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Current Opinion in Pharmacology

Therapeutic strategies for treating juvenile idiopathic arthritis

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Abstract

Recent development of new medications has changed the juvenile idiopathic arthritis (JIA) treatment goal to inactive disease. With numerous options, how does a clinician choose which medication to use? Treatment options may depend on the clinical classification and a new paradigm considers the JIA subtypes in reference to categories of adult inflammatory arthritis; poligo JIA, spondyloarthritis JIA, and systemic JIA that can help guide a clinician in determining treatment options. Treatment strategies such as consensus treatment plans can provide guidance on treatment escalation. However, a treat-to-target strategy using frequent standardized disease activity measurements, shared decision making with the patient, and treatment escalation to achieve the disease activity target can provide a personalized approach to managing JIA.

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Current Opinion in Pharmacology 2022, **64:**102226

This review comes from a themed issue on **Rheumatology (2023)**

Edited by **Larry Moreland** and **Kristine Kuhn**

For complete overview about the section, refer Rheumatology (2023)

Available online 20 April 2022

https://doi.org/10.1016/j.coph.2022.102226

Introduction

Juvenile idiopathic arthritis (JIA) is a chronic disease with childhood onset and no cure [1]. Individuals with JIA require treatment to control disease activity and prevent complications of chronic inflammation [2–4]. The development and availability of novel effective biologic treatments for chronic rheumatic disease in adults and children has led to the goal of achieving inactive disease. Fortunately, in the past 20 years there have been many new treatment options approved for JIA, but many children continue to have active disease [5]. With a myriad of medication choices, how can clinicians choose the best option for each patient? There are categories of JIA (e.g. systemic JIA) and specific circumstances (e.g. uveitis) that require specific treatment mechanisms of action. However, outside of these indications there is a paucity of data to determine the most effective medication for each patient. In addition, early aggressive treatment approaches may provide a greater opportunity for remission [6]. Like in adult rheumatoid arthritis (RA), there have been recent recommendations for a treat-to-target (T2T) strategy comprised of frequent standardized assessment of disease activity, treatment escalation to achieve a goal of inactive disease, and shared decision making between patient and provider to improve patient outcomes [7]. This review focuses on treatment of JIA with biologic medications and small molecule inhibitors and reviews common treatment strategies.

Review

One approach to determining treatment options is to utilize the category of JIA. Traditionally, JIA is categorized using the International League of Associations for Rheumatology (ILAR) [8] classification including clinical symptoms at presentation and extraarticular manifestations. However, a more recent classification paradigm considers JIA in a grouping scheme more in alignment with adult chronic arthritis: Poligo JIA, spondyloarthritis, and systemic JIA (Table 1). These distinctions help to improve the discussion of care along the lifetime spectrum of disease and can facilitate treatment choices based upon pathophysiology of disease [9]. Recategorization of JIA phenotypes is supported by genetic and biomarker principal components and cluster analysis [10]. These may help determine secondary treatment options as these categories likely reflect autoantibody autoimmune disease, non-autoantibody autoimmune disease, and auto-inflammatory disease. There are some differences between the pediatric and adult presentations, but it is unclear if this represents the same pathophysiology with varied phenotype due to age or different etiologies altogether [9].

The “Poligo” grouping includes the ILAR categories of oligoarticular (persistent and extended), rheumatoid factor negative (RF-) polyarticular, and RF positive (RF+) polyarticular JIA. RF + polyarticular JIA has the same clinical manifestations and severe disease course as seropositive RA and likely represents the same

Table 1

Comparison of ILAR classification criteria [8] and a newly proposed classification that aligns with adult inflammatory arthritis classification [9].

