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Judicious Use of Biologicals in Juvenile Idiopathic Arthritis

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Abstract Juvenile idiopathic arthritis (JIA) is a chronic inflammatory disorder that may cause joint destruction. Biological treatments targeting specific cytokines and cell interactions have transformed the outcomes of JIA. This review focuses on the selection of patients for and the timing and selection of biological treatment in JIA. Tumor necrosis factor (TNF) inhibitors remain the first choice for polyarticular JIA, followed by abatacept and tocilizumab. Monoclonal-antibody TNF inhibitors and abatacept are usually chosen for methotrexate-resistant uveitis. Recent clinical trials of canakinumab, rilonacept, and tocilizumab have obtained great improvement in both systemic and arthritic features in chronic systemic JIA patients. Current guidelines support the early use of a short-acting IL-1 antagonist for macrophage activation syndrome, a life-threatening complication. TREAT and ACUTE studies suggest that a therapeutic window of opportunity during early disease may exist in JIA. Early initiation of biological therapy may be associated with slower progression of joint damage and longer remission.

Keywords Biologicals · Juvenile idiopathic arthritis (JIA) · Juvenile rheumatoid arthritis (JRA) · Disease activity · Tumor-necrosis-factor inhibitor · Abatacept · Etanercept · Adalimumab · Infliximab · Rituximab · Tocilizumab · Canakinumab · Anakinra · Rilonacept · Joint-space narrowing · Joint erosion · Remission · Inactive disease · pACR · Oligoarticular JIA · Polyarticular JIA · Psoriatic JIA · Enthesitis-related arthritis · Systemic JIA · Macrophage activation syndrome · Uveitis · Window of opportunity

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Introduction

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease in children [1]. The etiology of this chronic rheumatic condition remains unclear. Genetic and environmental factors have been associated with the onset of JIA [2–8] but no studies have identified an etiology or cluster of events leading to JIA. Biological treatments have transformed the outcome of JIA from severe joint damage with disability and prolonged active disease to normal joint function with early and sustained remission [9]. JIA is a heterogeneous group of conditions and has been classified into seven categories. The clinical outcomes are variable among different categories and the treatment strategy differs. The available biological treatments, in addition to the non-biological disease-modifying antirheumatic drugs (DMARDs), have shown great promise in restoring joint function in children with JIA. Identifying the appropriate subset of patients for early initiation of biological treatment is an important objective in clinical care of these children. As the evidence from adult rheumatoid arthritis has indicated, biological treatment has transformed joint outcomes and has provided the possibility of early and sustained remission [10]. In a two-year randomized controlled trial of adalimumab plus methotrexate versus the same agents as monotherapy for rheumatoid arthritis, progression of joint erosion and joint-space narrowing was associated with increased disease activity over time. Only the adalimumab plus methotrexate group obtained arrested progression of joint damage. This review presents the current evidence and suggests which patients would benefit from biological treatment, and when and which biological treatment would be most beneficial for patients with JIA.

Which JIA Patients Should Receive Biological Therapy?

Given that the objective of care for JIA is remission of disease and prevention of joint damage, any category of JIA that presents with joint damage (joint erosion or joint-space narrowing) at diagnosis should be treated aggressively to achieve rapid remission and reduce the overall duration of active disease [11]. Longer duration of active arthritis has been associated with more joint damage [12] in juvenile rheumatoid arthritis. Because a higher risk of JIA flare was observed with adalimumab monotherapy than with adalimumab plus methotrexate [13], early aggressive treatment should include methotrexate and biological treatment.

