Review

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Literature analysis and implication of biologic therapy for children with non-systemic juvenile idiopathic arthritis in real-world settings

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SUMMARY: Juvenile idiopathic arthritis (JIA) is the most common rheumatological disease in children. Besides the more severe systemic form, non-systemic JIA is divided into 5 different subgroups. Polyarticular JIA (polyJIA), particularly rheumatoid factor (RF)-positive, which is defined as the disease involving five or more joints in the first 6 months of disease, has the worst prognosis. Biologic disease-modifying antirheumatic drugs (bDMARDs), particularly tumor necrosis factor inhibitors (TNFi), are the backbone of JIA treatment regimens. This research analyzed the published articles for: *i*) optimal sequence, timing and outcomes; *ii*) comparative effectiveness of various bDMARDs; and *iii*) safety concerns for use of bDMARDs. For patients with polyJIA, early effective treatment with bDMARDs is associated with drug-free remission, lower disease activity, better disease control and outcomes. Adalimumab, etanercept and tocilizumab have comparable effectiveness for treating polyJIA, and these drugs are also well-tolerated. JIA patients had a higher rate of hospitalized/serious infection and malignancy compared to the general population. The use of TNFi did not seem to significantly increase this risk further when compared to using methotrexate. Patients treated with IL-1 inhibitors or IL-6 inhibitors reported significantly more serious infections, compared with patients treated with TNFi. Clinicians and patients should consider potential risk in light of benefits of bDMARDs. The reimbursement policy and pricing issue of bDMARDs are out of the scope of the present literature analysis. The current review may help inform shared decision-making discussions between families and physicians as they weigh the risks and benefits of various treatment approaches for children with JIA.

Keywords: juvenile idiopathic arthritis, disease-modifying antirheumatic drugs, DMARDs, biologics, children

1. Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatological disease in children and has a prevalence of 1–4 per 1,000 (*1-7*). It is a heterogeneous collection of inflammatory arthritis diseases that begin before the age of 16 and persist for at least 6 weeks during which no other cause is identified (*8*). JIA is associated with short- and long-term disability due to its progressive destruction of cartilage and bones within joints (*9-11*). Around 50% of children with JIA continue to have the active form of the disease in adulthood, causing physical disability and impaired health-related quality of life (*11-13*).

Besides the more severe systemic form, non-systemic JIA is divided into 5 different subgroups, namely oligoarticular, polyarticular, enthesitis-related, psoriatic, and undifferentiated arthritis according to the International League of Associations for Rheumatology (ILAR) (*8*). Table 1 exhibits the major characteristics of these various subtypes of non-systemic JIA (*14*). Polyarticular JIA (polyJIA) is defined as the disease involving five or more joints. A polyarticular course of JIA could occur in most of these categories. Prior research indicated that polyJIA, particularly Rheumatoid Factor (RF)- positive has a worse prognosis and are less likely to achieve disease remission (*15-17*).

First-line pharmacotherapy for JIA usually consists of a combination of nonsteroidal anti-inflammatory drugs (NSAIDs), intra-articular glucocorticoids, and conventional synthetic disease-modifying antirheumatic drugs (csDMARDs), with methotrexate (MTX) being the most frequently used agent (*14*). In 2019, the American College of Rheumatology (ACR) and Arthritis Foundation updated treatment guidelines for JIA from their 2011 version, which defined patient populations by multiple clinical phenotypes (*18*). In the 2019, and then again in the 2021, treatment guidelines, NSAID monotherapy was removed as first-line treatment for polyarthritis (*19*). For patients with the presence of certain risk factors, such as joint damage or positive anti-cyclic citrullinated peptide (CCP) antibodies, biologic DMARDs (bDMARDs) could be the next first-line

Table 1. Main characteristics of various non-systemic JIA subtypes

Subtype	Gender Predominance	Adult Equivalent Type	Major Physical Findings	Major Lab Findings
Oligoarticular (OA)	Female	NA	• Usually, ≤ 4 joints affected and mostly large joints • Asymmetric, often only a single joint (*e.g.*, knee)	60% ANA positivity
Polyarticular (PA) (RF positive)	Female	Sero-Negative Rheumatoid Arthritis	• Usually, ≥ 5 joints affected • Affected both small and large joints; can be either symmetric or asymmetric • Most common affecting TMJ or cervical spine	40% ANA positivity
Polyarticular (PA) (RF negative)	Female	Rheumatoid Factor (RF) positive Rheumatoid Arthritis	• Usually, ≥ 5 joints affected • Mostly symmetric • Affecting mainly small joints (*e.g.*, wrists and metacarpophalangeal joints) • Aggressive and erosive progression	40% ANA positivity; Rheumatic Factor positivity; Anti CCP positivity
Enthesitis-related Arthritis (ERA)	Male	Spondylarthritis	• Affecting mostly lower limb joints affected with axial involvement • Most commonly affect joints are sacroiliac joint, hip or shoulder	45-85% HLA-B27 positivity
Psoriatic arthritis (PsA)	Equal gender	Psoriatic Arthritis	• Asymmetric arthritis • Affects both small and large joints	50% ANA positivity

treatment for polyJIA. This is an area of active research where what patients are most likely to benefit from initial bDMARDs is still being determined.

bDMARDs are powerful medications and JIA treatment has been improved dramatically with the introduction of the tumor necrosis factor inhibitors (TNFi) (*20*). Currently, TNFi are the backbone of JIA treatment regimens. TNFi are divided into two classes: monoclonal anti-TNF antibodies [adalimumab (ADA), golimumab (GOL), infliximab (INF), and certolizumab pegol (CER)] and receptor fusion proteins [etanercept (ETA)].

