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Comparative Effectiveness and Safety of the JAK Inhibitors and Biologic Disease-Modifying Antirheumatic Drugs in Treating Children With Nonsystemic Juvenile Idiopathic Arthritis: A Bayesian Meta-Analysis of Randomized Controlled Trials

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Objective. We evaluated the efficacy and safety profiles of JAK inhibitors (JAKi) and biologic disease-modifying antirheumatic drugs (bDMARDs) when used with or without methotrexate (MTX) for the treatment of nonsystemic forms of juvenile idiopathic arthritis (nsJIA).

Methods. Randomized clinical trials (RCTs) investigating efficacy and safety outcomes of JAKi or bDMARDs for the nsJIA population up to 2023 were searched in ClinicalTrial.gov, PubMed, EMBASE, and Cochrane databases. Bayesian arm-based network meta-analysis compared efficacy as measured by Juvenile Idiopathic Arthritis-American College of Rheumatology 70 (JIA-ACR70) improvement and safety based on rates of serious adverse events (SAEs) among all therapies.

Results. Eligible studies included 45 citations from 16 RCTs (7 parallel and 9 withdrawal trials) with a total of 1,821 participants that investigated nine bDMARDs, three with and six without MTX co-treatment, and two JAKis (tofacitinib and baricitnib). The reported SAE incidence rates ranged from 0 to 0.3 per person-year of follow-up; none of the pairwise comparisons were statistically significant. The JIA-ACR70 improvement by 16 weeks of treatment ranged from 11.3% to 89.5%. Compared with controls, significant JIA-ACR70 improvements were observed for etanercept, golimumab, and all three combination therapies (adalimumab+MTX, etanercept+MTX, and infliximab+MTX), with odds ratios ranging from 2.97 to 3.99. No significant pairwise comparisons between bDMARDs and JAKi versus bDMARDs were noted.

Conclusion. Overall, no significant evidence was found for efficacy and safety profiles in pairwise comparisons of JAKis and bDMARDs. Future studies will expand the meta-analysis by including non-RCT studies and individual participant data.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is an umbrella term for heterogeneous chronic inflammatory arthritic conditions of childhood onset that neither have a known etiology nor a cure. An estimated 300,000 children have a rheumatologic condition, and 80,000 children in the United States have JIA.[1] There are seven subtypes of JIA. Systemic JIA is clearly different from the other JIA subtypes due to a different disease mechanism (autoinflammatory) and is often studied separate from the other subtypes.

Many biologic disease-modifying antirheumatic drugs (bDMARDs) have been shown in placebo-controlled studies to be efficacious for treating children with nonsystemic forms of JIA (nsJIA).[2] But head-to-head comparisons have been lacking. Further, bDMARDs are administered either subcutaneous (SC) or intravenous, which is a burden for pediatric patients. Tofacitinib

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SIGNIFICANCE & INNOVATIONS

- This is the first meta-analysis comparing efficacy and safety profiles of JAK inhibitor (JAKi) versus commonly adopted biologic for treating children with nonsystemic forms of juvenile idiopathic arthritis (nsJIA).
- This Bayesian arm-based network meta-analysis updated the network meta-analysis of existing treatment options for nsJIA up to the end of 2023.
- Overall approved advanced treatments for nsJIA, including newly available secukinumab and JAKi, have comparable clinically relevant improvement and safety.

and baricitinib, two JAK inhibitors (JAKi) trials, have recently been approved for treating nsJIA.[3–6] These small-molecule drugs are available in oral formulations (pill and liquid) and thus might be preferrable for pediatric patients. However, little is known about the comparison of JAKi to the commonly prescribed bDMARDs and nonbiologic, conventional disease-modifying drugs (cDMARDs) for treating nsJIA. Synthesized evidence reported in randomized studies can inform comparative evidence of treatment effectiveness and safety profiles and thus better inform treatment choices for treating children with nsJIA. The objective of this network meta-analysis (NMA) study was to compare the efficacy and safety outcomes of approved advanced treatments for nsJIA (ie, JAKi and bDMARDs) that received regulatory approval for treating nsJIA.

PATIENTS AND METHODS

This study protocol was preregistered at PROSPERO (CRD42023402840), with reporting following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline, and the PRISMA checklist is provided in the Supplemental Materials. Only aggregated summary data are used. Institutional review board approval is not required.

Study population. The study population included all pediatric patients who were diagnosed with nsJIA, which includes all subtypes of JIA except systemic JIA with active systemic features (ie, rash, fever, or serositis).[7]

Information sources and study selection criteria. Randomized clinical trial (RCT) studies written in the English language and published in ClinicalTrial.gov, PubMed, EMBASE, or Cochrane, from establishment of the databases to December 2023, were searched and evaluated for eligibility. RCTs investigating one of the bDMARDs (etanercept, adalimumab, infliximab, anakinra, canakinumab, rilonacept, rituximab, certolizumab, golimumab, secukinumab, abatacept, and tocilizumab) or JAKi (tofacitinib or baricitinib) indicated for JIA were included. Exclusion criteria were (1) studies not reporting JIA-American College of Rheumatology 70 (JIA-ACR70) responses within 16 ± 4 weeks of treatment on one of investigational drugs, (2) studies conducted exclusively in children diagnosed with active systemic JIA, (3) studies focused on uveitis in patients with JIA, and (4) studies reporting conference abstract only or secondary analysis of RCTs. Two independent reviewers (Y.L. and X.Y.) conducted the literature search following the protocol prespecified search criteria (Supplemental Material). Any discrepancies were resolved via manual reviews and group consensus (see authors).