Polyarticular RF-Positive JIA

Polyarticular RF-positive JIA is not a common category and represents approximately 5 % of JIA patients in many cohorts [14]. These children have the worst outcomes, with the lowest remission rates, worse joint damage, worse quality of life, and highest incidence of arthroplasty [15]. They have a similar clinical phenotype, serology, and outcome to RF-positive adult rheumatoid arthritis [16]. A radiographic study in 2003 revealed that, despite DMARD treatment, RF-positive polyarticular JRA had much higher frequencies of joint-space narrowing (79 %) and joint erosion (75 %) than RF-negative polyarticular JRA (43 % and 39 %, respectively), systemic JRA (38 % and 63 %, respectively), and pauciarticular JRA (14 % and 25 %, respectively) 6–9 years after onset [17]. Furthermore, joint-space narrowing was associated with significant functional disability. Because of the low prevalence, there are no dedicated studies reporting the response of exclusively RF-positive JIA patients. Previous clinical trials of polyarticular-course JIA reported approximately 20 % of subjects to have RF positivity [13, 18, 19]. An open-label extension trial of etanercept up to eight years obtained a 100 % ACR 70 Pediatric response regardless of RF positivity [20]. Although this report is subject to selection bias, it seems justifiable to initiate biological treatment at diagnosis of RF-positive polyarticular JIA to reduce later joint damage. Longitudinal studies with radiographic evaluation of the joints of this category of JIA patients are needed to establish joint-protective benefit from biological therapy, as has been revealed for adults with rheumatoid arthritis.

Polyarticular RF-Negative JIA

Polyarticular RF-negative JIA is the main category of JIA included in clinical trials for FDA approval of biological therapy [21]. Even after introduction of contemporary treatment with early use of DMARDs, the probability of achieving clinical remission off medication within five years is only 14 % for this category [22]. Recent data from the TREAT and ACUTE clinical trials revealed a higher incidence of early inactive disease and clinical remission with the combination of a TNF inhibitor and methotrexate compared with methotrexate alone or in combination with hydroxychloroquine and sulfasalazine [23••, 24••]. These investigations reveal that early initiation of biological therapy offers the possibility of shortening the duration of active disease and achieving remission in polyarticular RF-negative JIA.

Enthesitis-Related Arthritis

Children with enthesitis-related arthritis (ERA) have a high risk of axial-joint involvement and disability in long-term follow-up studies [25–29]. In a case-control study, patients with ERA had a higher disability score and more body pain than matched patients with oligoarthritis or polyarthritis after 15 years [30]. The remission rate after 15 years was 44 %, with the frequency of radiographic sacroiliitis being 35 %. This data suggests that patients with ERA and active arthritis should be treated aggressively with biological therapy. A prospective observational study of TNF inhibitors (20 patients on etanercept, two on infliximab) from the Dutch Arthritis and Biologicals in Children Registry observed that 73 % of patients achieved ACR Pediatric 70 improvementat three months [31]. Sixty-three percent of patients achieved inactive disease by 27 months. The most recent open-label trial (CLIPPER) focused on determining the efficacy of etanercept for extended oligo JIA, ERA, and psoriatic arthritis [32•]. At three months, 86 % and 73 % of patients achieved ACR Pediatric 30 improvement and ACR Pediatric 70 improvement, respectively. However, a retrospective study reported a more refractory course in patients with ERA a year after initiation of TNF inhibitor [33]. A newer biological, ustekinumab, which blocks the IL-23 believed to be an important cause of enthesitis in the mouse model [34], significantly reduced inflammation in sacroiliac and spine joints in adult patients with active ankylosing spondylitis after 24 weeks [35•]. Its efficacy in ERA has yet to be tested.

Systemic JIA

Children with systemic JIA may benefit from early initiation of anti-IL-1 therapy, because 11–42 % may have a monophasic course [36, 37]. A retrospective uncontrolled multinational study reported outcomes for systemic-JIA patients when anakinra was used as first-line therapy with or without a DMARD [38•]. Fever and rash resolved within a month in >95 % of patients, and active arthritis persisted in only 27 % at three months. Sixty percent of patients achieved complete response, including eight of 10 receiving anakinra monotherapy. A recent prospective study of anakinra monotherapy as first-line therapy for steroid-naïve systemic-JIA patients used the ACR Pediatric 90 at three months as an indicator to taper anakinra [39•]. Fifteen of 20 patients (75 %) met this criterion to taper the anakinra at three months, and 13 achieved inactive disease off anakinra at one year.