Besides TNFi, other bDMARDs include Interleukin-1 (IL-1) inhibitors (anakinra (ANA), canakinumab (CAN), and rilonacept), IL-6 inhibitors (tocilizumab (TOC), sarilumab) and T-cell inhibitors (abatacept (ABA)) (*14*). Janus kinase inhibitors (JAKi) (tofacitinib, baricitinib, upadacitinib) are a newer class of drug, considered non-biologic DMARDs (or targeted synthetic DMARDs) for the treatment of JIA.

The expanded list of therapies available for JIA increases the complexity of treatment decisions for physicians and patients. The primary goals of treatment for JIA are to control inflammatory signs and symptoms, prevent joint damage and disease progression and achieve disease remission. However, not all patients respond to the first prescribed bDMARDs. The 2011 ACR guidelines recommended switching from one TNFi to another as one treatment approach (*21*). The 2019 ACR guidelines stated that switching to a non-TNFi is conditionally recommended over switching to a second TNFi, as a second TNFi may be appropriate for patients who had a good initial response to the first TNFi (*18*). Prior research indicated that ~17% of patients with JIA switched at least twice, and the most common reason for switching was inefficacy (57%) (*22*). The optimal choice of a second bDMARD remains unclear. No head-to-head trials have been conducted to compare the efficacy or effectiveness of bDMARDs.

In addition, the optimal sequence and timing of csDMARDs and bDMARDs administration in polyJIA patients needs to be further assessed to understand which patients are most likely to benefit from initial bDMARD therapy. Adverse events (AEs) associated with long term use of bDMARDs and targeted synthetic DMARDs need to be further assessed. A recent systematic review of contraindications and special warnings provided by EMA and FDA for bDMARDs and targeted synthetic DMARDs indicates that TNFi, IL-1i, IL-6i and JAKi all had contraindications and/or warning related to serious infections and malignancy (*23*). For JAK inhibitors, other warnings included major adverse cardiac events and thromboembolic events.

The objective of this article was to highlight recent developments on emergent topics related to use of bDMARDs among children with non-systemic JIA in real-world settings. We first described real-world studies that examined the optimal sequence and timing of csDMARDs and bDMARDs administration and associated outcomes in JIA or polyJIA patients. We then summarized real-world studies that examined comparative effectiveness, including treatment response, remission rate, drug adherence and persistence among polyJIA patients who received various bDMARDs. Lastly, we highlighted findings from real-world studies that assessed serious infections and malignancy for use of bDMARDs among JIA patients.

2. Research design and literature search strategy

2.1. Literature search

The literature search was conducted using the database PubMed and Google Scholar to identify English language studies in humans that had the predefined key search terms in their title, abstract, or full text and were published from 2004 to 2024. Two review authors (AF, XY) independently screened articles to determine eligibility. Review articles, case reports, studies in children with systemic JIA, studies with different focuses, and articles that were published before 2004 were removed.

Articles were further assessed for quality and those that met the following criteria were retained: *i*) Study objectives were clearly stated, *ii*) Study population was clearly specified and defined, *iii*) The exposure measures (independent variables) were clearly defined, *iv*) The outcome measures (dependent variables) were clearly defined, *v*) Key potential confounding variables were measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s), *vi*) Limitations of the study were included.

Final articles were chosen through consensus process and discrepancies were resolved through discussion. Figure 1 shows a flowsheet of literature review and study selection for analysis.

2.2. Optimal sequence and timing

A combination of search terms – "biologics", "bDMARDs", "timing", "frequency", "pattern", "combination therapy", "juvenile idiopathic arthritis", "polyarticular JIA" – were used. A total of 52 articles were found. After removing non-relevant articles, six studies were retained for the topic of optimal sequence and timing of csDMARDs and bDMARDs administration.

2.3. Comparative effectiveness

A combination of search terms – "biologics", "bDMARDs", "comparative effectiveness", "treatment response", "remission", "drug adherence", "drug persistence", "juvenile idiopathic arthritis", "polyarticular JIA" – were used. A total of 42 articles were found. After removing non-relevant articles, five studies were retained.

2.4. Safety

A combination of search terms – "biologics", "bDMARDs", "serious infections", "medically important infections", "malignancy", "cancer", "juvenile idiopathic arthritis", "polyarticular JIA" – were used. A total of 26 articles were found. After removing non-relevant articles, nine studies were retained.