ILAR classification	New proposed classification
Systemic JIA	Systemic JIA
Arthritis in one or more joints with fever for 2 weeks along with an additional symptom of rash, lymphadenopathy, hepatosplenomegaly, or serositis	
Oligoarticular	Poligo JIA
Arthritis in four or fewer joints in the first 6 months	
Persistent—throughout the disease course	
Extended—more than four joints after 6 months	
RF + Polyarticular	
Arthritis in five or more joints in the first 6 months with 2 or more positive tests for RF 3 months apart	
RF- Polyarticular	
Arthritis in five or more joints in the first 6 months with a negative RF	
Enthesitis related arthritis	Spondyloarthritis
Arthritis and enthesitis, or arthritis or enthesitis with sacroiliac involvement, HLA-B27 positive, acute anterior uveitis, first degree relative with spondyloarthropathy	
Psoriatic arthritis	
Arthritis and psoriasis	
Undifferentiated	
Arthritis that fulfills criteria for no category or fits 2 or more categories	

Abbreviations: ILAR – International League of Associations for Rheumatology, JIA – juvenile idiopathic arthritis, RF – rheumatoid factor, HLA-B27 – Human leukocyte antigen B27.

pathophysiology (shared epitope and CCP antibodies) in children and adults. RF + polyJIA and extended oligoJIA both require aggressive approaches to management [11]. RF-polyJIA and oligoJIA can be similar to seronegative RA in adults, but there is a group of children with early onset disease without a correlate in adults, those with monoarthritis, silent uveitis (mostly ANA+), and who have prolonged remission off of medication [9]. Some poligoJIA patients will respond to initial therapies like intraarticular glucocorticoids or conventional disease modifying anti-rheumatic drugs (cDMARDs) like methotrexate, but when escalation of treatment is needed, the options parallel those used in RA [12]. There are biologic treatments with 4 mechanisms of action approved by the United States Food and Drug Administration (FDA) for these patients with poligoJIA, tumor necrosis factor inhibitors (TNFi), T cell co-stimulation inhibitor, interleukin (IL)-6 receptor antagonist, and Janus kinase inhibitor (JAKi) (Table 2). The TNFi approved for JIA include etanercept, adalimumab, and golimumab [13]. The other TNFi, infliximab and certolizumab pegol, are approved for inflammatory arthritis in adults and are often used in pediatric patients, but do not currently have an FDA-indication for JIA [13]. Etanercept is a fusion protein TNF receptor and the other TNFi are monoclonal antibodies. Abatacept is a fusion protein containing a CTLA-4 analog that binds to CD80 or CD86 to prevent T cell co-stimulation via CD28. Tocilizumab is a monoclonal antibody to the IL-6 receptor, both soluble and membrane bound. Tofacitinib is a small molecule inhibitor of JAK1 and JAK3, intracellular signaling kinases, which associate with shared receptor components that bind several inflammatory cytokines. Systemic biologic therapies have had a dramatic impact on lowering the arthritis burden in children with poligoJIA.

Specific joints, like the temporomandibular joint (TMJ), is frequently affected in all categories of JIA and deserves specific considerations for treatment as these joints can be difficult to manage. TMJ arthritis in JIA may respond to intraarticular glucocorticoid injections; however, escalation of systemic therapy is often necessary to control inflammation and prevent orofacial deformities, pain, or limitations [14]. Systemic biologic therapies have indeed improved outcomes of children with TMJ arthritis, but it remains a challenging joint to keep quiet in growing children [15].

Silent, or asymptomatic, chronic anterior uveitis (CAU) is a clinical manifestation that is unique to JIA (mostly poligoJIA and early onset psoriatic JIA) and not seen in adult patients with inflammatory arthritis. CAU can result in permanent ocular changes and result in loss of vision if not recognized (routine ophthalmologic screening) and adequately treated. If topical glucocorticoids and cDMARDs do not resolve inflammation, current recommendations recommend starting a monoclonal TNFi, adalimumab, golimumab, or infliximab [16]. Other biological DMARDs, including tocilizumab and abatacept, have been reported to effectively treat refractory uveitis associated with JIA [17]. Both children and adults with spondyloarthritis are at risk for symptomatic anterior uveitis, and treatment recommendations are similar to those for silent uveitis.

The childhood onset spondyloarthropathies include the ILAR categories of enthesitis related arthritis (ERA) and older age onset psoriatic arthritis (PsA), and would include inflammatory bowel disease (IBD) related arthritis. These diseases are characterized by entheseal inflammation and risk for sacroiliitis that can progress to ankylosis. While TNFi are commonly used and frequently effective, medications that target the Th17 pathway are an alternative treatment option [18]. While peripheral arthritis can respond to cDMARDs, axial arthritis necessitates escalation to biologic therapy, typically TNFi [18]. An alternative to TNFi, secukinumab, a monoclonal antibody to IL-17A has recently been

Table 2

Table of biologic medications and small molecule inhibitors used to treat JIA.