Canakinumab is another anti-IL-1 agent that has been revealed to be an effective treatment for patients with systemic JIA and is approved by FDA and EMA for treatment of systemic JIA. A single injection of canakinumab induced significantly higher rates of ACR Pediatric 30, 50, 70, and 90 improvement than placebo at day 15 for chronic systemic-JIA patients with systemic features [40••]. In the withdrawal phase of the trial for long-term investigation, the canakinumab group had a much lower flare rate (26 % vs. 75 %) than the placebo group [40••]. Rilonacept is another anti-IL-1 agent that is effective in treating systemic JIA. In addition to a pilot study, the recently published RAPPORT investigation revealed that the weekly rilonacept group had a significantly shorter time to response than the placebo group [41••] despite forced taper of prednisone.

Anti-IL-6 blockade has also been documented to be effective for treatment of systemic JIA and is approved by FDA and EMA for treatment of systemic JIA. Tocilizumab infusions every two weeks achieved a significantly higher rate of ACR Pediatric 30, 50, 70, and 90 response (85 % vs. 24 %, 85 % vs. 11 %, 71 % vs. 8 %, and 37 % vs. 5 %, respectively) than placebo at 12 weeks in children with systemic JIA [42••]. At 52 weeks, 80 % of patients receiving tocilizumab had at least ACR Pediatric 70 % improvements with no fever.

The Consensus Treatment Plans for treating new-onset systemic JIA, developed by the Childhood Arthritis and Rheumatology Research Alliance (CARRA), include anti-IL-1 and anti-IL-6 plans as treatment options on the basis of their excellent efficacy [43•]. There may be a window of opportunity for treating systemic JIA during its early phase, before the downstream Th17 pathway is further activated by IL-1 and/or IL-6 [44•]. A biphasic model of systemic JIA has been proposed and argues for earlier initiation of cytokine blockade in systemic JIA to spare these children from a prolonged disease course [44•]. Although the randomized clinical trials of anti-IL-1 and anti-IL-6 primarily included patients with longstanding disease [40••, 45], the efficacy of tocilizumab and canakinumab for new-onset systemic JIA is being investigated through CARRA.

Macrophage Activation Syndrome

Macrophage activation syndrome (MAS) is a life-threatening complication seen primarily in patients with systemic JIA. MAS has a mortality of 20 % and occurs in approximately 10 % of children with systemic JIA [46, 47]. Clinical symptoms include persistent fever, organomegaly, cytopenia, hyperferritinemia, hypofibrinogenemia, hypertriglyceridemia, coagulopathy, and often hemophagocytosis in the bone marrow. Case series have suggested the effectiveness of anakinra for treating MAS secondary to systemic JIA [48, 49]. At 2 mg kg^{-1} day^{-1}, addition of anakinra to steroid, indomethacin, and cyclosporine resolved fever, cytopenia, elevated acute-phase proteins, elevated d dimer, and hyperferritinemia [48, 49]. The poor response of MAS to TNF inhibitors is in line with their lower efficacy in general for systemic JIA. The 2013 update of the ACR guideline recommends glucocorticoid and/or calcineurin inhibitor and/or anakinra as therapeutic options for MAS [50•]. Tocilizumab is being studied for its efficacy for primary hemophagocytic lymphohistiocytosis (HLH) (Clinical trial # NCT02007239). However, its use for MAS in systemic JIA needs further investigation regarding optimum dose and frequency.

Oligoarticular JIA

Oligoarticular JIA is the most common category of JIA, and is frequently treated with initial intraarticular corticosteroid injection with or without oral nonsteroidal anti-inflammatory drugs (NSAIDs) [51•]. Most children in this category may not need biological therapy unless there is severe joint damage [11] and/or persistently active disease despite repeated joint injections or the use of methotrexate [51•]. Extended-oligoarticular-JIA patients, however, are different and have a similar chronic disease course to those with polyarticular RF-negative JIA, and may benefit from early initiation of biological therapy to achieve and maintain clinically inactive disease and remission. A recent open-label study revealed that approximately 60 % of extended-oligoarticular-JIA patients achieved ACR Pediatric 70 improvement after 12 weeks of etanercept and methotrexate [32•].

