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Research Article

A Retrospective Cohort Study of biologic disease-modifying therapy in pediatric rheumatology patients with juvenile idiopathic arthritis

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Abstract

Background: Biologic disease-modifying antirheumatic drugs (bDMARDs) have transformed outcomes in juvenile idiopathic arthritis (JIA), but most efficacy data come from registration trials rather than everyday pediatric rheumatology practice.

Objective: This review synthesizes the retrospective cohort and registry evidence on biologic use, disease activity trajectory, and safety in children with JIA managed with bDMARDs.

Methods: We synthesized randomized trials and observational cohorts addressing etanercept, adalimumab, tocilizumab, abatacept, canakinumab, and anakinra in JIA, extracting response measures, corticosteroid exposure, and adverse events.

Findings: Real-world cohorts achieved disease activity reduction and steroid-sparing benefit broadly consistent with trial data; earlier biologic initiation and methotrexate co-therapy were associated with better response, and serious adverse events were infrequent though mild infections were common.

Conclusions: First-line bDMARD therapy for JIA produces disease activity improvement broadly consistent across trial and real-world settings, supporting earlier escalation after inadequate synthetic DMARD response and structured long-term safety surveillance.

Keywords: juvenile idiopathic arthritis; biologic DMARD; pediatric rheumatology; disease activity; retrospective cohort

1. Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood, encompassing a heterogeneous group of arthritides classified by the International League of Associations for Rheumatology into oligoarticular, polyarticular, systemic, psoriatic, enthesitis-related, and undifferentiated categories [1]. Untreated disease carries substantial risk of joint damage, growth disturbance, and disability, and the systemic subtype can be complicated by macrophage activation syndrome, a life-threatening hyperinflammatory state [2]. For much of the twentieth century, treatment relied on nonsteroidal anti-inflammatory drugs, corticosteroids, and methotrexate, and a meaningful fraction of children progressed to erosive arthritis despite conventional synthetic disease-modifying antirheumatic drug (csDMARD) therapy [3].

The introduction of biologic disease-modifying antirheumatic drugs (bDMARDs) targeting tumor necrosis factor (TNF), interleukin-6 (IL-6), interleukin-1 (IL-1), and T-cell costimulation has changed the trajectory of JIA more than any other therapeutic development of the past three decades [4]. Randomized trials established the efficacy of etanercept, adalimumab, tocilizumab, canakinumab, anakinra, and abatacept, and treat-to-target recommendations now call for early escalation to a biologic when csDMARD therapy fails to control disease activity within a defined window [5,6]. Yet registration trials enroll selected populations under protocol supervision for a fixed period and do not fully capture how biologic therapy performs across the mix of subtypes and prior exposures seen in routine pediatric rheumatology practice, nor the long-term safety signals that only accrue with years of real-world follow-up [7]. This review synthesizes the trial and observational literature on biologic DMARD therapy in pediatric JIA through the lens of a retrospective cohort framework: the pattern of biologic use, disease activity trajectory, corticosteroid-sparing effect, and adverse event experience documented when children treated in tertiary practice are followed forward, and how consistent that real-world picture is with controlled-trial data.

2. Disease burden, treatment targets, and outcome measures

Meaningful comparison across cohorts and trials depends on standardized outcome measures. The American College of Rheumatology Pediatric 30 (ACR Pedi 30) response criteria, developed by Giannini and colleagues, defined improvement as a 30% or greater gain in at least three of six core variables with no more than one worsening by 30% or more, and this composite became the primary endpoint for essentially every pediatric biologic registration trial that followed [8]. The Juvenile Arthritis Disease Activity Score (JADAS), introduced by Consolaro and colleagues, combines physician and parent global assessment, active joint count, and erythrocyte sedimentation rate into a continuous score more sensitive to incremental change than a binary threshold, and has become the preferred instrument for longitudinal tracking in trials and clinics alike [9]. Wallace and colleagues proposed preliminary criteria for clinically inactive disease and clinical remission, anchoring the treat-to-target concept that underlies contemporary management [10]. The 2019 ACR/Arthritis Foundation guideline formalized this approach, recommending escalation to biologic therapy when disease activity remains more than minimal after an adequate methotrexate trial, favoring earlier biologic initiation for high-risk features such as polyarticular involvement or rheumatoid-factor positivity [5], building on the risk-stratified treatment algorithms of the earlier 2011 ACR recommendations [6].