Data collection. For RCTs meeting the study selection criteria, their reported summary statistics (mean or median) of the following data elements were extracted: trial characteristics included RCT registration number, sample size, trial start and end dates, type (parallel and/or random withdrawal), and investigational drugs. The sample characteristics included patient age, sex, race, duration of disease, JIA categories, percentage of patients on different background drugs, and whether the study-eligible criteria required participants to have demonstrated inadequate responses to cDMARDs or nonsteroidal anti-inflammatory drugs (NSAID) at baseline. For parallel randomized trials, data were extracted for each study arm. For randomized withdrawal trials (RWTs), data were extracted for the open-lead-in phase only. Any discrepancies between the two reviewers were brought up for discussion with additional group members to achieve resolution by agreement. Risk of bias of the RCTs was assessed using the Risk of Bias 2 tool and reported as overall risk of bias based on five domains of bias.[8] Two review authors (Y.L. and B.H.) independently rated the quality for each outcome.

The primary outcome of clinical efficacy was measured by the JIA-ACR70 level of response within 16 ± 4 weeks of the initiation of the bDMARD or JAKi as part of the RCT. This efficacy outcome was chosen because it constitutes a widely recognized clinically relevant superior response to treatment. The primary safety outcome was the incidence rate of serious adverse events (SAE) calculated by the number of events reported divided by the total cumulative person-time exposure.[9] SAEs are untoward medical occurrences in a patient or trial participant that do not necessarily have a causal relationship with the treatment. They included events that are fatal or life-threatening for the patient, require hospital admission or an extension of the admission, cause persistent or significant invalidity or work disability, manifest itself in a congenital abnormality or malformation, or could have developed to a serious undesired medical event but was prevented due to timely intervention by the researcher.[10,11]

For the efficacy outcome, we calculated the odds ratio (OR) and corresponding 95% credible intervals (CI) of the JIA-ACR70 response rate between any pair of treatments.[12] Similarly, incidence rate ratios (IRR) of SAEs were estimated for the safety outcome.

Analysis method. The literature search identified two types of trial designs, the randomized parallel trial and RWT. Of note, there was a clear separation of the two types of trial designs based on receiving Food and Drug Administration (FDA) approval for the studied drug before or after 2010. Specifically, the RWT design was exclusively used in trials for drugs that received FDA approval for JIA after 2010. For the RWT, all patients were treated with the bDMARD intervention for a prespecified period (ie, open-lead-in phase) before the qualified patients were randomized to placebo control withdrawal or continued bDMARD treatment; thus, directly comparable JIA-ACR70 improvement data for cDMARD control were not available for these RWT studies. To include the data related to newer approved drugs (after 2010) from RWT, we employed an arm-based Bayesian modeling approach to NMA. Transitivity assumption is required for NMAs.[13] Under this assumption, the arm-based sample should be homogeneous (ie, they should come from the same underlying patient population). However, we have noted that some studies may intentionally include or exclude some JIA subtypes, such as enthesitis-related arthritis (ERA) and/or psoriatic arthritis (PsA). The distribution of JIA subtypes varied by study. To address this potential threat to transitivity assumption, we included the percentages of JIA subtypes as arm-level covariates. Additionally, we conducted a sensitivity analysis excluding trials exclusively conducted in ERA and/or PsA.