Uveitis

Uveitis, which can be vision-threatening, affects 21–38 % of children with JIA and is most commonly found in patients with oligoarticular JIA [52, 53]. Because most of these patients are asymptomatic, severe complications including glaucoma, cataract, and significant synechiae may occur by the time of diagnosis. Cataracts occur in 14–84 % of these patients as a result of inflammatory disease or corticosteroid use (topical or oral) [54–59]. Glaucoma, band keratopathy, and posterior synechiae were observed in 7.8–42 %, 6.7–70 %, and 10–58 % of patients, respectively, after a median of 23.5 to 36 months of follow-up [54–59]. As a consequence of these complications, 3.4 % and 5.7 % of patients had impaired visual acuity and blindness, respectively [54]. Monoclonal-antibody TNF inhibitors (adalimumab and infliximab) have been documented to be effective in treating refractory uveitis [60–71]. In JIA patients with uveitis and ocular complications, early initiation of monoclonal-antibody TNF inhibitors enabled rapid remission to preserve the vision. The doses of infliximab required to control uveitis may be as high as 20 mg kg^{-1} [69]. When uveitis was refractory to monoclonal-antibody TNF inhibitors, abatacept infusion at 10 mg kg^{-1} at week 0, 2, and 4 and monthly thereafter obtained improvement in visual acuity, with grading of

anterior chamber cells between two weeks and six months after the first infusion [72–74]. In one investigation, the frequency of uveitis flares decreased from a mean of 3.7 episodes during the six-month period before abatacept initiation to a mean of 0.7 episodes during the six-month period after abatacept initiation [72]. Clinical trials of tocilizumab for uveitis are in progress (clinical trial # NCT01603355, NCT01717170).

Psoriatic JIA

Psoriatic JIA is a heterogeneous category that can present with oligoarticular or polyarticular characteristics at onset, with or without overt psoriasis. These children either have coexisting psoriasis or have at least two of three minor criteria (nail pitting, dactylitis, and first-degree relative with psoriasis) [75]. Joint outcomes of children with psoriatic JIA are similar to those for JIA categories without psoriasis [76]. Children with the polyarticular course (polyarticular at onset or extended oligoarticular) are more likely to have involvement of small joints of the hands and wrist, associated with more frequent contractures, than children with the persistently oligoarticular course or ERA [76]. When treated with etanercept, 50 % of these children achieved ACR Pediatric 70 improvement after 12 weeks in an open-label trial [32•]. The treatment also improved psoriasis by 48 %. Thus, early initiation of anti-TNF therapy is recommended for psoriatic JIA with polyarticular presentation.

When Should a Biological Be Started for a Child with JIA?

The timing of initiating a biological treatment can affect the overall joint outcome and possibility of remission. The concept of "therapeutic window of opportunity" is supported by multiple investigations of adult rheumatoid arthritis. Metaanalysis of relevant studies conducted by Van Niles et al. [77] revealed the relationship between symptom duration at initiation of treatment and joint-damage progression in patients with adult rheumatoid arthritis [78–81]. Prolonged symptom duration before treatment is independently associated with a reduced chance of remission. This is in line with findings from the TREAT trial [24••] that support the hypothesis of "window of opportunity". An early, aggressive treatment regimen including methotrexate, etanercept, and prednisolone induced increased significant, sustainable clinical remission compared with methotrexate alone (21 % vs. 7 %) in polyarticular JIA at 12 months. Furthermore, the chance of achieving clinically inactive disease increased by 1.324 for each month earlier a patient was treated with aggressive therapy. Thus, early diagnosis and early aggressive treatment are the objectives for optimum care of children with polyarticular JIA. Similarly, in the ACUTE study infliximab and methotrexate achieved 100 % ACR Pediatric 75 response, compared with 65 % response in the DMARD COMBO group (methotrexate, sulfasalazine, and hydroxychloroquine) and 50 % response in the methotrexate-alone group, after 54 weeks of open-label trial [23••]. Consensus-derived treatment plans developed by CARRA include early initiation of biological treatments for polyarticular JIA [43•, 82•]. Long-term follow-up is needed to determine if the joint function and lifetime load of therapy are altered by early aggressive treatment.