Medication	Mechanism of action	Route of administration	Frequency of administration	Specific indication	Special concern
Etanercept	Fusion protein TNF receptor	SQ	Weekly or twice a week	Sacroiliitis	TB, malignancy boxed warning
Adalimumab	TNF mAb	SQ	Every 2 weeks or weekly	Sacroiliitis, IBD, uveitis	TB, malignancy boxed warning
Golimumab	TNF mAb	IV	Every 8 weeks after loading at week 0 and 2	Sacroiliitis, IBD, uveitis	TB, malignancy boxed warning
Infliximab	*TNF mAb*	*IV*	*Every 4–8 weeks after loading at week 0 and 2*	*Sacroiliitis, IBD, uveitis*	*TB, malignancy boxed warning*
Certolizumab pegol	*TNF mAb*	*SQ*	*Every 2 or 4 weeks*	*Sacroiliitis, IBD, uveitis*	*TB, malignancy boxed warning*
Abatacept	Fusion protein CTLA-4 analog	SQ/IV	SQ: weekly IV: every 4 weeks after loading at week 0 and 2		
Tocilizumab	IL-6 receptor mAb	SQ/IV	PolyJIA SQ: every 2 or 3 weeks IV: every 4 weeks sJIA SQ: weekly or every 2 weeks IV: every 2 weeks	Cytokine storm	Neutropenia
Tofacitinib	JAK1 and JAK3 small molecule inhibitor	oral	Twice a day		Malignancy, MACE, thrombosis boxed warning
Secukinumab	IL-17A mAb	SQ	Every 4 weeks	Sacroiliitis	IBD
Ustekinumab	mAb p40 subunit of IL-12/23	SQ	Every 12 weeks	IBD	
Canakinumab	IL-1β mAb	SQ	Every 4 weeks		
Anakinra	IL-1 receptor antagonist	SQ	Daily	MAS	
Rilonacept	*Fusion protein IL-1 receptor*	*SQ*	*weekly*		
Emapalumab	IFNy mAb	SQ	Twice a week	MAS	
Tadekinig alfa	*IL-18 binding protein*	*SQ*	*Three times a week*	*MAS*	

Italicized medications are not FDA-approved for JIA.

Abbreviations: TNF – tumor necrosis factor, SQ – subcutaneous, TB – tuberculosis, mAb – monoclonal antibody, IBD – inflammatory bowel disease, IV – intravenous, IL – interleukin, polyJIA – polyarticular juvenile idiopathic arthritis, sJIA – systemic juvenile idiopathic arthritis, JAK – Janus kinase, MACE – major adverse cardiac events, MAS – macrophage activation syndrome, IFNy – interferon gamma, FDA – United States Food and Drug Administration.

FDA-approved to treat children and adolescents with ERA and PsA [13]. In addition, ustekinumab, a monoclonal antibody to the p40 subunit of IL-12 and IL-23, has FDA-approval to treat plaque psoriasis in children age 6 and over, and has approval for use in adults over age 18 for PsA, and IBD [13]. Anecdotally, ustekinumab has been reported to benefit children with difficult to treat JIA/ERA [19]. Interestingly, secukinumab is not indicated for individuals with IBD and has been reported to uncover IBD in at risk individuals [20]. In adult trials, secukinumab has demonstrated efficacy towards delayed spinal radiographic progression [21], but the trial of ustekinumab for ankylosing spondylitis was stopped early for clinical inefficacy [22].