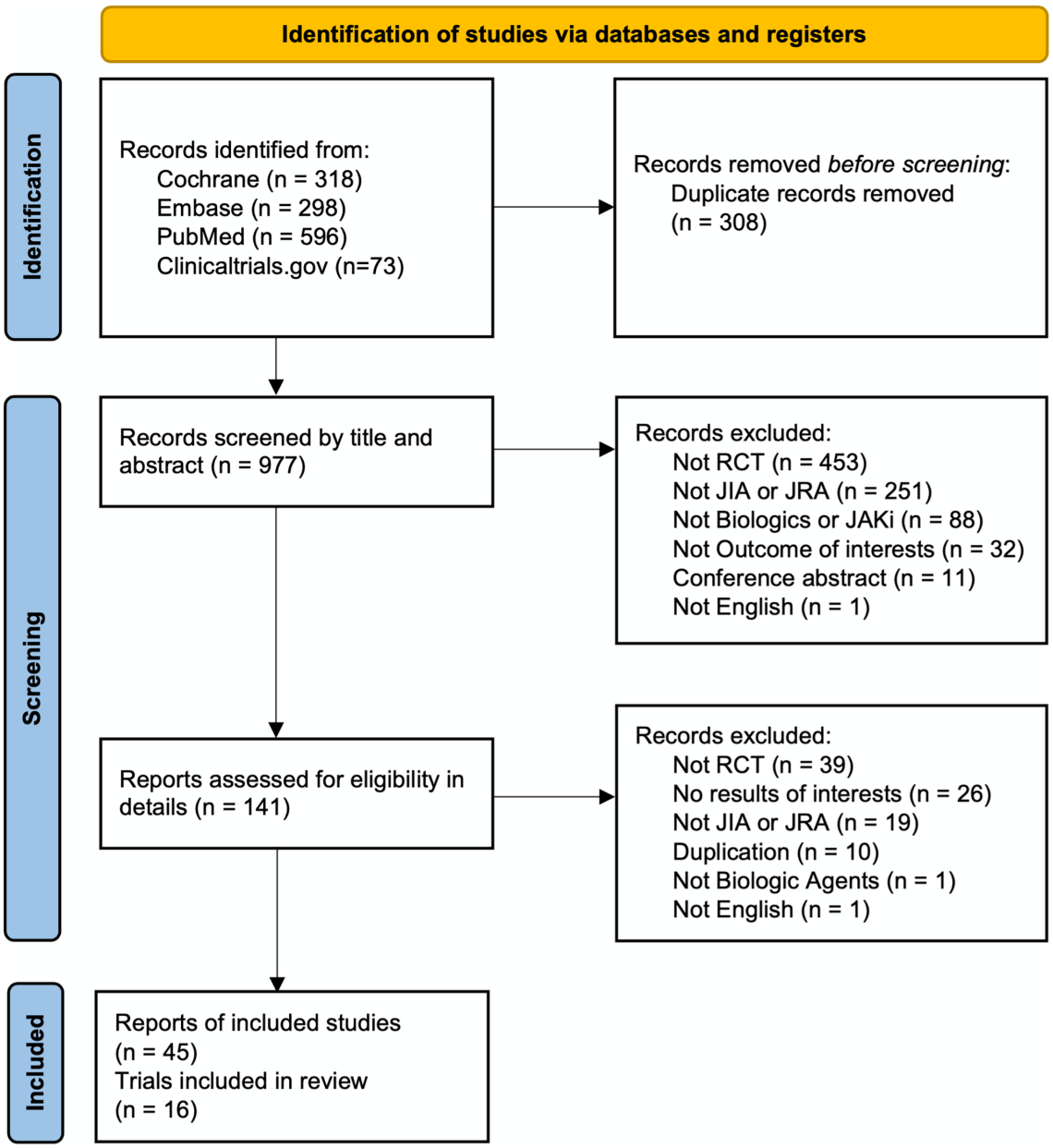

Figure 1. Flow chart of literature search. JIA, juvenile idiopathic arthritis; JRA, juvenile rheumatoid arthritis; RCT, randomized clinical trial.

The Bayesian approach produces a formal update of a prior distribution (or belief) as expressed by prior distribution incorporating the information obtained from an experiment. The updated belief is expressed as posterior distribution. When a noninformative prior is used, the Bayesian posterior is largely driven by the observed data, not influenced by the prior distribution, and thus commonly leads to the same conclusion as the most frequent results.[14] Furthermore, the Bayesian approach offers much flexibility to handle various data complexities. We used hierarchical modeling to enable shared information pooled across different drugs within the same class. Please find more modeling details in the Supplemental Material.

NMA allows for synthesis of relative effects from more than two treatments in a single model; thus, it can be used to compare treatments that are never directly compared in a randomized trial. The arm-based NMA combines the arm-specific effect,[15,16] offers greater flexibility to handle different types of trial designs, and allows for accounting between-trial and within-trial correlation by partial pooling based on hierarchical data structure. Simulation studies conducted comparing contrast-based and arm-based methods found that arm-based NMA performed the same or better than the contrast-based NMA with respect to bias, mean-squared error, and coverage.[17] The geometry of the network for the analysis was summarized in a network diagram based on the study type, number of participants, and trials. The node-split method was used to evaluate the inconsistency between direct and indirect evidence.[18]

Two sensitivity analyses were performed. The first sensitivity analysis excluded a trial with high risk of bias. The second excluded trials that focused on patients with ERA and/or PsA.

RESULTS

The study identified 45 citations published from the findings of 16 RCTs that met study inclusion and exclusion criteria. Data from a total of 1,821 patients were considered in this NMA. The detailed study selection process is presented in the flow diagram in Figure 1.

The 16 trials included 7 parallel trials and 9 RWT trials, involving six bDMARDs (three combined with methotrexate [MTX]) and two JAKis (ie, tofacitinib and baricitinib). Figure 2 presented the geometry of the network of the 16 trials. The only direct pairwise

