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Review Article

Impact of biologic disease-modifying therapy on Quality of Life in Patients with juvenile idiopathic arthritis

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Abstract

Background: Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood, and biologic disease-modifying antirheumatic drugs targeting tumor necrosis factor, interleukin-1, interleukin-6, and T-cell costimulation have transformed disease control across its subtypes since the late 1990s.

Objective: This review synthesizes the published evidence on how biologic therapy affects health-related quality of life in JIA, beyond the joint-count and laboratory endpoints reported in most pivotal trials.

Methods: We synthesized randomized controlled trials, long-term registry cohorts, and validation studies of disability and quality of life instruments in children treated with biologic disease-modifying therapy for JIA.

Findings: Biologic therapy produces durable improvement in disability indices and patient-reported quality of life across subtypes, with the largest relative gains in systemic disease and the smallest, most variable gains in fatigue, pain interference, and family-reported burden; sustained disease control through treat-to-target strategies tracks closely with preserved quality of life over long-term follow-up.

Conclusions: Biologic disease-modifying therapy meaningfully improves quality of life in JIA primarily through sustained control of disease activity and reduced corticosteroid burden, but psychosocial and family-level domains require attention alongside joint-focused treatment targets to fully realize the benefit of modern therapy.

Keywords: juvenile idiopathic arthritis; biologic therapy; quality of life; disease-modifying antirheumatic drugs; pediatric rheumatology

1. Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood, encompassing a heterogeneous group of arthritides that begin before age sixteen and persist for at least six weeks after other causes are excluded [1]. The International League of Associations for Rheumatology classification divides JIA into oligoarticular, polyarticular, systemic, psoriatic, enthesitis-related, and undifferentiated categories, each with a distinct course but a shared potential for joint damage, growth disturbance, and functional impairment if inflammation is not controlled early [2]. Long-term cohorts from the pre-biologic era documented that a substantial proportion of children with JIA carried active disease or functional limitation into adulthood, with polyarticular and systemic subtypes at greatest risk [3].

The therapeutic landscape changed decisively with biologic disease-modifying antirheumatic drugs (bDMARDs) targeting tumor necrosis factor (TNF), interleukin-1 (IL-1), interleukin-6 (IL-6), and T-cell costimulation. Etanercept was the first biologic shown in a randomized withdrawal trial to control polyarticular JIA refractory to methotrexate [4], followed within a decade by infliximab [5], adalimumab [6], abatacept [7], and, for systemic JIA, the IL-6 antagonist tocilizumab [8,9] and the IL-1 antagonists anakinra and canakinumab [10,11]. These agents produced pediatric ACR response rates [12] far exceeding conventional synthetic DMARDs, and disease activity, joint counts, and acute-phase reactants became the standard trial endpoints.

Clinical response, however, is not the same as a return to normal life. Health-related quality of life (HRQoL) captures the physical, emotional, social, and school-related consequences of chronic arthritis, and it is this outcome, more than a joint count, that determines whether treatment is judged successful by patients themselves [13,14]. This review synthesizes the evidence on how biologic therapy has affected HRQoL in JIA: the

instruments used to measure it, the magnitude and durability of improvement with individual agents, the psychosocial and family domains beyond joint-focused outcomes, and the safety and treat-to-target considerations shaping current practice.

2. Burden of disease and rationale for biologic therapy

Before biologics were widely available, JIA carried a well-documented burden of functional disability, pain, growth impairment, and psychosocial disruption despite conventional treatment with nonsteroidal anti-inflammatory drugs, intra-articular corticosteroids, and methotrexate. Long-term outcome studies found that between a quarter and a half of patients with polyarticular or systemic disease had active arthritis, joint damage, or functional limitation ten or more years after diagnosis [3,15]. Uncontrolled systemic inflammation was also linked to growth retardation, osteopenia, and, in systemic JIA, macrophage activation syndrome, a life-threatening complication that further amplified disease burden [15].

The rationale for biologic therapy rests on the principle that cytokine-driven synovitis, if suppressed early and sustained, prevents the joint damage and functional decline that defined the pre-biologic era. Pascual and colleagues showed that serum from children with active systemic JIA induced IL-1-dependent gene expression in healthy monocytes and that response to IL-1 blockade tracked this biomarker signature, providing mechanistic support for targeting IL-1 in this subtype [10]. Parallel work implicating IL-6 in the systemic features of fever, rash, and acute-phase response justified IL-6-directed therapy [8,9]. For polyarticular disease, TNF has long been recognized as a central driver of synovial inflammation, the rationale behind the TNF inhibitors that remain the most widely used biologic class in JIA [4].