3. Key findings based on a literature analysis

3.1. Optimal sequence and timing of csDMARDs and bDMARDs administration

The studies that assessed optimal sequence and timing of csDMARDs and bDMARDs are summarized in Table 2. The Start Time Optimization of Biologics in Polyarticular JIA (STOP-JIA) was a prospective, observational Childhood Arthritis and Rheumatology Research Alliance (CARRA) patient registry (*24*). The study compared the effectiveness of three different treatment plans for untreated polyJIA: *i*) Step-Up Plan (initial csDMARD monotherapy with a bDMARD added later if necessary), *ii*) Early Combination Plan (csDMARDs and bDMARDs started together), and *iii*) bDMARDs First Plan (bDMARDs monotherapy). Overall, the study

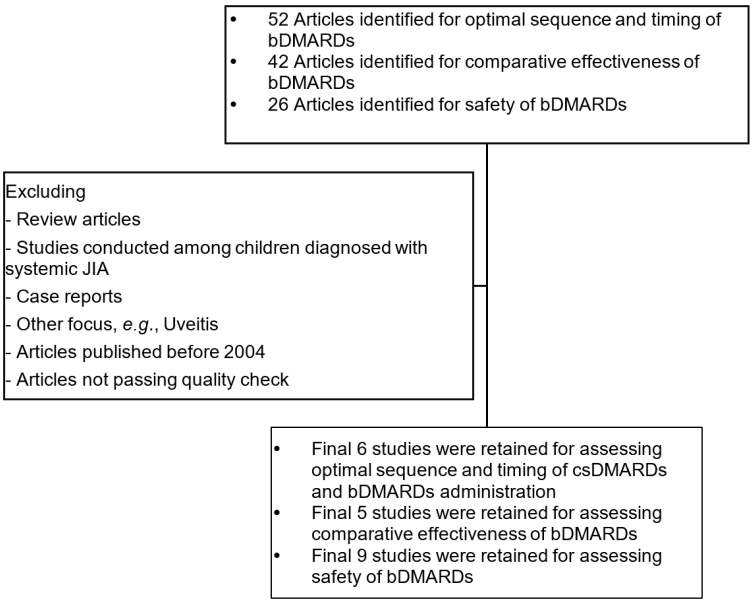

Figure 1. Flowsheet of literature review and study selection for analysis.

found no significant differences between the groups in achieving the ACR provisional criteria for clinical inactive disease without glucocorticoids at 12 months. However, there was a significantly greater likelihood of early combination therapy achieving inactive disease according to the clinical Juvenile Arthritis Disease Activity Score 10 (JADAS10) and ACR Pedi 70.

JADAS-10 is a less stringent categorization of disease inactivity. ACR criteria reflect disease inactivity at only one point in time, which may be transient, and may not be the most important target outcome. JADAS-10 may be a better target outcome than clinically inactive disease according to the ACR criteria. A potential benefit of the early combination therapy based on the clinical JADAS-10 merits additional evaluation in future studies. These results show that for many patients with polyJIA, earlier bDMARD treatment may result in more immediate improvement, but the impact on long-term outcomes remains unproven.

The effectiveness of early aggressive use of csDMARD+bDMARD versus the conservative strategy was assessed using the electronic medical record (EMR) system for treating children with newly diagnosed polyarticular course JIA in at a large US Midwest pediatric rheumatology clinic from 2009 to 2018 (*25*). Study results suggest that, compared with csDMARD only, early aggressive use of bDMARD achieves more than two points of additional reduction in disease activity at 6 months. In contrast, adding bDMARD after 6 months to the initial treatment provides very little added benefit. The study suggests timing matters, early use of bDMARDs is more effective than delayed bDMARD use in achieving early and sustained improvement in treating children with newly diagnosed polyarticular course of JIA.

Table 2. studies assessing optimal sequence and timing of csDMARDs and bDMARDs

Author	Year Published	Data Source	Patient Population	Sample Size	Major Findings
Minden *et al.* (*27*)	2019	German BIKER Registry	JIA	701	Early bDMARD treatment is associated with better disease control & outcomes. Patients categorized in 3 groups based on time from symptoms onset to bDMARD start (G1: ≤ 2 yrs, G2: > 2 to ≤ 5 yrs, and G3: > 5 yrs). At 10-yr mark, G1 pts (18.5%) more likely in drug-free remission than G2 (10.1%) & G3 (4.9%). G1 pts also had lower disease activity than G3 pts (cJADAS10 = 4.9 *vs.* 7.1), better overall well-being (18.2% *vs.* 8.4%), and higher functional status (59.2% *vs.* 43.7%). G1 pts also required arthroplasty less frequently than G3 pts and had lower disease activity over time than both G2 & G3 pts.
Huang *et al.* (*25*)	2020	EMRs of Cincinnati Children Hospital	Polyarticular JIA	2,082	Compared with csDMARD alone, early aggressive use of bDMARD in treating pts with polyJIA soon after diagnosis achieves > 2 points of additional reduction in disease activity at 6 months. Adding bDMARD after 6 months provides little added benefit.
Kimura *et al.* (*24*)	2021	CARRA Patient Registry	Polyarticular JIA	401	No sig differences among groups in achieving the ACR provisional criteria for clinical inactive disease without glucocorticoids in 1 yr. However, a significantly greater likelihood of early combination therapy achieving inactive disease according to cJADAS-10 & ACR Pedi 70.
Yue *et al.* (*26*)	2021	EMRs of Cincinnati Children Hospital	Polyarticular JIA	821	The timing of bDMARD initiation was influenced by factors such as # of joints with limited range of motion, erythrocyte sedimentation rate, and JIA category. % of pts using bDMARDs within 3 months of diagnosis each yr exhibited a positive correlation with the proportion of pts achieving inactive/low disease outcomes each yr for polyarthritis pts.
Montag *et al.* (*28*)	2022	JuMBO Registry	JIA	1,306	JIA patients with a late start of bDMARDs were significantly more likely to use DMARDs and other medications in adulthood than those with early bDMARD treatment. Early effective treatment in JIA can reduce the need for multiple meds in adulthood.
Ramos *et al.* (*29*)	2023	Rheumatic Diseases Portuguese Register (Reuma.pt)	JIA	361	The patients were categorized into three groups based on the time between disease onset and bDMARD initiation: ≤ 2 years, 2–5 years, and > 5 years. Patients who began bDMARD treatment >5 yrs after disease onset were less likely to achieve drug-free remission (OR = 0.24; 95% CI: 0.06 – 0.92; $p = 0.038$). These patients also had a greater physical disability, worse HRQoL, and required more joint surgeries compared to those who started treatment earlier.