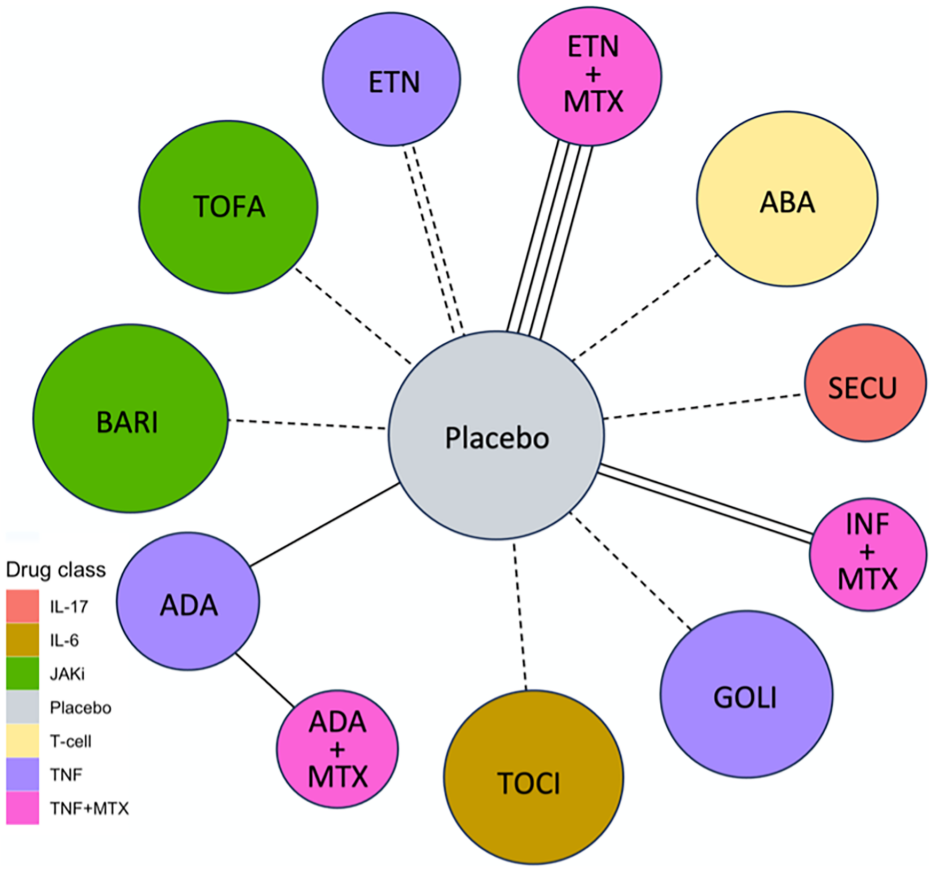

Figure 2. Evidence network diagram for trials included in the meta-analysis. The size of node represents the number of participants who received the treatment. Each line represents a trial containing the nodes as study arms. Solid lines represent multiarm trial. Dashed lines represent withdrawal trial that needed to borrow information from the control arm of other trials for contrast estimation. ABA, abatacept; ADA, adalimumab; BARI, baricitinib; ETN, etanercept; GOLI, golimumab; INF, infliximab; MTX, methotrexate; SECU, secukinumab; TOCI, tocilizumab; TOFA, tofacitinib.

comparison for bDMARDs was adalimumab versus adalimumab +MTX, and the rest of comparisons among bDMARDs relied on indirect evidence. Table 1 reported study and sample characteristics of included trials. All seven randomized parallel trials investigated a tumor necrosis factor (TNF) inhibitor: adalimumab, etanercept with and without MTX, or infliximab+MTX. The nine RWTs were abatacept (not SC), adalimumab, etanercept (two trials), golimumab (not intravenous), secukinumab, tocilizumab (not SC), tofacitinib, and baricitinib. Sample sizes of the arms of the trials ranged from 12 to 220, totaling 400 (five trials) patients treated with a TNF inhibitor (TNFi), 284 (seven trials) treated with TNFi +MTX, 404 (two trials) treated with a JAKi, and 269 controls. Mechanism of action of other bDMARDs besides TNFis included inhibiting the action of T cell (abatacept, n = 190), interleukin-6 (tocilizumab, n = 188), and interleukin-17a (secukinumab, n = 86), respectively. Nine RCTs required an inadequate response to cDMARD or NSAIDs to be eligible for participation. Detailed characteristics of the arms per RCT are reported in Tables 1 and 2. The sample mean ± SD of age at enrollment ranged from 8.3 ± 2.7 to 13.4 ± 2.9 years. Most patients were girls, White, and of the polyarticular JIA category. Only three trials were conducted in patients with newly diagnosed JIA.

Detailed information on the background therapies was presented in Table 2. Except for the NCT01166282, all RCTs mandated background therapy of MTX or equivalent cDMARD treatment (sulfasalazine [SSZ] in NTR1574; NCT01015547 also included a SSZ and hydroxychloroquine combo). We used "100M" to indicate the protocol mandated that all participants be treated on the given cDMARD and "P" to indicate that protocol permitted the usage. In the case of trial NTR1575, protocol mandated treatment with either MTX or SSZ; as a result, 53% and 47% participants were treated on MTX or SSZ, respectively. The aggregated summary (mean or median) statistics on baseline disease activities were also reported in Table 2, with the sample mean of loss of range of motion and active joint count ranged from 2 to 18.4 and 5.4 to 20.3, respectively. The minimum ratings of Medical Doctor global and patient wellbeing were 4.8 and 1.8,