3. Biologic agents and clinical efficacy in JIA

Randomized controlled trials over the past two and a half decades have established biologic efficacy across JIA

subtypes. Etanercept, a soluble TNF receptor fusion protein, was studied in a randomized withdrawal design in which responders to open-label treatment later randomized to placebo flared significantly more often and more quickly than those continued on etanercept, a design that became the template for subsequent pediatric rheumatology trials [4]. Infliximab combined with methotrexate produced ACR Pediatric 30 responses in most treated children with polyarticular-course JIA, though the placebo-controlled phase was complicated by an unexpectedly high placebo response rate [5]. Adalimumab, studied with and without background methotrexate, showed durable ACR Pediatric 30/50/70/90 responses through 48 weeks, including in the methotrexate-naïve subgroup [6]. Abatacept, a T-cell costimulation modulator, was effective in children who had failed at least one prior biologic, with long-term extension data confirming sustained response and acceptable safety over several years [7,16].

Table 1: Pivotal randomized trials underlying biologic selection in juvenile idiopathic arthritis, by target and subtype [4,5,6,7,9,11,17].			
Agent	Target	Principal indication	Key trial finding
Etanercept	TNF (soluble receptor)	Polyarticular JIA	Significantly fewer/slower flares on continued therapy vs placebo withdrawal [4]
Infliximab	TNF (mono clonal antibody)	Polyarticular-course JIA	Majority achieved ACR Pedi 30 with methotrexate co-therapy [5]
Adalimumab	TNF (mono clonal antibody)	Polyarticular JIA; JIA-associated uveitis	Durable ACR Pedi response to 48 weeks; reduced uveitis treatment failure [6,17]
Abatacept	T-cell costimulation (CTLA4-Ig)	TNF-inhibitor-refractory polyarticular JIA	Effective after prior biologic failure; sustained long-term response [7]
Tocilizumab	IL-6 receptor	Systemic and polyarticular-course JIA	ACR Pedi 30 with fever resolution in systemic JIA [9]
Canakinumab	IL-1 beta	Systemic JIA	Rapid resolution of systemic features; corticosteroid tapering [11]

For systemic JIA, where TNF inhibitors have shown modest efficacy, IL-1 and IL-6 blockade transformed outcomes. Tocilizumab produced ACR Pediatric 30 responses with fever resolution in most children with active systemic JIA [9]. Canakinumab, a long-acting anti-IL-1-beta antibody, produced rapid resolution of systemic features and allowed corticosteroid tapering in two pivotal trials, cementing IL-1 blockade as a preferred first-line strategy for the systemic phenotype [11]. Adalimumab has also shown efficacy for JIA-associated chronic anterior uveitis, reducing treatment failure substantially compared with methotrexate alone in the SYCAMORE trial, a benefit not captured by joint-focused outcome measures but highly relevant to overall quality of life [17]. Table 1 summarizes the pivotal trials underlying current biologic selection by JIA subtype.

4. Measuring quality of life in JIA

Interpreting the effect of biologic therapy on quality of life depends on the instrument used, since generic and disease-specific tools capture different aspects of a child's experience. The Childhood Health Assessment Questionnaire (CHAQ), adapted from the adult Health Assessment Questionnaire, measures functional disability across eight domains and remains the most widely used disease-specific functional outcome in JIA trials, including the pivotal biologic trials themselves [18]. The Child Health Questionnaire (CHQ) is a broader generic health-status instrument capturing physical and psychosocial domains, while the Pediatric Quality of Life Inventory (PedsQL), including its Rheumatology Module, was designed specifically to assess symptom burden, treatment side effects, and worry in children with rheumatic disease and has shown strong reliability, validity, and responsiveness across cohorts [19,13]. The Juvenile Arthritis Quality of Life Questionnaire (JAQQ) was developed as a responsive, disease-specific index intended to detect clinically meaningful change over short treatment intervals, making it useful in trial settings [20]. Table 2 summarizes the principal instruments used to

capture quality of life outcomes in the biologic-era JIA literature.