Unlike more traditional autoimmune forms of JIA, systemic JIA (sJIA) and adult onset Still disease (AOSD) represent autoinflammatory disorders characterized by dysregulation of the innate immune system in addition to an adaptive immunopathology [23]. Treatment is initially focused on controlling the systemic inflammation, typically through either non-steroidal anti-inflammatory drugs (NSAIDs) and corticosteroids or cytokine blockade, specifically targeting IL-1 and IL-6 [24,25]. The only IL-1 inhibitor FDA-approved to treat sJIA is canakinumab, a monoclonal antibody to IL-1β; however, anakinra, an IL-1 receptor antagonist, is frequently used for sJIA off-label, and rilonacept, a fusion protein for the IL-1 receptor, is approved for other autoinflammatory diseases and is sometimes used in sJIA. Individuals with sJIA are at risk of developing a life-threatening cytokine storm complication, macrophage activation syndrome (MAS) [26]. Higher doses of anakinra are often used to treat MAS [27]; however, some individuals require other cytokine blockade to reduce the hyperinflammatory state. Emapalumab is a monoclonal antibody to interferon gamma (IFNy) that is FDA approved to treat primary hemophagocytic lymphohistiocytosis (HLH) [28], a condition that is pathophysiologically similar to MAS in sJIA. As elevated levels of IL-18 are a hallmark of MAS, tadekinig alfa is a recombinant IL-18 binding protein that is currently under investigation for the treatment of sJIA, AOSD [29], and HLH. Treatment for MAS in the setting of sJIA has made substantial progress in reducing mortality [30].

Treatment strategies

After determining the best collections of treatments for the category of JIA or specific extraarticular manifestations, how does a clinician choose the best medication for each patient? While methotrexate and intraarticular corticosteroid joint injections remain the foundation of recommended treatment, many children require escalation of treatment, some at diagnosis. Initial and subsequent ACR treatment recommendations represent historical treatment strategies including step-up and early combination [14,18,31,32]. These strategies are expressed more clearly in the creation of the Childhood Arthritis and Rheumatology Research Alliance (CARRA) consensus treatment plans (CTPs) for polyarticular JIA [33], sJIA [24], and uveitis [34] (Table 3). The CTPs were developed through consensus methodology generated from North American pediatric rheumatologists self-reported disease management practices to improve comparative effectiveness research. Each disease category has multiple plans for the provider to choose from. Polyarticular JIA has 3 CTPs: step-up (cDMARD followed by biologic DMARD (bDMARD)), early combination therapy (cDMARD and bDMARD started concurrently), and biologic monotherapy) [33]. sJIA has 4 CTPs (glucocorticoid, methotrexate, anakinra, and tocilizumab) [24], and uveitis has 2 CTPs (methotrexate in DMARD naïve patients and TNFi) [34]. CTPs have allowed for real world data to help guide best practices for children with JIA.

Comparison between step-up therapy and early aggressive treatment has been studied most frequently in the polyarticular JIA population. Two randomized controlled trials of patients with recently diagnosed, treatment naïve polyarticular JIA compared disease activity response to a TNFi plus methotrexate or methotrexate monotherapy [35] or methotrexate, hydroxychloroquine, and sulfasalazine (triple therapy) [36] and found that individuals receiving the TNFi had earlier achievement of clinically inactive disease (CID) [35,36] and longer time in inactive disease [36]. An earlier trial comparing TNFi and methotrexate to methotrexate alone did not demonstrate a difference in achievement of inactive disease; however, both arms of the trial received prolonged oral corticosteroids that may have blunted the effect [37]. Nevertheless, more aggressive therapy resulted in a higher likelihood and longer duration of CID [38]. As an alternative to randomized clinical trials, the use of CTPs in polyarticular JIA was assessed using the Start Time Optimization of biologics in Polyarticular JIA (STOP-JIA) trial, a prospective comparative effectiveness study [39]. While the frequency of CID by the American College of Rheumatology (ACR) provisional criteria for CID [40] off steroids at 12 months was not statistically different by CTP choice, the frequency of clinical juvenile arthritis disease activity score (cJADAS) inactive disease was higher in the early combination CTP compared to the step-up CTP [39]. Using all participants enrolled in the CARRA Registry who were part of STOP-JIA or met criteria for STOP-JIA, 3 distinct disease activity trajectories over the first 12 months were identified; slow improvement, moderate improvement, and rapid improvement [41]. This latent class trajectory modeling found that disease activity at 3 months was predictive of disease activity at 12 months, and individuals who received a bDMARD in the first 3 months after diagnosis were more likely to have rapid improvement [41].

