that, after the induction period, efficacy was maintained for most endpoints through week 52. Concerning safety, the authors reported that over 52 weeks, the upadacitinib safety profile was consistent with studies in rheumatoid arthritis. However, patients in the twice-daily 12 mg and 24 mg upadacitinib groups had

A

Upadacitinib 6 mg BID									
1.72 (0.64,4.61)	Upadacitinib 24 mg BID								
2.13 (0.59,7.66)	1.24 (0.35,4.32)	Filgotinib							
3.29 (0.83,13.01)	1.92 (0.50,7.36)	1.55 (0.46,5.23)	Tofacitinib 1 mg BID						
4.05 (1.50,10.92)	2.36 (0.91,6.11)	1.90 (0.54,6.67)	1.23 (0.32,4.73)	Upadacitinib 24 mg OD					
4.86 (1.55,15.28)	2.83 (0.93,8.60)	2.29 (0.88,5.92)	1.48 (0.59,3.72	1.20 (0.39,3.66)	Tofacitinib 5 mg BID				
5.07 (1.58,16.31)	2.95 (0.95,9.18)	2.38 (0.89,6.35)	1.54 (0.56,4.25)	1.25 (0.40,3.91)	1.04 (0.58,1.87)	Tofacitinib 10 mg BID			
5.40 (2.02,14.46)	**3.14 (1.22,8.08)**	2.54 (0.73,8.84)	1.64 (0.43,6.28)	1.33 (0.52,3.44)	1.11 (0.37,3.36)	1.07 (0.34,3.31)	Upadacitinib 3 mg BID		
6.14 (2.22,16.92)	**3.57 (1.35,9.47)**	2.88 (0.81,10.29)	1.86 (0.48,7.29)	1.52 (0.57,4.04)	1.26 (0.41,3.92)	1.21 (0.38,3.86)	1.14 (0.43,3.01)	Upadacitinib 12 mg BID	
6.62 (1.82,24.10)	**3.85 (1.09,13.61)**	**3.11 (1.01,9.58)**	2.01 (0.72,5.60)	1.63 (0.46,5.79)	1.36 (0.61,3.03)	1.31 (0.55,3.09)	1.23 (0.35,4.32)	1.08 (0.30,3.89)	Tofacitinib 15 mg BID
6.38 (2.32,17.55)	**3.71 (1.40,9.82)**	**3.00 (1.37,6.58)**	1.94 (0.77,4.91	1.58 (0.59,4.19	1.31 (0.77,2.24	1.26 (0.70,2.26)	1.18 (0.45,3.12)	1.04 (0.38,2.83)	0.96 (0.43,2.15)	Placebo