Another study using the same data source was conducted to investigate time to initiation of bDMARDs, and evaluate the impact of clinical and other baseline factors associated with the time to first bDMARD in treating children with newly diagnosed non-systemic JIA (*26*). The study found that the timing of bDMARD initiation is influenced by multiple factors such as the number of joints with limited range of motion, erythrocyte sedimentation rate, and JIA category. The percentage of patients using bDMARDs within 3 months of diagnosis each year exhibited a positive correlation with the proportion of patients achieving inactive/low disease outcomes each year for polyJIA patients.

To assess long-term outcomes associated with early bDMARD treatment, a study was conducted to assess whether the time of bDMARD initiation determined the outcomes of JIA in young adulthood using data from the German JIA biologic register BiKER (biologics in pediatric rheumatology) and JuMBO (Juvenile Arthritis Methotrexate/Biologics Long-Term Observation) registry (*27*). The researchers concluded that early bDMARD treatment is associated with drug-free remission, better disease control and outcomes in adulthood.

A subsequent study was conducted to evaluate medication and disease burden of young adults with JIA JuMBO registry (*28*). The authors concluded that early effective treatment in JIA can reduce the need for multiple medications in adulthood.

In summary, the collective data above underscore the importance of early and aggressive bDMARD treatment in managing polyarticular course of JIA. Early effective treatment with bDMARDs is associated with drug-free remission, lower disease activity, better disease control and outcomes, as well as reducing the need for multiple medications and joint surgeries in adulthood.

3.2. Comparative effectiveness of bDMARDs

The efficacy of bDMARDs such as ADA, ETA, or TOC for the treatment of polyJIA was well established in placebo-controlled trials, but no head-to-head trials have been conducted to compare their efficacy or effectiveness. Observational study design approaches using real-world data are useful to assess comparative effectiveness of these drugs. In addition, treatment persistence computed from real-world data has been considered a surrogate for long-term clinical effectiveness. Poor persistence and adherence have been found to reduce effectiveness of bDMARDs among rheumatoid arthritis (RA) patients (*30*). Below is the summary from real-world studies that examined comparative effectiveness of bDMARDs, including treatment response, remission rate, drug adherence and persistence among polyJIA patients who received various bDMARDs (Table 3).

One analysis was conducted using data from the German BIKER registry to assess comparative effectiveness among patients with polyJIA who started treatment with ADA (n = 236), ETA (n = 419), or TOC (n = 74) from 2011 to 2015 (*31*). A propensity score was computed based on baseline characteristics of each study cohort and an inverse probability of treatment weight (IPTW) was used to create balanced samples of patients. Overall, the researchers concluded that ETA, ADA, and TOC had comparable efficacy for treating polyJIA, and these drugs are also well-tolerated. Treatment adherence was highest among patients receiving TOC and lowest among those receiving ADA.

Another study investigated the treatment effectiveness, safety and drug survival among bDMARD with or without MTX for the treatment of polyJIA using the German BIKER registry (*32*). Efficacy of MTX for the treatment of JIA is established; however, use of MTX needs to be carefully monitored, as a small percentage of patients developed elevated liver enzymes (*33*). In this study, 1464 patients received combination therapy and 684 patients received monotherapy. The bDMARDs include ETA, ADA, TOC, and GOL. A propensity score was computed and IPTW method was used to create balanced samples of patients. The results showed a significant decline in disease activity among patients undergoing combination therapy compared to those on bDMARD monotherapy. The authors concluded that administering additional MTX enhances the effectiveness of bDMARD treatment in polyJIA without seriously affecting safety profile.

Another analysis utilizing longitudinal patient-level data extracted from the EMR at Cincinnati Children's hospital from 2009 to 2018 was conducted to investigate the effectiveness and persistence of TNFi *vs.* non-TNFi among newly diagnosed non-systemic JIA patients following the initiation of bDMARD (*34*). The propensity score approach and IPTW analysis were also performed for this study. Overall, undergoing TNFi experienced a significantly greater reduction in cJADAS at the 6-month visit compared to patients in the non-TNFi cohort. However, the study did not identify significant differences in the effectiveness of TNFi *vs.* non-TNFi after 12 months of treatment.

Dara from the "Pharmacovigilance in JIA patients treated with biologic agents and/or MTX" (Pharmachild) registry was used to assess if ETA and ADA have a differential effect on patient-reported well-being in non-systemic JIA (*35*). The authors concluded that both ETA and ADA improve well-being in non-systemic JIA, with a slightly stronger effect for ETA.