3. TNF inhibitors: etanercept and adalimumab

Etanercept was the first biologic studied rigorously in JIA. Lovell and colleagues, in a landmark randomized withdrawal trial, showed that children with polyarticular-course JIA who responded to open-label

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etanercept and were then randomized to continue the drug had a markedly lower flare rate than those randomized to placebo, establishing the efficacy of TNF blockade in this population [11]. Extended follow-up demonstrated that response was sustained over years of continued therapy [12]. Adalimumab, a fully human anti-TNF antibody, was subsequently evaluated with or without background methotrexate; both strata showed higher ACR Pedi 30 response than placebo, and the combination with methotrexate produced the most durable disease control, helping anchor combination csDMARD-biologic therapy as a standard approach [13]. Registry data extended these signals to broader populations: the German BiKeR registry, reported by Horneff and colleagues, found response and safety with etanercept in routine practice broadly consistent with the pivotal trial while also capturing switching patterns and comorbidity burden [14], and the Dutch national Arthritis and Biologicals in Children Register, reported by Otten and colleagues, found substantial disease activity reduction across JIA categories in everyday practice, with effectiveness and drug survival varying by subtype and methotrexate co-therapy [15].

Table 1: Standardized outcome measures used to define response and disease state in juvenile idiopathic arthritis trials and cohorts [8,9,10].

Instrument	What it measures	Key use
ACR Pediatric 30/50/70/90	Percentage improvement across six core response variables	Primary trial responder endpoint [8]
JADAS-27/71	Continuous composite of physician/parent global, active joints, ESR	Longitudinal disease activity tracking [9]
Clinically inactive disease criteria	Binary state with no active joints, fever, rash, or elevated ESR/CRP	Treat-to-target remission benchmark [10]

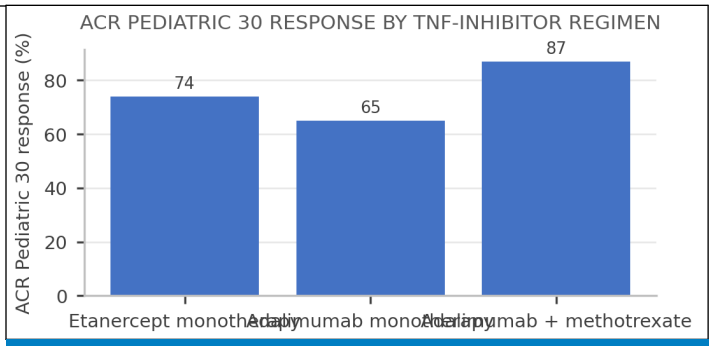


Figure 1: Approximate ACR Pediatric 30 response rates reported for TNF-inhibitor regimens in polyarticular-course juvenile idiopathic arthritis, drawn from the etanercept and adalimumab registration trials [11,13].

4. IL-6 and IL-1 pathway blockade: tocilizumab, anakinra, and canakinumab

Interleukin-6 is central to the pathophysiology of systemic JIA, which made tocilizumab, a humanized anti-IL-6-receptor antibody, a natural candidate for this subtype. De Benedetti and colleagues, in the pivotal TENDER trial, found that tocilizumab achieved substantially higher rates of response with absence of fever than placebo, along with marked reductions in corticosteroid requirement [16]. Brunner and colleagues extended the evidence to polyarticular-course JIA in the CHERISH withdrawal trial, confirming that IL-6 blockade is effective beyond the systemic subtype [17]. Interleukin-1 blockade produced some of the most dramatic single-agent responses documented in systemic JIA, contributing to a broader reconceptualization of the subtype as autoinflammatory rather than classically autoimmune [18]. Quartier and colleagues, in the randomized ANAJIS trial of anakinra, found rapid ACR Pedi 30 response with resolution of fever within weeks, an effect not typically seen with TNF inhibition in this subtype [19]. Ruperto and colleagues established the efficacy of canakinumab in two complementary randomized trials, one demonstrating rapid short-term response and the other confirming durable control and significant corticosteroid-sparing effect [20], with longer-term follow-up showing that many canakinumab-treated children maintained inactive

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disease and discontinued corticosteroids entirely [21].