B

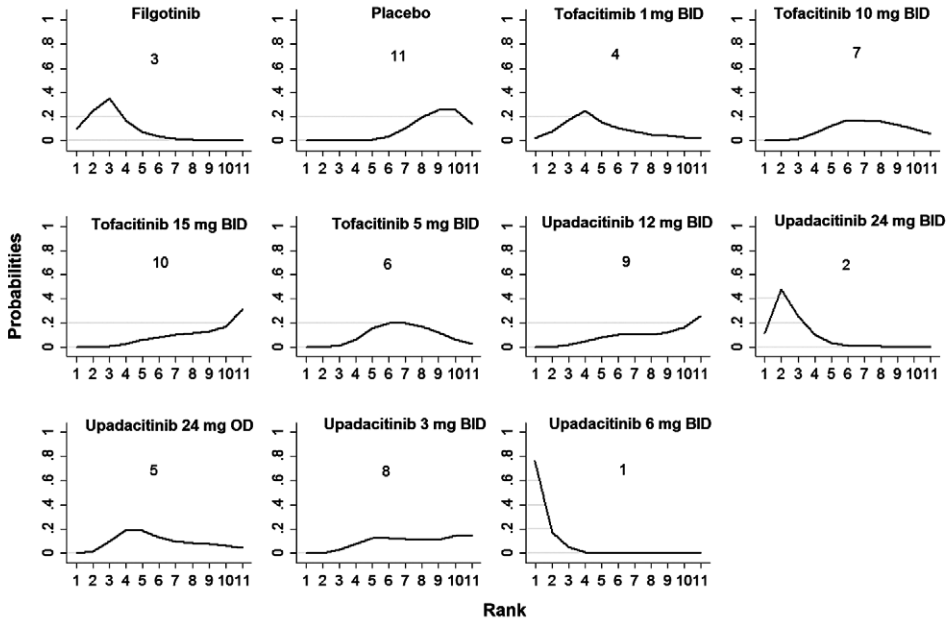

Fig. 6. A. SUCRA (surface under the cumulative ranking) based efficacy ranking league matrix showing the comparative efficacies of the treatments included in this network meta-analysis. B. Rankograms derived from relevant SUCRA values for the regimens evaluated in the included RCTs, showing the cumulative rank order for each intervention (1-11).

significant increases in total, high-density lipoprotein, and low-density lipoprotein cholesterol levels compared with patients in the placebo group. In general, the safety profile needs to be further investigated. Special attention should be given to thromboembolic events and herpes zoster, since an increased rate has been found in patients with UC and rheumatoid arthritis [33].

The approval of tofacitinib for the treatment of moderate-to-severe UC marked the first of several JAK inhibitors that are likely to enter the IBD treatment landscape within the next few years with significant implications for clinical practice. There are several reasons in favor of this hypothesis. Firstly, the oral bioavailability makes this treatment attractive, taking into account that all biologics in use are available as injections, with consequences concerning patients' compliance. Furthermore, JAK inhibitor efficacy after anti-TNF failure and its lack of immunogenicity, make this treatment a potentially viable option for combination with biologics, such as vedolizumab, which has a favorable safety profile in patients with severe disease. Nevertheless, some unanswered questions remain. The fact that JAK inhibitors are oral therapies, does not necessarily mean that these drugs are safer than parenterally administered biologics. Furthermore, it is unclear whether JAK inhibitors will be more cost effective than currently available biosimilars. Finally, the efficiency of JAK treatment has to be improved by identifying individual patient predictors of response.

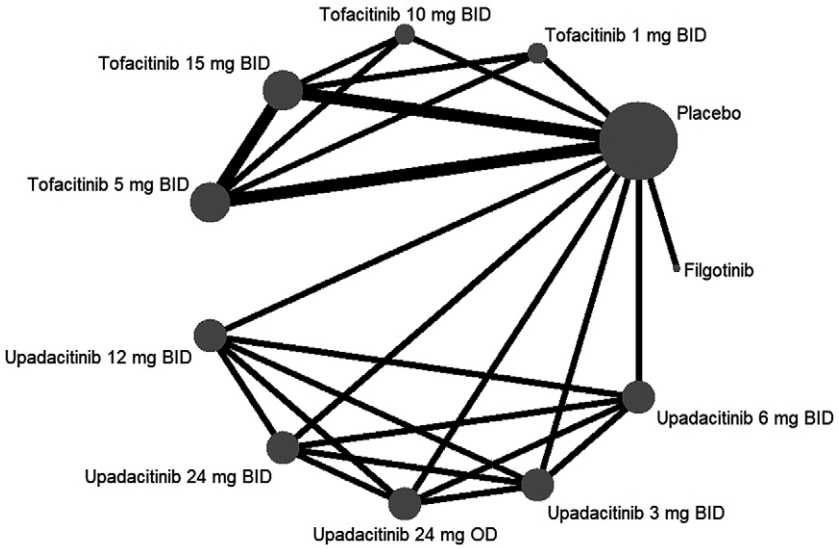

Fig. 7. Tolerability network map. The node size reflects the number of patients allocated to each regimen, whereas edge thickness is in proportion to the precision, i.e. the inverse of variance of each direct comparison.