Table 1. Study and sample characteristics of included trials*

Trial ID[a]	Study year	Arms (n)	Female, n (%)	Age (y)	Race[b] (%)	JIA Dur, y	JIA subtype[c] (%)	Inadqt. Resp.	OROB
1	2010–2012	ADA (31)	9 (29)	13.4	81/0/0/19	2.6	0/0/0/0/100	Yes	LR[e]
		C (15)	6 (40)	11.9	67/0/0/33	2.7	0/0/0/0/100		
2	2015	ETN+MTX (35)	22 (66.71)	9.8[d]	NA	0.81[d]	23/63/0/0/14	No	SC[f]
		C (33)	25 (75.76)	6.6[d]	NA	0.74[d]	36/54/0/0/9		
3	2009–2013	C1 (32)	24 (75)	8.8[d]	NA	0.65[d]	16/68/16/0/0	No	SC[f]
		C2 (32)	19 (59)	10.2[d]	NA	0.49[d]	9/69/22/0/0		
		ETN+MTX (30)	20 (67)	8.6[d]	NA	0.7[d]	7/80/13/0/0		
4	2007–2010	ETN+MTX (42)	29 (69)	9.9[d]	83/10/0/7	0.4	0/100/0/0/0	No	LR[e]
		C (43)	34 (79.1)	11.1[d]	88/2/0/10	0.43	0/100/0/0/0		
5	2000–2002	ETN+MTX (13)	6 (46)	11.4	77/0/15/8	≥0.25	31/69/0/0/0	Yes	LR[e]
		C (12)	7 (58)	8.8	83/17/0/0	≥0.25	8/58/0/33/0		
6	2001–2006	C (62)	49 (79)	11.1	88/0/0/12	3.6	25/62/0/13/0	Yes	LR[e]
		INF+MTX (60)	53 (88.3)	11.3	86/0/0/14	4.2	22/60/0/18/0		
7	2003–2007	INF+MTX (19)	13 (68.4)	10.5	NA	1.5	0/95/0/0/5	No	HR[g]
		C1 (20)	14 (70)	8.3	NA	2.3	0/85/0/0/15		
		C2 (20)	11 (55)	10.1	NA	1.8	0/75/5/0/20		
8	2003–2006	ABA (190)	137 (72)	12.4	77/8/0/15	4.4	16/64/0/20/0	Yes	e
9	2002–2005	ADA+MTX (85)	68 (80)	11.4	95/0/0/5	4.0	0/100/0/0/0	Yes	e
		ADA (86)	67 (78)	11.1	88/3/0/9	3.6	0/100/0/0/0		
10	1997–1998	ETN (69)	43 (62)	10.5	75/9/0/16	5.9	10/58/0/32/0	No	f
11	2011–2014	ETN (41)	10 (24)	13.3	NA	2.8	0/0/0/0/100	Yes	e
12	2010–2013	GOLI (173)	131 (75.7)	11.2	NA	≥0.5	13/72/9/7/0	Yes	e
13	2018–2020	SECU (86)	29 (33.7)	13.1	95/0/0/5	≥0.5	0/0/40/0/60	Yes	e
14	2009–2011	TOCI (188)	144 (77)	11.0	NA	4.2	0/100/0/0/0	Yes	e
15	2016–2019	TOFA (184)	142 (77)	13[d]	88/2/0/10	2.5[d]	15/78/0/7/0	Yes	e
16	2018–2022	BARI (220)	152 (69)	14	69/2/22/7	2.7	7/66/5/0/23	Yes	e

*Details of rating presented in Supplemental Material. ABA, abatacept; ADA, adalimumab; BARI, baricitinib; C, control; ETN, etanercept; GOLI, golimumab; ID, identifier; Inadqt. Resp., inclusion criteria mandate participants have inadequate response to disease-modifying antirheumatic drug or nonsteroidal anti-inflammatory drug at baseline; INF, infliximab; JIA, juvenile idiopathic arthritis; JIA Dur, JIA duration; MTX, methotrexate; NA, not available; OROB, overall risk of bias; TOCI, tocilizumab; TOFA, tofacitinib.
[a]Trial 1 to 7 are parallel trials; trial 8 to 16 are withdrawal trials.
[b]The sequence of race percentage: White/Black/Asian/other.
[c]The sequence of JIA subtype percentage: oligoarticular JIA or pauciarticular JIA (in trials 5, 6, and 10), polyarticular JIA, psoriatic arthritis, systemic JIA, and/or enthesitis-related arthritis.
[d]Medium is reported instead of mean.
[e]LR: Low risk.
[f]SC: Some concerns.
[g]HR: High risk.

respectively. The sample mean of child health assessment questionnaires ranged between 0.5 to 1.5. The baseline disease characteristics could be retrieved from all but one trial. Only one trial (NCT01015547, n = 59) was deemed high in risk-of-bias evaluation (Table 1, Supplemental Figure 1).

The aggregate summary statistics for both efficacy and safety outcomes were reported in Figure 3. The reported JIA-ACR70 response rates ranged from 11.29% to 89.47%. The reported incidence rate of SAE ranged from 0 to 0.32 per person-year. Total person-year exposures ranged from 3.46 to 58.46 person-years among all trials. The evaluation of the convergence of Bayesian models found good model convergence (Supplemental Materials, Supplemental Figure 2, Supplemental Figure 3, and Supplemental Table 1).

Figure 4 presented all pairwise indirect comparisons from NMA, with the panel A (blue) reporting efficacy, and the panel B (pink) reporting safety estimates. The 95% CIs of the estimated ORs and IRRs were shown in Supplemental Figure 4. The results reported are ratios of the column versus row entries, thus value >1 indicated that the treatment of the column has a higher rate of efficacy or safety outcome than the treatment of the row. For example, compared with controls, the ORs (95% CI) of JIA-ACR70 improvement were significant for adalimumab+MTX (OR 3.99, 95% CI 1.7–11.3), etanercept (OR 2.91, 95% CI 1.16–8.03), etanercept+MTX (OR 3.46, 95% CI 1.89–6.65), golimumab (OR 3.78, 95% CI 1.37–12.95), and infliximab+MTX (OR 2.97, 95% CI 1.31–6.61). Pairwise indirect comparisons of bDMARDs versus JAKi did not identify significant differences. Overall, no significant evidence was found for the efficacy and safety profiles in pairwise comparisons of JAKis and bDMARDs.