Table 2: Principal instruments used to assess health-related quality of life in juvenile idiopathic arthritis [18,19,13,20].			
Instrument	Domain	Respondent	Typical use
CHAQ	Functional disability (8 activity domains)	Parent/patient proxy	Primary disability endpoint in most biologic trials [18]
CHQ	Generic physical and psychosocial health	Parent proxy	Broad health-status comparison across cohorts [19]
PedsQL Rheumatology Module	Pain, symptoms, treatment worry, communication	Child and parent	Disease-specific quality of life in trials and registries [13]
JAQQ	Gross/fine motor, psychosocial function	Parent-reported, patient-weighted	Responsive index for short-interval treatment trials [20]

Composite disease activity measures have also been developed to complement, rather than replace, these patient-reported tools. The Juvenile Arthritis Disease Activity Score (JADAS) combines physician global assessment, parent/patient global assessment, active joint count, and acute-phase reactant into a single score, and preliminary remission criteria established quantitative thresholds against which biologic response could be benchmarked in trials and registries [21]. Because these composite measures correlate only moderately with patient-reported quality of life, particularly for fatigue, pain, and school participation, most contemporary trials and registries now report physician-oriented and patient-reported outcomes side by side rather than treating one as a proxy for the other [14].

5. Impact of biologic therapy on quality of life outcomes

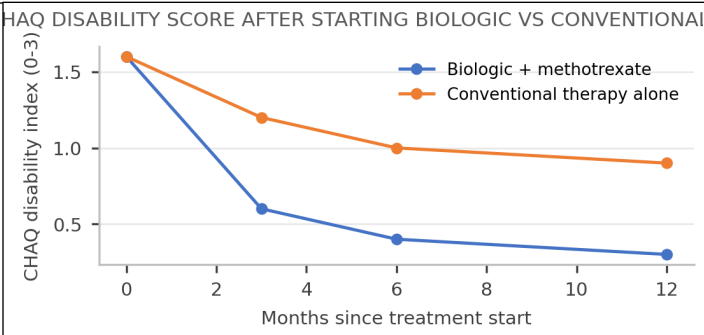


Figure 1: Representative trajectory of functional disability (CHAQ) and generic quality of life (PedsQL) scores in children with polyarticular juvenile idiopathic arthritis started on a TNF inhibitor, showing rapid gains in the first three months and sustained improvement through one year of continued biologic therapy relative to conventional therapy alone [4,6,22].

Across the major randomized trials and the observational registries that followed patients into long-term use, biologic therapy has been associated with clinically meaningful improvement in CHAQ disability scores, PedsQL domain scores, and parent- and child-reported global assessments, generally tracking joint-count and acute-phase-reactant improvement but with a slower, more variable course in psychosocial domains. In the etanercept withdrawal trial, CHAQ disability improved substantially during open-label treatment and was preserved in patients continued on therapy, while those randomized to placebo experienced flare alongside a parallel deterioration in functional status [4]. The adalimumab trial reported similarly durable CHAQ improvement through 48 weeks, with gains concentrated in the first three months and more gradual improvement thereafter [6]. Long-term registry follow-up from the German BiKeR cohort found that functional gains achieved in the first year of biologic therapy were largely sustained over several years, though a meaningful minority discontinued therapy for inadequate response or adverse events, with plateau or reversal of quality of life gains in that subgroup [22,23]. Figure 1 illustrates the general pattern of CHAQ and PedsQL improvement observed across these cohorts relative to conventional therapy.

Systemic JIA, historically the subtype with the greatest quality of life burden owing to fever, rash, growth failure, and corticosteroid dependence, has shown some of the largest relative gains with targeted biologic therapy. Tocilizumab and canakinumab trials both reported rapid resolution of systemic symptoms alongside improved physical function and reduced glucocorticoid exposure, a secondary benefit with substantial implications for growth, bone health, and body-image-related quality of life domains not captured by joint counts alone [9,11]. Determinant analyses of health-related quality of life in JIA cohorts consistently identify disease activity, pain, and corticosteroid burden as the strongest modifiable predictors of poor quality of life, consistent with biologic therapy's benefit operating substantially through disease and steroid-burden control rather than an independent psychosocial mechanism [24].

6. Psychosocial, family, and school functioning outcomes

Quality of life in JIA extends beyond joint function to fatigue, pain interference, school attendance, family strain, and psychological adjustment, domains where biologic therapy has been less uniformly favorable than the improvement seen in disability indices. Fatigue is a prominent, persistent symptom in JIA, present even in children with well-controlled joint disease, and a systematic review found it correlated more strongly with pain, sleep disturbance, and psychosocial factors than with inflammatory markers, implying that biologic control of synovitis alone does not fully resolve this domain [25]. Before the biologic era, school attendance was measurably reduced in children with active juvenile chronic arthritis compared with healthy peers [25].