The good quality of the included RCTs, the lack of heterogeneity and publication bias and the lack of inconsistency strengthens the results of this NWM. However, some limitations should be mentioned. Thus, although heterogeneity was not observed for pooled efficacy or safety estimates, there was heterogeneity in the trial design, concerning treatment duration and endpoint definitions between trials that may have influenced the assessments. Furthermore, although potential risks associated with JAK inhibitors are likely to be dose-dependent, the small number of trials for each treatment precludes the accurate dose-response analysis. For all these reasons, more studies are needed. Thus, head-to-head RCTs are needed to evaluate the precise role of JAK inhibitors for the treatment of patients with moderate-to-severe CD together with biologics in use. Moreover, research is required to determine the exposure-response relationship of these drugs at the site of action, i.e. in the gut tissue. This might help the development of safer drugs when considering targeted therapies with less systemic exposure. An additional point of consideration would be to identify the suitable JAK inhibitor efficacy biomarkers and predictors which could guide CD patients more efficiently to the most effective therapy.

In summary, this NWM showed that JAK inhibitors could be an attractive therapeutic option in patients with moderate to severe CD, both naïve and previously exposed to anti-TNF biologics with demonstrable efficacy and tolerability. This is strengthened when taking into account the fact that this class of drugs is administered orally. However, all included RCTs in this NWM were phase II studies. Therefore, carefully designed phase III RCTs are needed considering both efficacy and tolerability. In particular, carefully defined enrolment criteria with central reading of endoscopy for enrolment and endpoint adjudication can reduce biases. Additionally, further research can lead to predictors of response to JAK inhibitors. This is of importance when considering proper patients' guidance to the most effective treatments.

Table II. SUCRA values for efficacy and tolerability. For efficacy high SUCRA denotes good efficacy. For tolerability high SUCRA denotes good tolerability

TREATMENT	EFFICACY			TOLERABILITY		
	SUCRA (%)	PrBest	Mean Rank	SUCRA (%)	PrBest	Mean Rank
Placebo	20.1	0.0	9.0	41.8	22.0	6.8
Tofacitinib 1mg BID	60.5	2.4	5.0	37.6	11.4	7.2
Tofacitinib 5 mg BID	40.5	0.0	7.0	37.5	13.5	7.2
Tofacitinib 10 mg BID	37.5	0.0	7.2	65.0	6.4	4.5
Tofacitinib 15mg BID	21.8	0.0	8.8	29.7	2.4	8.0
Filcotinib 200 mg OD	78.7	9.9	3.1	47.7	11.8	7.1
Upacitinib 3 mg BID	33.7	0.0	7.6	64.1	6.8	4.6
Upacitinib 6 mg BID	96.7	76.0	1.3	47.9	11.9	6.2
Upacitinib 12 mg BID	26.4	0.0	8.4	47.2	0.4	6.3
Upacitinib 24 mg OD	49.5	0.0	6.0	57.0	1.8	5.3
Upacitinib 24 mg BID	84.6	11.5	2.5	58.4	11.6	5.2