A single-center, retrospective analysis of the EMR from the Wilhelmina Children's Hospital (Utrecht, The Netherlands) was conducted to assess medication prescription patterns for JIA patients receiving systemic therapy (*36*). The results showed that conventional synthetic DMARDs were prescribed to almost all patients with non-systemic JIA (99.5%), while 43.9% received a bDMARD (mostly ADA or ETA). Remission was the most common reason for both bDMARD and

Table 3. Studies assessing effectiveness of bDMARDs in patients with polyarticular JIA

Author	Year Published	Data Source	Patient Population	Sample Size	Major Findings
Horneff *et al.* (*31*)	2016	German BIKER Registry	Polyarticular JIA	729 Patients (ETA 419, ADA 236, TOC *n* = 74).	Pediatric ACR30/50/70/90 improvement was achieved by ETA (68%/60%/42%/24%), ADA (67%/59%/43%/27%) and TOC (61%/52%/35%/26%) in 3 months. JADAS minimal disease activity was achieved by ETA (61.3%), ADA (52.4%) and TOC (52.4%) in 24 months. JADAS remission was achieved in ETA (34.8%), ADA (27.9%) and TOC (27.9%). There were no statistically significant differences between the three groups in these outcomes, after adjusting for baseline differences between the three cohorts. Lastly, ETA (49.4%), ADA (60.4%), and TOC (31.1%) of patients discontinued therapy, respectively.
Thiele *et al.* (*32*)	2023	German BIKER Registry	Polyarticular JIA	2,148 Patients (684 bDMARD monotherapy, 1,464 combination with MTX)	A significant decline in disease activity among patients undergoing MTX combination *vs*. bDMARD monotherapy. Patients who received TNFi experienced greater benefits from the additional MTX compared to patients receiving TOC. Median survival time of bDMARD was significantly longer in the combination group (3.1 years) than in the monotherapy group (2.7 years).
Yue *et al.* (*34*)	2021	EMR of Cincinnati Children Hospital	Non-sJIA	667 patients	Median persistence of the first-line bDMARD is 320 days, with TNFi having longer persistence than the non-TNFi (395 *vs.* 320 days). Reduction in the clinical Juvenile Disease Activity Score (cJADAS) of TNFi users was significantly higher than non-TNFi users (6.6 *vs*. 3.0) during a 6-month follow-up.
van Straalen *et al.* (*35*)	2022	International Pharmachild Registry	Non-sJIA	134 patients before propensity sore matching (45 ETA and ADA matched patients)	The estimated mean difference in changes in visual analogue scale (VAS) well-being score from baseline for ETA versus ADA was 0.89 (95% CI: -0.01 – 1.78; $p=0.06$). Both ETA and ADA improved patient-reported well-being in non-systemic JIA, with a slightly stronger effect for ETA.
Kip *et al.* (*36*)	2023	EMR of Wilhelmina Children's Hospital	Non-sJIA	236 patients	Remission was the most common reason for both bDMARD and csDMARD discontinuation (44.7%), followed by AEs (28.9%) and ineffectiveness (22.1%).

synthetic DMARD discontinuation (44.7%), followed by AEs (28.9%) and ineffectiveness (22.1%).

In summary, administering additional MTX enhances the effectiveness of bDMARD in polyJIA without seriously affecting safety profile. ADA, ETA and TOC have comparable efficacy for treating polyJIA, and these drugs are also well-tolerated. The reduction in disease activity, as indicated by clinical JADAS for TNFi users was significant greater compared with non-TNFi users at 6-month follow-up visit. Nevertheless, no significant differences in the effectiveness of TNFi *vs.* non-TNFi were recorded after 12 months of treatment. Significantly more patients discontinued ADA due to inefficacy, and significantly more patients discontinued ETS due to remission. A small percent (2–6%) of patients discontinued these drugs due to intolerance.

3.3. Safety of bDMARDs

Infections (either serious or medically important) are one of the most common AEs occurring among JIA patients receiving bDMARDs. Due to immunosuppressive effects, bDMARDs may be associated with an increased risk of infections. In addition, most JIA patients receive additional immunosuppressive medications, which may also contribute to an increased risk of infections.

In addition, there are significant concerns about the potential increased rate of malignancy associated with the use of TNFi. Malignancy was first reported by the FDA in 2009 (*37*). There are limitations in this analysis. It did not account for a possible increased risk of malignancy associated with the underlying conditions being treated with TNFi or the increased risk associated with other immunosuppressive drugs, *e.g.*, thiopurines.

bDMARDs, including TNFi, IL-1i, IL-6i all have contraindications and/or warnings related to serious infections and malignancy (*23*). The placebo-controlled trials of ETA, ADA and GOL did not show an increased number of infection or serious infections in patients with non-systemic JIA (*38-40*). Use of TOC was associated

with an increased risk of infections in trials (*41*). Findings on malignancy and other rare AEs associated with bDMARDs from clinical trials are limited. Real-world data is useful to monitor long-term safety of bDMARDs.

Results from real-world studies that assessed serious infections and malignancy among patients receiving bDMARDs are summarized in Table 4.

3.3.1. Serious infections

Risk of serious infections was assessed among JIA patients under treatment of ETA, ADA, and MTX using the data from the German BIKER Registry (*42*). The researchers concluded that the overall rate of serious infections reported was relatively low. Treatment with ETA or ADA slightly increased the risk of serious infections compared to MTX among these patients. Disease activity, as indicated by cJADAS10, was identified as an independent risk factor.