Family-level burden, including caregiver strain, missed workdays, and out-of-pocket costs, correlates with disease activity and functional disability in web-based survey cohorts, and predictors of poorer family-reported quality of life include younger age at diagnosis, higher pain

scores, and lower family income, factors biologic therapy can partially but not completely offset through disease control [24]. The transition from pediatric to adult rheumatology care is an additional quality of life inflection point for a generation of patients who, unlike earlier cohorts, frequently enter adulthood on continued biologic therapy; unmet training needs among adult providers in adolescent-specific care have been identified as a barrier to maintaining gains achieved during pediatric treatment [26].

7. Safety, treat-to-target, and long-term considerations

The durability of quality of life gains from biologic therapy depends on sustained disease control, which has made treat-to-target strategies increasingly central to JIA management. An international task force convened to develop treat-to-target recommendations for JIA endorsed regular, structured disease-activity assessment with a low threshold for escalation, framing the goal of therapy as inactive disease or remission rather than partial improvement, a strategy expected to maximize both joint outcomes and quality of life [27]. Trials of early aggressive combination therapy, initiating a biologic alongside methotrexate at diagnosis, achieved inactive disease in a majority of patients within six months, suggesting earlier biologic use may shorten the interval of active disease that most directly damages quality of life [28]. Biomarker-guided withdrawal studies have also begun identifying which patients in sustained remission can safely discontinue biologic therapy without early relapse [29].

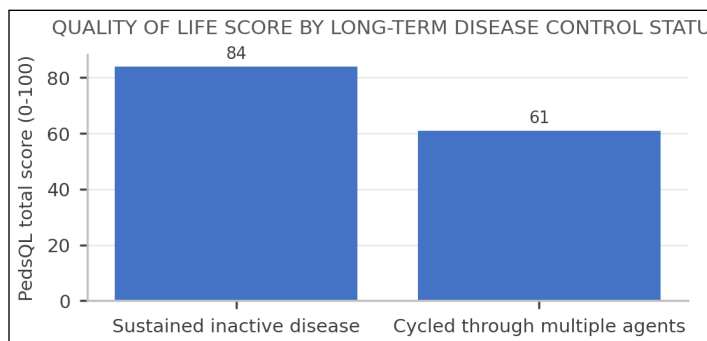


Figure 2: Relationship between sustained clinical inactive disease and quality of life trajectory across long-term biologic registries, with patients maintaining inactive disease showing preserved functional and psychosocial scores compared with those who cycle through multiple agents without sustained remission [27,32,23].

Long-term safety data from national registries have supported this earlier, more sustained use of biologics. Population-based cohort analyses found serious bacterial infection rates modestly elevated with biologic exposure compared with methotrexate alone but low in absolute terms, and malignancy rates in biologic-treated JIA cohorts, after accounting for the elevated baseline malignancy risk of JIA itself, did not show a consistent excess directly attributable to biologic exposure [30,31]. Registry data have also identified a subgroup with biologic-refractory disease who cycle through multiple agents without sustained remission, a group in whom quality of life gains are correspondingly attenuated [32]. Figure 2 summarizes the relationship between sustained disease control and quality of life trajectory across these long-term cohorts.

8. Conclusion

Biologic disease-modifying therapy has fundamentally altered the trajectory of juvenile idiopathic arthritis, converting a disease that historically left a substantial proportion of children with lasting functional impairment into one in which inactive disease and preserved function are realistic treatment goals for most patients [4,27]. The weight of trial and registry evidence across TNF, IL-1, IL-6, and T-cell-costimulation-targeted agents shows consistent, durable improvement in disability indices such as the CHAQ and in generic and disease-specific

quality of life instruments including the PedsQL, CHQ, and JAQQ, improvement that is most pronounced in the domains most directly tied to joint inflammation and least complete in domains such as fatigue, pain interference, and family strain that are only partly explained by measurable disease activity [18,13,25,24]. Sustaining these gains appears to depend less on any single agent than on the strategy surrounding its use: early initiation, structured treat-to-target monitoring, and attention to corticosteroid burden and psychosocial domains alongside joint-focused outcomes [27,28]. Continued long-term registry follow-up, together with quality of life instruments validated specifically for the biologic-treatment era, will be needed to determine how durably these gains are maintained as the first generation of children treated with biologics from diagnosis reaches adulthood [22,26].

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