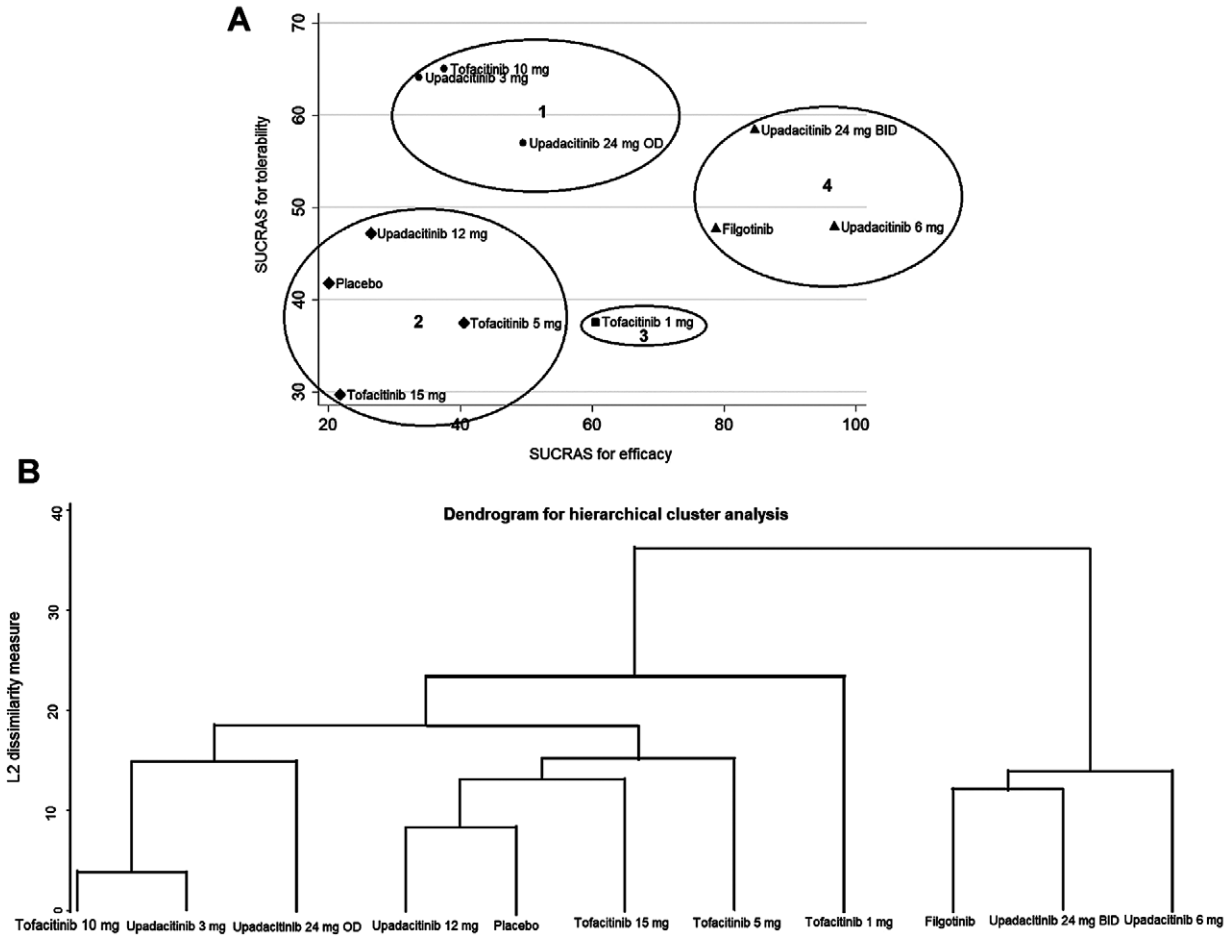

Fig. 8. A. Clustered ranking plot showing jointly the relative ranking of treatments (based on SUCRA values) for both efficacy and tolerability. Different plotting symbols represent different clusters of treatments. B. The respective dendrogram of the hierarchical clustered ranking.

CONCLUSIONS

In this NWM, among 11 interventions tested as induction treatments in patients with moderate-to-severe CD, upadacitimib 6 mg BID, upadacitimib 24 mg BID and filgotinib 200 mg OD formed a cluster showing the best performance concerning efficacy and tolerability. However, additional well-designed RCTs are required to better understand the role of this class of drugs in the management of CD, alongside therapies in use.

Conflicts of interest: None to declare.

Authors' contributions: T.R. conceived and designed this study, analyzed data and drafted the manuscript. K.E and Y.N. extracted and analyzed data, edited, and revised the manuscript. T.R. critically revised the paper. All the authors approved the final version of the manuscript.

Supplementary material: To access the supplementary material visit the online version of the *J Gastrointestin Liver Dis* at http://dx.doi.org/10.15403/jgld-3804

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