The long-term safety of various bDMARDs (ABA, ADA, ETA, GOL, INF and TOC) was examined for patients with polyJIA using data from the German BIKER registry (*43*). Among 3,873 patients included in the analysis, patients with GOL and MTX combination treatment had the highest rate of medically important infections (5.32 per 100 person-years; 95% CI: 2.2–12.8). It may be related to the low number of patients on GOL (n = 86) included in this analysis. The lowest rate was observed in bDMARD-naïve patients with MTX. Rates in patients undergoing other treatments were comparable. No significant differences in the occurrence of medically important infections were found between patients receiving any TNFi and patients receiving TOC.

Additional analyses were conducted to examine whether treatment with IL-1i (ANA, CAN), IL-6i (TOC), TNFi (ADA, ETA, GOL, INF) and ABA was associated with an increased risk of common infections, infections requiring hospitalization (SAE) among JIA patients using the data from the German BIKER Registry (*44*). IL-1i and IL-6i cohorts had significantly more infections and serious infections, compared to TNFi cohort. The influencing covariates identified for various infectious diseases include the use of corticosteroids, younger age, cardiac comorbidities and higher JIA-activity, this is useful for the choice of a suitable bDMARD for treating JIA.

One study examined the safety of adding MTX to bDMARD treatment among patients with polyJIA using data from the German BIKER registry (*32*). The authors concluded additional MTX moderately affected AE occurrence, primarily due to increased incidence of GI and hepatic AEs. An equal rate of SAEs was found between both cohorts.

All the above analyses conducted were based on the data from the German BIKER registry. Results from other data sources are described below:

The STRIVE registry was designed to evaluate safety and effectiveness of ADA with/without MTX *vs.* MTX monotherapy using new user designs in patients with polyarticular-course of JIA from 16 countries (*45*). Serious infection rates were slightly higher in the ADA ± MTX arm. Similar to those from the German BIKER registry, the authors concluded that ADA with/without MTX is well tolerated.

One study was conducted using the U.S. Medicaid data to assess hospitalized infections among JIA patients who initiated TNFi, ANA and MTX (*46*). The results showed no increased risk of infection associated with TNFi monotherapy *vs.* MTX or with TNFi+MTX combination therapy *vs.* MTX. Baseline high-dose oral glucocorticoid use (defined as ≥ 10 mg/day of prednisone) was associated with infection. ANA was significantly associated with infection, compared with MTX.

Another study was conducted to examine the risk of serious bacterial infection requiring hospitalization among children with JIA who initiated monotherapy with TNFi or csDMARD using the Truven Health MarketScan Commercial Claims and Encounters database (*47*). The results showed that new use of TNFi was associated with a 2.7-fold increase in risk of serious bacterial infection *vs.* new use of csDMARD (aHR = 2.72, 95% CI: 1.08–6.86), adjusting for potential confounders obtained through high-dimensional propensity scores (HDPS) method and time-varying corticosteroid use.

In summary, although most studies indicated that no increased risk of serious infection associated with TNFi monotherapy *vs.* MTX or with TNFi+MTX combination therapy *vs.* MTX. One study showed new use of TNFi was associated with a 2.7-fold increase in risk of serious bacterial infection *vs.* new use of csDMARD in children with JIA. Patients treated with IL-1i or IL-6i reported significantly more infections, compared with patients treated with TNFi. The influencing covariates/factors identified for various infectious diseases include the use of corticosteroids, younger age, cardiac comorbidities and higher JIA-activity. This information is useful in deciding on a suitable bDMARD for treating JIA.

3.3.2. Malignancies

Cases of suspected malignancies documented in patients treated for JIA in the German BIKER Registry were assessed (*48*). A total of 12 suspected cases of malignancies were identified, with 7 being lymphomas. The authors concluded that the occurrence of malignancies in JIA patients was higher than in the general population. Whether JIA patients had an increased risk for malignancies from rheumatic disease, or related to their treatment remains unclear. They did not observe an increase in the rate of malignancy following ETA use compared to no TNFi use.

A retrospective cohort study was conducted among

Table 4. Studies assessing safety of bDMARDs in patients with JIA

Author	Year Published	Data Source	Patient Population	Sample Size	Serious Infections	Malignancies	Other Adverse Events
Horneff *et al.* (*48*)	2016	German BIKER Registry	JIA	3,695 JIA patients, totaling 13,198 observation years, the analysis spanning until December 31, 2015	NA	1 patients had received MTX, while 9 patients were exposed to bDMARDs: 1 received ETA, 6 received ETA+MTX, 1 received ETA+ADA+MTX, and one patient underwent a sequence of treatments with MTX, ADA, ETA, INF and ABA. A total of 12 suspected cases of malignancies were identified, with 7 being lymphomas. Use of etanercept did not appear to further elevate the risk.	NA
Beukelman *et al.* (*46*)	2016	Medicaid claim database	JIA	3,075 new MTX users, 2,713 new TNFi users and 247 new ANA users	No increased risk of hospitalized infection by all organisms associated with TNFi monotherapy or with TNFi+MTX combination therapy *vs.* MTX (adjusted hazard ratio (aHR) 1.19, 95% CI: 0.72, 1.94; 1.23, 95% CI: 0.69, 2.17, respectively). Baseline high-dose oral glucocorticoid was associated with infection (aHR 2.03, 95% CI: 1.21, 3.39).	NA	NA
Becker *et al.* (*42*)	2017	German BIKER Registry	JIA	3,350 patients for 5,919 observation-years	Treatment with ETA or ADA slightly increased the risk of serious infections compared to MTX among these patients (MTX *vs.* ETA *vs.* ADA = 1.6 *vs.* 8.1 *vs.* 9.7/1,000 person-years).	NA	NA
Beukelman *et al.* (*49*)	2018	Medicaid and MarketScan claims database	JIA, pediatric inflammatory bowel disease (pIBD) and pediatric plaque psoriasis (pPsO)	15,598 children with TNFi use and 73,839 with no TNFi use	NA	There was no significantly increased risk of malignancy among children undergoing treatment with TNFi compared to those receiving other treatments. However, it did show a doubled risk of malignancy in children with JIA overall when compared to an age-matched control of patients with an unrelated condition (standardized incidence risk (SIR): JIA + TNFi: 3.1 (95% CI: 1.3–6.1), JIA without TNFi: 2.1 (95% CI: 1.1–3.5), Control: 0.97 (95% CI: 0.91–1.05).	NA