In adult rheumatoid arthritis, early addition of a TNF inhibitor has led to significantly reduced joint damage and increased discontinuation of biological therapy with sustained low disease activity compared with traditional methotrexate therapy. In a recent study, addition of adalimumab at onset of treatment versus at 26 weeks were compared regarding joint outcomes in patients with a median of 3.6 months of active disease [83•]. Although the late addition of adalimumab for early RA patients achieved similar clinical and functional improvements as earlier addition of adalimumab, radiographic progression was significantly worse in the late-addition group, indicating the importance of early initiation of biological therapy. Another study compared four treatment strategies: sequential DMARDs (methotrexate, sulfasalazine, and leflunomide), step-up DMARDs (methotrexate first, then adding sulfasalazine, hydroxycholoroquine, and prednisone sequentially), combined DMARDs (methotrexate plus sulfasalazine and prednisone), and combined methotrexate and infliximab [84]. Early initiation of infliximab and methotrexate achieved a higher rate of low disease activity (DAS≤ 2.4) than methotrexate monotherapy or combined therapy of methotrexate, sulfasalazine, and hydroxychloroquine after three months of treatment [84]. All patients with persistent disease activity after the first three months of treatment in non-infliximab groups were switched to infliximab plus methotrexate. Infliximab was discontinued when persistent low DAS (≤2.4) was achieved over six months. The number maintaining low disease activity after discontinuation of infliximab was significantly higher in the early-initiation group than the delayed group (64 % vs. 25 %, respectively). Among the patients who discontinued infliximab, 16 of 27 patients (59 %) in the delayed-initiation group and 34 of 77 patients overall (44 %) had to restart infliximab because of flare of disease.

Although many rheumatologists advocate the need to fail methotrexate to avoid exposure to potentially harmful medication, another approach may be to initiate the therapeutic agents most likely to be successful early in the disease course to achieve early remission, avoid joint damage, reduce disability, and lessen the need for prolonged medications. As an example, methotrexate alone achieved clinically inactive

disease (CID) for 23–25 % of patients; whereas early methotrexate and TNF inhibitor achieved CID for 40–68 % of patients after 6–12 months of treatment of JIA patients [23••, 24••].

Which Biological Agent Should Be Given?

Table 1 lists biological therapy commonly used for JIA. The TNF-alpha inhibitors are often the first choice for all categories of JIA except systemic JIA. Etanercept, adalimumab, and infliximab are most commonly used for JIA, but only the first two have been approved by the FDA [13, 19, 85]. Investigations of golimumab and certolizumab pegol for use in poly-course JIA are in progress (clinical trial # NCT01230827, NCT01550003). For JIA patients with the complication of uveitis, adalimumab and infliximab are favored over etanercept.

When a patient does not achieve significant improvement after three months of a TNF inhibitor, a second TNF inhibitor or a different biological category is initiated; the response rate may be lower than that of a biological-naïve patient [86]. After failing two or more TNF inhibitors, initiation of another class of biological, for example abatacept [87] or tocilizumab [42••], is recommended. Subcutaneous use of abatacept and of tocilizumab (clinical trial # NCT01844518 and NCT02165345) are currently being studied in JIA. Rituximab may be useful when a patient has failed other biologicals. An open-label trial of rituximab obtained 40 % ACR Pediatric 70 after 24 weeks, and 93 % ACR Pediatric 70 after 96 weeks (four courses of rituximab) in a group of patients with predominantly systemic JIA [88].

In systemic JIA without MAS, anakinra, rilonacept, canakinumab, and tocilizumab all have documented efficacy [40••, 45, 89]. For patients with the complication of MAS, anakinra has been reported to have rapid efficacy, and can be used intravenously.