Table 3

Childhood Arthritis and Rheumatology Research Alliance (CARRA) consensus treatment plans (CTP) for juvenile idiopathic arthritis.

New onset polyarticular JIA [33]	Step-up Non-biologic DMARD followed by a biologic DMARD Early combination Non-biologic and biologic DMARD combined within a month of treatment initiation Biologic Only
New onset systemic JIA [24]	Glucocorticoids only Methotrexate (+/– GC) Anakinra (+/– GC) Tocilizumab (+/– GC)
Chronic anterior uveitis [34]	Methotrexate Naïve to steroid-sparing therapy TNFi (adalimumab or infliximab) MTX failure, MTX intolerant, severe disease

Abbreviations: DMARD – disease modifying anti-rheumatic drug, GC – glucocorticoids, TNFi – tumor necrosis factor inhibitor, MTX - methotrexate

Thus, early aggressive therapy may be the preferred choice for treating polyarticular JIA.

Treatment strategies that aim for a specific outcome have been adapted from RA in adults and other chronic diseases like asthma and diabetes. Current RA treatment guidance recommends a T2T approach with evidence that the treatment strategy is more important than the specific medication choice in achieving low disease activity and acceptable outcomes [12]. This is not the case for all inflammatory arthritides, as the most recent guidance for ankylosing spondylitis does not recommend a strict T2T approach given the challenges with measuring and assessing disease activity [42]. The development of the JADAS and the cJADAS provided an absolute, composite measure for disease activity of poligo JIA [43], and an international consensus group recommended a T2T approach for JIA [7]. These recommendations suggest making a treatment goal and management plan based on shared decision making (SDM) with parents and patients. In addition, measurement of disease activity using a validated composite instrument should be performed and documented on a regular basis, treatment should be escalated until the treatment goal is attained, and inactive disease should be maintained with regular follow-up and medication adjustments [7].

A quality improvement initiative to implement the T2T components of disease activity measurement, disease activity target setting, and clinical decision support related to medication escalation resulted in increased TNFi prescription and significant reductions in cJADAS for patients with both early and late disease [44]. In an open-label intervention comparing a T2T strategy to a matching cohort in a registry who received unguided treatment demonstrated significantly more of the T2T cohort reached JADAS remission or minimal disease activity [45]. Those in the T2T cohort also received biologic treatment more often by 12 months and systemic steroids less often after 12 months compared to the registry comparators [45].

Conclusions

The fortunate development and availability of effective and relatively non-toxic treatments for JIA has also led to increased clinical challenges in choosing the right treatment for each patient. Until personalized medicine using genetic and clinical/laboratory biomarkers are available, a more personal approach that includes SDM with the patient and family, frequent assessments, and adjustments to treatments can improve the outcomes for patients with JIA. A T2T strategy highlights the role of the patient in disease management with a focus on goal setting, SDM with the patient and family to determine treatment, and frequent treatment changes to achieve the goal. Future studies should focus on disease activity improvement from the overall treatment strategy rather than between specific treatments or combinations.

Conflict of interest statement

Melissa L. Mannion – none.

Randy Q. Cron - Tofacitinib for sJIA Adjudication of MAS Committee Chair, Pfizer, 2017-Present.

- Strategies for transitioning one therapy to another, Consultant, Novartis, Houston, TX, 2019.
- Changing treatment landscape for MAS/sHLH advisory board, SOBI, Atlanta, GA, 2019.
- "The Cytokine Storm Syndrome: What clinicians need to know" WebMD funded by Sobi, 2020.
- "A Tale of Two Storms: COVID-19 and the Cytokine Storm" WebMD funded by Sobi, 2020.
- "COVID-19 from Cytokine Signature to Cytokine Storm" WebMD funded by Sobi, 2020.
- Co-Principal Investigator on an ongoing investigator initiated clinical trial to study anakinra in a randomized, double-blinded placebo-controlled trial

for treating hemophagocytic lymphohistiocytosis in children and adults (funded by SOBI), 2020.

Acknowledgements

Funding: This work was supported by the Rheumatology Research Foundation Norman B. Gaylis, MD Clinical Investigator Award (MLM) and the Arthritis Foundation, Alabama Chapter Endowed Chair (RQC).

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