Two trials investigated adalimumab. The NMA estimated its effect versus control using both direct evidence based on the data reported in NCT01166282[19] (adalimumab vs control) and indirect evidence using data reported from NCT00095173[20] (adalimumab vs adalimumab+MTX) combined with data reported from the other 14 included trials. Checking consistency of direct to indirect evidence, the node-split method did not identify any statistically significant evidence (P = 0.709) for the inconsistency.

The first sensitivity analysis excluded the only trial (NCT01015547) with high risk of bias. Compared with the main analysis, the notable changes (Supplemental Figure 5) were efficacy results of tocilizumab versus control, in which OR (95% CI) increased from 3.07 (0.99–10.92) to 4.06 (1.31–14.32). Additionally, the effects of adalimumab and

Table 2. Background therapy and baseline disease characteristics of the study sample in included trials*

Trial ID	Registry	Arms	MTX/SSZ/HCQ/NSAID/CS	Mean LOM	Mean AJC	Mean MDG	Mean PtWell	Mean CHAQ
1	NCT01166282[19,39,40]	ADA	52/19/P/87/P	5.1	8.4	5.33	5.26	0.8
		C	53/20/P/93/P	4.5	6.7	5.26	4.9	0.8
2	EUCTR2015-003384-11[41]	ETN+MTX	100M/P/0M/P/P	6[a]	7[a]	8[a]	8[a]	1.5[a]
		C	100M/P/0M/P/P	6[a]	7[a]	6[a]	7[a]	1[a]
3	NTR1574[42–45]	C1	53M/47M/P/P/P	2[a]	7.5[a]	4.8[a]	4.8[a]	0.88[a]
		C2	100M/0M/P/P/P	2[a]	7.5[a]	5.0[a]	5.9[a]	0.94[a]
		ETN+MTX	100M/0M/P/P/P	3[a]	8.5[a]	5.1[a]	5.8[a]	0.88[a]
4	NCT00443430[46–49]	ETN+MTX	100M/0M/0M/NA/100M	13.6	18.3	7.0	5.6	1.1
		C	100M/0M/0M/NA/100M	16.3	25.5	7.1	5.2	1.3
5	NCT03781375[50]	ETN+MTX	100M/NA/NA/NA/NA	NA	NA	NA	NA	NA
		C	100M/NA/NA/NA/NA	NA	NA	NA	NA	NA
6	NCT00036374[51–54]	C	100M/NA/NA/P/P	17.6	18.5	4.9	4.1	1.2
		INF+MTX	100M/NA/NA/P/P	18.4	19.5	5.2	4.5	1.2
7	NCT01015547[55,56]	INF+MTX	100M/0M/M/P/P	11	18	4.9	1.8	0.51
		C1	100M/100M/100M/P/P	10	17	5.5	3.1	0.71
		C2	100M/0M/0M/P/P	10	18	6.0	4.1	1.06
8	NCT00095173[20,57,58]	ABA	74/NA/NA/P/P	16.3	16.2	5.42	4.45	1.3
9	NCT00048542[59–62]	ADA+MTX	100M/NA/NA/P/P	12.7	15	5.8	4.32	0.9
		ADA	0M/NA/NA/P/P	14.3	19.4	5.97	5.34	1.2
10	NCT03780959[63,64]	ETN	0M/0M/0M/P/P	10	28	7	5	1.4
11	EUCTR2010-020423-51[65,66]	ETN	0M/17/0M/54/12	5.2	5.4	5.2	5.8	0.7
12	EUCTR2009-015019-42[67,68]	GOLI	99/NA/NA/P/24	12.2	15	5.6	4.4	1.0
13	NCT03031782[69–71]	SECU	65/P/P/P/P	5.5	7.7	4.73	4.85	0.8
14	NCT00988221[72–77]	TOCI	79/NA/NA/NA/46	17.6	20.3	6.14	5.29	1.4
15	NCT02592434[4,78]	TOFA	65/NA/NA/32/P	6.0[a]	10.0[a]	6.0[a]	5.0[a]	0.9[a]
16	NCT03773978[3,79]	BARI	58/12/2/P/33	8.8	12.8	6.5	5.36	1.2

*ABA, abatacept; ADA, adalimumab; AJC, active joint count; BARI, baricitinib; C, control; CHAQ, Child Health Assessment Questionnaire; CS, glucocorticoid; ETN, etanercept; GOLI, golimumab; HCQ, hydroxychloroquine; ID, identifier; INF, infliximab; LOM, loss of joint range of motion; M, mandated by design; MDG, medical doctor global; MTX, methotrexate; NA, not available; NSAID, nonsteroidal anti-inflammatory drug; P, permitted but not reported; PtWell, patient wellbeing; SECU, secukinumab; SSZ, sulfasalazine; TOCI, tocilizumab; TOFA, tofacitinib.
[a]Medium is reported instead of mean.