*Outcomes were not statistically powered.

Table 4. Studies assessing safety of bDMARDs in patients with JIA (continued)

Author	Year Published	Data Source	Patient Population	Sample Size	Serious Infections	Malignancies	Other Adverse Events
Lee *et al.* (*47*)	2018	MarketScan claims database	JIA	482 TNFi initiators and 2013 csDMARD initiators; TNFis included ETA, ADA, INF, CER, GOL, csDMARDs included MTX, hydroxychloroquine (HCQ), sulfasalazine (SSZ) and leflunomide (LEF))	TNFi initiators were associated with an increased risk of serious bacterial infection compared with csDMARDs initiators (aHR 2.72, 95% CI: 1.08–6.86), adjusting for potential confounders obtained through high-dimensional propensity scores (HDPS) method and time-varying corticosteroid use.	NA	NA
Brunner *et al.* (*45*)	2020	STRIVE Registry	Polyarticular JIA	838 patients (MTX 301; ADA ± MTX 537)*	Serious infection rates were slightly higher in the ADA ± MTX arm (MTX: 1.5 events/100 patient-years; ADA ± MTX: 2.0 evens/100 patient-years). ADA ± MTX is well tolerated.	NA	Common AEs included nausea, sinusitis, and vomiting for MTX monotherapy while arthritis, upper respiratory tract infection, sinusitis, tonsillitis, and injection site pain reported in the ADA ± MTX patients.
Klein *et al.* (*43*)	2020	German BIKER Registry	Polyarticular JIA	3,873 patients with a cumulative exposure to bDMARDs of 7467 years	No significant differences in occurrence of medically important infections were found between patients receiving any TNFi and patients receiving TOC (RR = 0.85, 95% CI: 0.27–2.70).	Eight cases of malignancy were reported but the significance remains unclear.	The most common AEs were uveitis (n = 231) and medically important infections (n = 101). Cytopenia and elevation of transaminases were more frequently reported for patients on TOC.
Thiele *et al.* (*44*)	2021	German BIKER Registry	JIA	3,258 patients – TNFi 3044, IL-1i 105, IL-6i 400 and T-cell activation inhibitors 105	Patients treated with IL-1i or IL-6i reported significantly more infections (IR = 17.3, 95% CI: 12.5–24; IR = 16.7, 95% CI: 13.9–20), compared with patients treated with TNFi (IR = 8.7, 95% CI: 8.1–9.4). Infections classified as SAEs also occurred more frequently in the IL-1i or IL-6i cohorts.	NA	Incidence of herpes zoster and varicella was higher in patients on TNFi. Other opportunistic infections were rare.
Thiele *et al.* (*32*)	2023	German BIKER Registry	Polyarticular JIA	2,148 Patients (684 bDMARDs monotherapy, 1,464 combination with MTX); bDMARDs included ADA, ETA, GOL, and TOC	NA	NA	1,757 AEs reported, most commonly viral upper respiratory infections, GI disorders (*e.g.* nausea), and transaminase elevation, with 116 classified as SAEs. A higher incidence of AEs in patients on combination therapy was observed. No significant differences in the rate of SAEs between the two groups.

*Outcomes were not statistically powered.

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children with JIA, pediatric inflammatory bowel disease (pIBD) and pediatric plaque psoriasis (pPsO) using the US Medicaid and MarketScan database to assess risk of malignancies among TNFi users compared with no TNFi use (*49*). The study revealed that there was no significantly increased risk of malignancy among children undergoing treatment with TNFi compared to those receiving other treatments. However, it did show a doubled risk of malignancy in children with JIA overall when compared to an age-matched control of patients with an unrelated condition.

In summary, children diagnosed with JIA had a higher rate of malignancy compared to the general population. The use of TNFi did not seem to significantly increase this risk further when compared to not using TNFi.

4. Discussion

4.1. Biologic therapy for children with non-systemic JIA

The current review summarizes studies that examined the optimal sequence and timing of csDMARDs and bDMARDs administration, comparative effectiveness and safety concerns of these agents in JIA or polyJIA patients in real-world settings.

The collective data from several real-world studies support that early effective treatment with bDMARDs in managing polyarticular course of JIA is associated with drug-free remission, lower disease activity, better disease control and outcomes, as well as reduce the need for multiple medications and joint surgeries in adulthood.

In addition, real-world studies showed that administering additional MTX enhances the effectiveness of bDMARDs treatment in polyJIA without seriously affecting safety profile. ADA, ETA and TOC have comparable efficacy for treating polyJIA, and these drugs are also well-tolerated. The reduction in disease activity, for TNFi users was significant greater compared with non-TNFi users at 6-month follow-up visit.