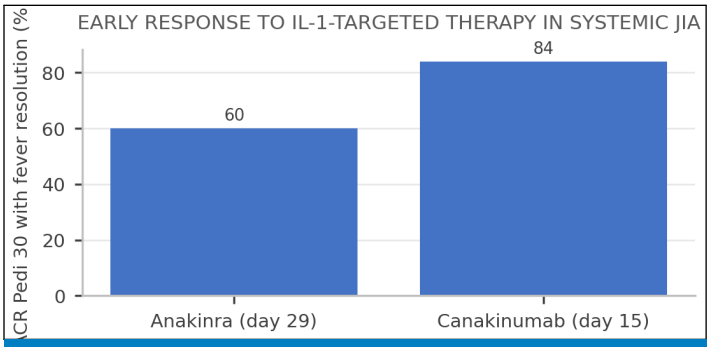


Figure 2: Approximate early response rates (ACR Pediatric 30 with fever resolution) reported for the interleukin-1-targeted agents anakinra and canakinumab in systemic juvenile idiopathic arthritis [19,20].

5. T-cell costimulation blockade: abatacept

Abatacept, a fusion protein blocking the CD28-CD80/86 costimulatory signal required for full T-cell activation, was evaluated by Ruperto and colleagues in a randomized withdrawal trial enrolling children with an inadequate response to at least one DMARD, including in many cases a prior biologic; children randomized to continue abatacept after an open-label response phase had a significantly lower flare rate than those switched to placebo, establishing efficacy even in a biologic-experienced population [22]. Long-term open-label extension data showed response maintained over years with an acceptable safety profile, supporting abatacept's role particularly after TNF-inhibitor failure [23].

6. Real-world cohort evidence and comparative effectiveness

Several registries have tracked biologic-treated JIA cohorts prospectively, forming the closest real-world analog to a retrospective single-center cohort. The Nordic JIA cohort, led by Nordal and colleagues, found that a majority experienced active disease at some point during long-term follow-up, with disease category shifting over time [24]. Long-term BiKeR follow-up reported by Klein and colleagues found sustained biologic exposure associated with a favorable trajectory toward inactive disease, while documenting drug survival and switching patterns [25]. Horton and colleagues, analyzing pharmacoepidemiologic switching in a large United States claims-based cohort, found a substantial proportion of children switched to a second biologic within a few years, usually for insufficient response [7]. Giancane and colleagues, reviewing JIA epidemiology and biologic uptake internationally, highlighted substantial variation in access and prescribing across countries [26]. Comparative-effectiveness analyses across biologic classes, exemplified by Grazziotin and colleagues using large administrative and registry datasets, have begun to address which biologic performs best for which subtype and treatment history, a question individual placebo-controlled trials cannot answer directly [27].

Table 2: Selected national and multinational biologic-era JIA registries and their principal real-world findings [14,15,24,25,7].