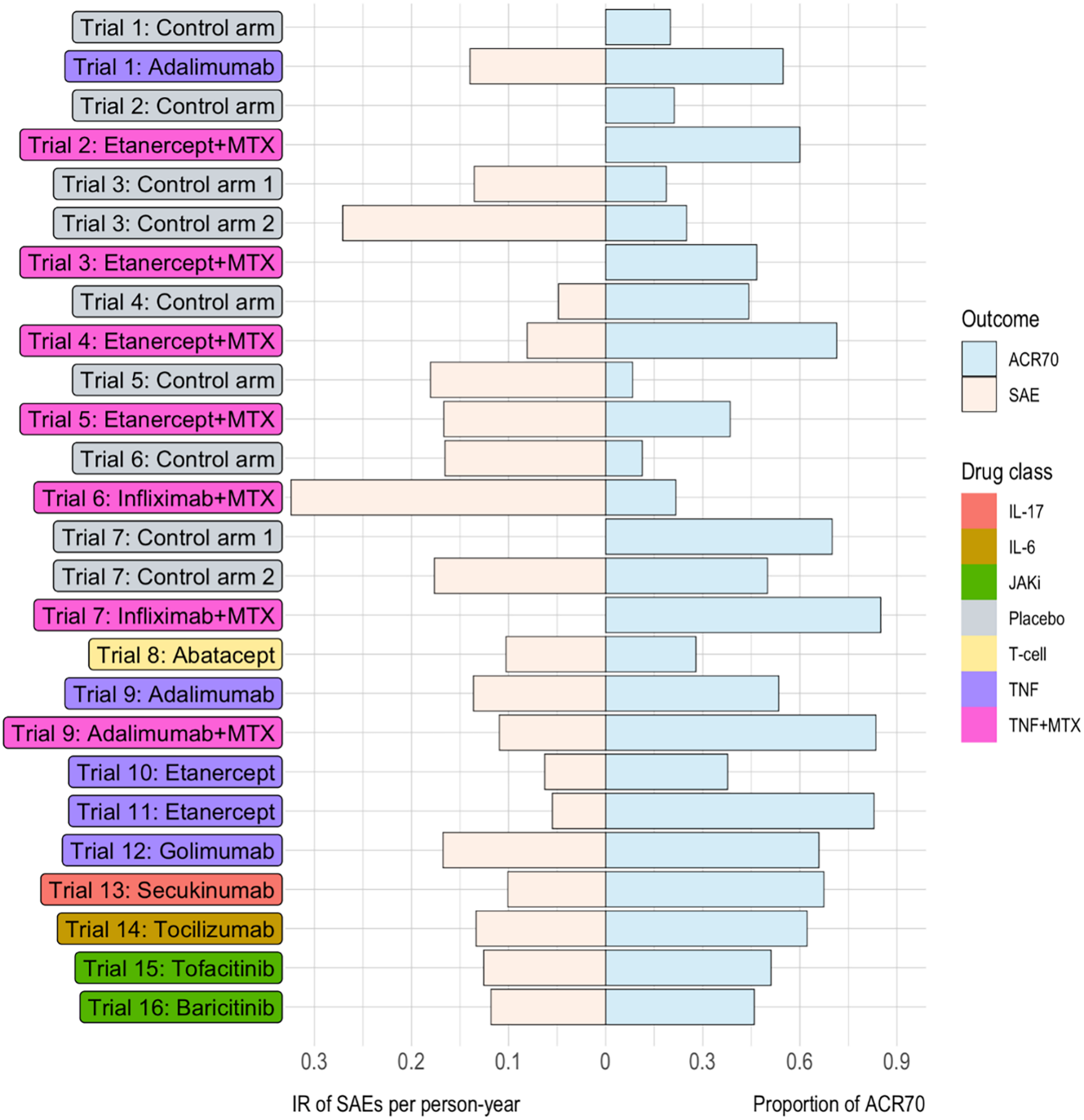

Figure 3. Reported summary statistics of efficacy (proportion of JIA-ACR70) and safety (incidence rate of SAEs per person-year) results by study arm. IR, incidence rate; MTX, methotrexate.

tofacitinib versus control became significant. Supplemental Figure 6 reported the results from the second sensitivity analysis, excluding three trials (NCT01166282, EUCTR2010-020423-51, and NCT0303178; adalimumab, etanercept, and secukinumab; n = 173) conducted exclusively in patients with ERA or PsA subtypes. The notable changes were diminished in significance in monotherapy of etanercept compared with the control.

DISCUSSION

When it comes to choosing a treatment, clinicians, patients, and policymakers want to know how similar treatment options compare against each other. However, such head-to-head comparison of efficacy trials in patients with JIA rarely exist, and it can be difficult, if not impossible, to perform individual trials to compare all the currently available treatments against each other. For

Figure 4. Pairwise comparison of estimated odds ratio for (A) efficacy (odds ratio of JIA-ACR70) and (B) safety (incidence rate ratio of SAE) outcomes from the Bayesian arm-based network meta-analysis. The numbers reported were the estimates of the outcomes between the column treatment versus row treatment. Values >1 suggested the column treatment has higher rate than the row treatment. For example, 2.17 in the second row and second column of (A) represented that the odds ratio of JIA-ACR70 for adalimumab (column treatment) versus control (row treatment) was 2.17; 1.59 in the second row and second column of (B) indicated that the incidence rate ratio of SAE for adalimumab (column treatment) versus control (row treatment) is 1.59. The number with bold font represents OR estimate with significant 95% CI; the details of 95% CIs for OR are shown in Supplemental Figure 4. IRR, incidence rate ratio; MTX, methotrexate; NMA, network meta-analyses; OR, odds ratio; SAE, severe adverse event.

nsJIA, there are 12 FDA-approved bDMARDs and 2 new JAKis recently approved or under review with trial data publicly available. Many trials have already been conducted in treating patients with JIA. These data can be synthesized by NMAs. Several studies have conducted NMA to evaluate the comparative effectiveness via indirect comparisons for patients with JIA.[21–27] Otten et al and Amarilyo et al compared efficacy of bDMARDs in JIA and polyarticular JIA, respectively, predated to 2016.[23,25] In both cases, a contrast-based method was used, for both the parallel trial and RWT. In an RWT, the treatment contrast reflects longer versus shorter treatment on the bDMARD rather than the bDMARD versus non-bDMARD control. By adopting a novel Bayesian arm-based approach, our study was able to compare outcomes of bDMARDs/JAKi versus cDMARD control, as well as JAKi versus others. In addition, our study included the newly available treatment (ie, secukinumab and JAKis).