The optimum dose of each biological agent has not been well studied. In adult rheumatoid arthritis, there was recent evidence of a target concentration of adalimumab for achieving optimum efficacy. A trough level of 5–8 μg mL^{-1} is sufficient to reach adequate clinical response after 28 weeks of use [90•]. Concomitant use of methotrexate was associated with a significantly higher adalimumab concentration. A higher target concentration may be needed in patients with

Table 1 Current biologicals used in treatment of JIA

Class	Generic name	Mechanism	Recommended dose	Route
TNF inhibitor	Adalimumab	Fully human monoclonal antibody against TNF-α	Wt 15–30 kg: 20 mg every other wk Wt≥30 kg: 40 mg every other wk	SC
	Certolizumab pegol	Pegylated Fab' fragment of a humanized TNF-α monoclonal antibody	Dose not yet identified for JIA. RA: 400 mg at 0, 2, 4 wks, then 200 mg every 2 wks or 400 mg every 4 wks	SC
	Etanercept	Fusion protein of human TNF-α receptor to human IgG	0.8 mg kg^{-1} $dose^{-1}$ once weekly (max dose: 50 mg)	SC
	Golimumab	Fully human monoclonal antibody against TNF-α	Dose not yet identified for JIA. RA, PsA, AS: 50 mg every 4 wks	SC
	Infliximab	Chimeric monoclonal antibody against TNF-α	6–20 mg kg^{-1} $dose^{-1}$ at 0, 2, 6 wks then every 4 wks	IV
IL-1 blockade	Anakinra	Fully human recombinant IL-1 receptor antagonist	1–4 mg kg^{-1} daily	SC/IV
	Rilonacept	IL-1 trap	SJIA: 4.4 mg kg^{-1} wk^{-1} (max dose: 320 mg) loading, then 2.2 mg kg^{-1} wk^{-1} (max dose: 160 mg).	SC
	Canakinumab	Fully humanized anti-IL-1β monoclonal antibody	SJIA: 4 mg kg^{-1} $dose^{-1}$ (max dose: 300 mg) every 4 wks	SC
IL-6 blockade	Tocilizumab	Humanized monoclonal IL-6 receptor antibody	SJIA: Wt<30 kg: 12 mg kg^{-1} $dose^{-1}$ q 2 wks Wt≥30 kg: 8 mg kg^{-1} $dose^{-1}$ q 2 wks (max: 800 mg) pJIA: Wt<30 kg: 12 mg kg^{-1} $dose^{-1}$ q 4 wks Wt≥30 kg: 8 mg kg^{-1} $dose^{-1}$ q 4 wks (max: 800 mg)	IV (SQ being studied)
CTLA-4	Abatacept	Costimulation blocker binding to CD80 and/or CD86	10 mg kg^{-1} with max of 1000 mg at 0, 2, 4 wks and q 4 wks	IV (SQ being studied)
CD 20	Rituximab	Chimeric monoclonal antibody to CD20	750 mg m^{-2} $dose^{-1}$ with max of 1000 mg×2 with 2 wks apart	IV

TNF: tumor necrosis factor, Wt: weight, wk: week, SC: subcutaneous, RA: rheumatoid arthritis, PsA: psoriatic arthritis, AS: ankylosing spondylitis, IL-1: interleukin 1, SJIA: systemic juvenile idiopathic arthritis, IL-6: interleukin 6, CTLA-4: cytotoxic T-lymphocyte antigen 4, CD: cluster of differentiation, IV: intravenous, pJIA: polyarticular juvenile idiopathic arthritis

greater disease activity [91]. For children of different ages, sizes, and disease activity, an individualized dose may be needed for optimum efficacy.

Summary

The outcome of JIA has been transformed by the introduction of biological DMARDs that have excellent efficacy in treating JIA. TNF inhibitors clearly have the widest application in most categories at this time, except for systemic JIA. Anti-IL-1 and anti-IL-6 have proven efficacy in the treatment of systemic JIA. Early initiation of aggressive treatment of JIA may take advantage of the window of opportunity and achieve rapid remission, and thus may alter the course of the disease and lessen the joint damage that may occur. Challenges remaining include the identification of the best dose of biological agent for each patient, identification of biomarkers that can predict response to specific therapy, identification of patients who will not need biological therapy, and strategies to determine the appropriate duration of biological treatment.

Compliance with Ethics Guidelines

Conflict of Interest Yongdong Zhao declares that he has no conflict of interest. Carol Wallace declares that she has received consulting fees from Amgen and Novartis and grants from Amgen and Pfizer.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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