With regards to safety of bDMARDs, patients treated with IL-1i or IL-6i reported significantly more infections, compared with patients treated with TNFi. Most studies indicated that there was no increased risk of serious infection associated with TNFi in children with JIA. However, one study showed new use of TNFi was associated with a 2.7-fold increase in risk of serious bacterial infection *vs.* new use of csDMARD in children with JIA. This study might have overestimated the TNFi–infection relationship. As TNFi are indicated for moderately to severely active polyJIA, JIA severity was likely higher in the TNFi group. JIA patients who were not currently taking MTX or TNFi were found to have a 2-fold increase in the rate of hospitalized bacterial infection, compared to a comparator cohort of children without JIA after adjusting for potential confounders (*50*). The inflammatory or autoimmune process of JIA may predispose children to infection in the absence of therapy (*51*). Similar findings have also been observed in adults with RA (*52*).

Regarding malignancy, children diagnosed with JIA had a higher rate of malignancy compared to the general population. The use of TNFi did not seem to significantly increase this risk further when compared to not using TNFi.

4.2. Limitations of real-world evidence

Limitations of the observational study design including missing data and confounding by indication (*53*) should be noted. First, there are differences in baseline characteristics between the two groups, the early bDMARD group had more patients with RF-positive polyJIA and enthesitis-related arthritis and had higher disease activities, which may be associated with worse outcome measures. Although statistical methods, such as propensity score method were used to adjust for potential bias, residual bias (*54*) may still be present. When assessing comparative effectiveness of bDMARDs, it is important to know that unmeasured confounders, such as physician behavior, patients' comorbidities, insurance reimbursement policies, that were not considered in the analyses may have affected the treatment assignment to patients and associated outcomes.

In addition, some studies included a small number of patients, low sample size plus missing data resulted in few analyzable patients to assess outcomes. Multiple imputation (*55*) was employed to impute missing values. It should be noted that multiple imputations rely on the assumption missing at random, *i.e.*, missing values depend on observed data only.

For studies using EMR, records of actual medication dispensing and treatment adherence are not available. Also, a common approach adopted in clinics is that physicians may prescribe a bDMARD after patients receive 3 months of MTX. Studies that were based on a single center have limited generalizability.

4.3. Clinical implications

The influencing covariates/factors identified for various infectious diseases include the use of corticosteroids, younger age, cardiac comorbidities and higher JIA-activity. This information is useful in deciding on a suitable bDMARD for treating JIA. Patients who have one or more of these factors should be monitored closely regarding infections.

For the use of corticosteroids, compared with no use of corticosteroids, use of high-dose oral corticosteroids (≥ 10 mg prednisone daily) was consistently and independently associated with a more than doubling of the rate of subsequent infection. Similar findings have been observed in adults with RA (*56*). One implication is that the use of steroid-sparing treatment strategies may

reduce the risk of serious infections in children with JIA.

Overall, clinicians and patients need to balance the benefits of these highly effective bDMARDs against the risk of infection they pose. To minimize potential risk, risk management plan should incorporate appropriate screening, monitoring and withholding of treatment as needed to mitigate the potential harm to children with JIA.

4.4. Future research

For future direction, long-term outcomes from early effective treatment with bDMARDs in children with JIA warrant further assessment. Future studies may also further evaluate the various benefits and detriments of newly approved bDMARDS, especially in a large population to ensure the appropriate use of these therapies.

In addition, long-term assessment of JIA patients treated with bDMARDs into adulthood is an important task. Further studies incorporating a larger cohort of children with JIA would further characterize the risk of serious infection and malignancy across individual TNFi medication.

4.5. Future perspectives

The current review did not include new classes of drugs, such as JAK inhibitors (JAKi). Although they provide a useful alternative for some patients, JAKi, including tofacitinib, baricitinib and upadacitinib have a boxed warning regarding risk of cardiovascular disease (CVD), venous thromboembolic events (VTE) and its use should be limited to those failing or intolerant of TNFi. Safety signals from adult RA tofacitinib trials warrant caution, currently data on risk of CVD and VTE in pediatric patients are limited. Future research to assess the risk of CVD/VTE among patients receiving JAKi in real-world settings is necessary before its routine use in patients with JIA.

In conclusion, for patients with polyJIA, early effective treatment with bDMARDs may result in more immediate improvement including drug-free remission, lower disease activity, better disease control and outcomes. Potential impacts on long-term outcomes warrant further assessment.

Additional MTX enhances the effectiveness of bDMARDs treatment in polyJIA without seriously affecting safety profile. ADA, ETA and TOC have comparable efficacy for treating polyJIA, and these drugs are also well-tolerated.

Children with JIA have higher rates of serious infection than children without JIA independent of the treatment effect. The use of TNFi did not seem to significantly increase risk of serious infection further when compared to using MTX. Patients treated with IL-1i or IL-6i reported significantly more infections, compared with patients treated with TNFi. In addition, children diagnosed with JIA had a higher rate of malignancy compared to the general population. The use of TNFi did not seem to significantly increase this risk further when compared to using MTX.

Clinicians and patients should consider potential risk in light of the benefits of bDMARDs. The reimbursement policy and pricing issue of bDMARDs are out of the scope of the present literature analysis. The current review may inform shared decision-making discussions between families and physicians as they weigh the risks and benefits of various treatment approaches for children with JIA.

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