For the RWTs, which contain no classic placebo control arm, only the data reported during the open-lead-in phase were used, given that comparative JIA-ACR70 responses after the start of the study drug were unavailable. Thus, we constructed arm-based Bayesian models under the transitivity assumption and partially pooled participants by drug class. Partial pooling is commonly used in Bayesian meta-analysis, allowing estimates from one study borrowing information from other studies that share a common underlying patient population.[28] Specifically, we assume all arms of the same drug class from both parallel randomized trials and RWTs share similar treatment effects. Thus, we were able to borrow the information from the control arms provided from

parallel studies, given that the same control treatment effect was expected, even though the RWTs did not involve a control arm.

The study findings were consistent with previous research in that bDMARDs presented similar safety profiles.[23] The effectiveness of bDMARDs is evident when compared with the cDMARD therapies, but no significant pairwise comparisons were observed among all bDMARDs. For the two JAKis considered, we did not find any significant differences in neither safety nor efficacy outcomes compared with bDMARDs from both main and sensitivity analyses. The indirect comparisons of efficacy between tofacitinib and control was marginally statistically significant at $P < 0.05$ in the NMA of all 16 trials and became significant after removing the 1 trial deemed high risk of bias. Sensitivity analysis in the subset of 13 trials, after excluding 3 trials conducted in patients with ERA or PsA, suggested similar but less significant results, which is likely due to diminished study power given the reduced sample size and/or potential heterogeneous treatment effect.

In contrast to JIA, numerous head-to-head trials have been conducted for adult patients with rheumatoid arthritis (RA) with respect to adalimumab.[29] Among the bDMARDs and JAKis examined in this study, tocilizumab[30] and baricitnib[31] have been found to be superior to adalimumab for patients with RA, whereas tofacitinib[32] and abatacept[33] have shown to be comparable to adalimumab. An NMA that pooled these head-to-head trials found no significant pairwise comparison, consistent with our findings.[29] The safety profile of tocilizumab[30] and abatacept[33] were similar to that of adalimumab from clinical trials, but cardiovascular and other safety signals have emerged for tofacitinib and baricitnib from a safety clinical trial[34] and real-world evidence,[35] respectively. For patients with JIA, future NMA studies could focus on specific adverse events, such as incidence rate of major adverse cardiac events, malignance, and infection, to determine whether similar safety signals can be identified.

The study has some important limitations. Although transitivity assumption is commonly adopted in NMA, violation of the assumption can lead to significant inconsistency within the network. When both direct and indirect evidence is available, consistency can be assessed between the two sets of evidence. In this study, the node-split approach for inconsistency evaluation did not identify any statistically significant evidence for the inconsistency. However, an insignificant inconsistency test does not rule out deviation from the transitivity assumption. JIA is a heterogeneous mixture of arthropathies; even patients within a single JIA subtype demonstrate a range of treatment responses. Secondly, the differences in the trial design and samples may raise concerns over transitivity assumption. Our sensitivity analyses showed that most results of NMA indirect comparisons remain consistent, whereas numerical results could be somewhat sensitive. Lastly, the analysis of safety outcomes in this study only included what was available in the clinical trials, so the analysis does not have the ability to assess late toxicity or rare adverse events. Future studies should consider meta-analyses of individual participant data. The validity of the transitivity assumption in a network can be understood better when the individual participant data are available. Further, it can better quantify causal effect with respect to a target population and heterogeneous treatment effect.[37,38] New NMA methods development is needed to account for trial-level confounding.

In conclusion, we conducted a novel meta-analysis to indirectly compare different options of bDMARDs and JAKis for the treatment of nsJIA using a Bayesian arm-based method. The approach allows for synthesizing trial results from both parallel trial and RWT and comparisons of all the currently approved treatments including JAKi versus bDMARDs, as well as cDMARD control. Similar to previous findings,[23] our analyses did not reveal any statistically significant difference among the advanced treatment options for patients with nsJIA in terms of both efficacy and safety outcomes. New in this study, comparisons between JAKi and control arms did not show a statistically significant difference. The study is limited by the analyses using arm-level data from randomized trial only. Meta-analyses of individual participant data are required to fully account for heterogeneity of the JIA condition. Future study may also consider including nonexperimental studies to compare clinical effectiveness in the general patient population.

AUTHOR CONTRIBUTIONS

All authors contributed to at least one of the following manuscript preparation roles: conceptualization AND/OR methodology, software, investigation, formal analysis, data curation, visualization, and validation AND drafting or reviewing/editing the final draft. As corresponding author, Dr Huang confirms that all authors have provided the final approval of the version to be published and takes responsibility for the affirmations regarding article submission (eg, not under consideration by another journal), the integrity of the data presented, and the statements regarding compliance with institutional review board/Declaration of Helsinki requirements.

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