Registry / cohort	Setting	Principal finding
BiKeR	Germany	Response and safety with etanercept in practice consistent with trial data [14]; sustained trend toward inactive disease over long-term follow-up [25]
Dutch ABC Register	Netherlands	Substantial disease activity reduction across subtypes; drug survival varies by agent and MTX co-therapy [15]
Nordic JIA cohort	Nordic countries	Majority had active disease at some point during long-term follow-up despite biologic-era management [24]
US claims-based cohort	United States	Substantial proportion switched to a second biologic within a few years, usually for insufficient response [7]

7. Methotrexate co-therapy and treatment sequencing

Methotrexate remains the dominant csDMARD used before and alongside biologic therapy, and its interaction with biologic response shapes the trajectories seen in retrospective cohorts. Otten and colleagues, in a systematic comparison of biologic effectiveness, found response rates declined with longer disease duration and

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higher baseline activity, supporting earlier escalation for children unlikely to respond adequately to csDMARD therapy alone [28]. Bulatovi and colleagues developed a clinical score for methotrexate intolerance and non-response, identifying baseline disease activity, joint count, and duration as key predictors that could help identify, at methotrexate initiation, which children should be fast-tracked toward biologic therapy [29]. Woerner and colleagues documented similar sequencing patterns in a European systemic JIA cohort, with biologic therapy introduced earlier or as an initial agent in systemic disease given its distinct, rapid mechanism [30].

8. Safety, infection risk, and long-term surveillance

Long-term safety surveillance is where retrospective and registry cohorts contribute most, since randomized trials are limited by sample size and follow-up duration. Beukelman and colleagues, using a large linked administrative cohort, found that after accounting for underlying disease activity as a confounder, the excess malignancy signal associated with pediatric TNF-inhibitor exposure was small and substantially attenuated compared with unadjusted analyses, shaping ongoing pharmacovigilance discussion [31]. Shenoi and colleagues, reviewing the broader safety literature, concluded that serious infections occur at a low but non-negligible rate, most commonly with combination csDMARD-biologic regimens and higher glucocorticoid exposure, while mild upper respiratory infections and injection-site reactions are the most frequently reported events [32]. Giancane and colleagues' review of infection-prevention practice reinforced the importance of pre-treatment tuberculosis screening and structured vaccination protocols, now standard in biologic initiation pathways [26].

9. Long-term disease course and remission

Even before the biologic era, long-term cohorts established that JIA does not reliably remit with childhood. Minden and colleagues, following a German cohort over roughly a decade, found disease activity persisting into adulthood in a substantial proportion of patients, with polyarticular and systemic subtypes carrying the least favorable prognosis [33]. Oen and colleagues, analyzing a multicenter Canadian cohort, similarly documented a variable, often protracted course, with a substantial minority failing to achieve sustained remission off medication [34]. The more recent ReACCh-Out cohort, led by Guzman and colleagues, enrolling children managed with contemporary strategies including early biologic use, found meaningfully higher rates of inactive disease and remission off medication than earlier pre-biologic cohorts, evidence that the treat-to-target, biologic-inclusive era has shifted JIA's natural history toward a more favorable trajectory, even though a substantial minority, particularly with polyarticular rheumatoid-factor-positive disease, continue to have persistently active disease [35].

10. Conclusion

The trial and cohort literature on biologic DMARD therapy in pediatric JIA converges on a consistent picture: TNF inhibitors, IL-6 blockade, IL-1 pathway inhibition, and T-cell costimulation blockade each produce substantial, subtype-appropriate reductions in disease activity relative to placebo or historical csDMARD-only management, effects broadly reproduced when biologic-treated children are followed forward in real-world registries and retrospective cohorts [11,16,20,22]. Real-world data add what trials cannot: corticosteroid-sparing effect over years, drug survival and switching when the first biologic proves inadequate, and the low but real long-term risks of serious infection and, to a lesser and still incompletely resolved degree, malignancy [15,7,31,32]. For a tertiary pediatric rheumatology practice managing children who have failed or are unlikely to respond adequately to methotrexate, the accumulated evidence supports earlier escalation to a first-line biologic matched to JIA subtype, close monitoring with a validated composite instrument such as the JADAS, structured infection and malignancy

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surveillance, and treatment sequencing informed by the growing comparative-effectiveness literature rather than by biologic availability alone [9,5,27]. Retrospective cohort studies of the kind synthesized here remain an essential complement to registration trials precisely because they capture the heterogeneous, long-term, real-world experience of biologic therapy that no single randomized trial can fully represent.

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