

Treatment options with biologics for juvenile idiopathic arthritis

Due to recent years' innovative developments in the pharmacotherapy of juvenile idiopathic arthritis (JIA) the induction of remission has become a reachable goal. Remission will lead to less structural damage and fewer disabilities. In this review, treatment options will be discussed on the basis of clinical trials and long-term documentation of treatment experience for the different drugs. In persistent oligoarticular JIA intra-articular corticosteroids and NSAIDs are both used as a first-line treatment. Despite this, for polyarticular JIA including seropositive and seronegative polyarthritis, extended oligoarthritis and polyarticular course of psoriasis arthritis early treatment with disease-modifying drugs is indicated. Methotrexate is currently the most commonly used 'first-line' disease-modifying drug in these JIA categories, while sulfasalazine has been proven effective in HLA-B27-associated enthesitis-related arthritis patients. After failure of these first-line treatment options, step up strategies introducing treatment with either of the TNF inhibitors etanercept and adalimumab is indicated. Leflunomide, infliximab or abatacept are alternatives for treatment of polyarticular JIA, while biological agents targeting IL-1 (anakinra, rilonacept and canakinumab) and IL-6 activity (tocilizumab) are successful in treating patients with systemic-onset JIA. While these strategies have already entered national and international treatment guidelines, the superiority of combination regimens of disease-modifying drugs and biologics remains to be established and switching strategies for patients with resistant or residual disease have to be developed.

KEYWORDS: abatacept • adalimumab • anakinra • canakinumab • etanercept
• infliximab • juvenile arthritis • rituximab • tocilizumab

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Release date: 17 June 2011; Expiration date: 17 June 2012

Learning objectives

Upon completion of this activity, participants should be able to:

- Distinguish the most common DMARD used as first-line therapy for JIA
- Evaluate biologic agents for the management of JIA
- Identify a biologic agent particularly effective in cases of uveitis associated with JIA
- Analyze treatments for JIA with prominent systemic symptoms

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Financial & competing interests disclosure

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Disclosure: Charles P Vega, MD, has disclosed no relevant financial relationships.

Author and Disclosures

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Disclosure: Gerd Horneff, MD, has disclosed the following relevant financial relationships: received financial support from the following pharmaceutical companies: Abbott, Bristol-Myers Squibb, Chugai, Novartis, Nycomed, Pfizer, Roche, Sandoz and Wyeth. The author has disclosed no other relevant financial relationships.

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Disclosure: Elisa Manzotti has disclosed no relevant financial relationships.

Juvenile idiopathic arthritis (JIA) is the most common chronic inflammatory disease in childhood and can lead to severe disability [1–3]. The term JIA encompasses a group of clinically heterogeneous disorders with arthritis that begin prior to age 16 years, are of unknown cause and present with joint pain, stiffness and swelling that persists for longer than 6 weeks. It substitutes earlier terms such as juvenile rheumatoid arthritis and juvenile chronic arthritis, although different disease are covered by each of these terms. The incidence in Caucasian children <16 years has been reported to be 19.8/100.000 children [4]. According to the International League of Associations for Rheumatology (ILAR) classification, JIA is subclassified into seven distinct categories by the use of definitions and exclusion criteria [5]. The ILAR classification is mainly based on the number of joints affected, the presence of extra-articular manifestations, the presence or absence of rheumatoid factors and HLA-B27 and finally the family history (TABLE 1). The primary aim of this subclassification was the description of more homogenous groups of patients for a better understanding of the pathogenesis.

The choice of drugs today is based mainly on a trade-off between disease severity, prognostic factors, proven efficacy of the drug and risk of drug side effects. Furthermore, in recent years there has been a shift towards early aggressive treatment since delayed treatment has been shown to be associated with a lesser efficacy [6].

While oligoarticular course of the disease, with the exception of chronic recurrent uveitis, is mainly associated with a tolerable prognosis, this is not true for the majority of patients with polyarticular course JIA and systemic-onset JIA [1].

For decades, the primary goal of treatment of JIA has been managing pain and other inflammatory symptoms combined with

physiotherapy. In recent years innovative developments in the pharmacotherapy of JIA enabled not only prevention of long-term damage and disability but also induction of remission as a reachable goal. Drug therapy should, if possible, be guided by controlled, randomized clinical trials. This should of course be considered especially in children. However, only a minority of drugs have been studied in formal trials on children. Substances not yet approved for use in children and juvenile patients were also included in this review, depending on the results of current studies, since the current legal situation allows 'off-label' therapy. In Germany, health insurance is obliged to compensate costs for off-label treatment, if either a severe impairment of health or a medical condition involving pain is present, it cannot be treated efficiently for a lack of approved therapeutic alternatives and study results sustain expectations for an approval of the drug for the respective indication.

Pharmacomedical treatment

Intra-articular corticosteroids and symptomatic treatment with NSAIDs are often sufficient for those JIA patients presenting with a few affected joints only. Primary introduction of so-called DMARDs is increasingly immediately recommended for polyarticular JIA and systemic-onset JIA. The use of intra-articular corticosteroids and NSAIDs in these patients may be needed as bridging treatment until DMARD treatment is successful.

For clinical trials, a set of criteria has been established [7]. These six pediatric American College of Rheumatology (ACR) criteria (PedACR) consist of parents' global assessment of overall well-being, physicians' global assessment of disease activity, disability as measured by the Childhood Health Assessment Questionnaire, erythrocyte sedimentation

Table 1. Categories of juvenile idiopathic arthritis.

Category	Marked extra-articular manifestations	Exclusion criteria
Systemic arthritis (Still's disease)	Fever, rash, hepatosplenomegaly, pericarditis, pleuritis, lymphadenopathy, vasculitis, short stature, dystrophy	a, b, c, d
Seronegative polyarthritis [†]	Tenosynovitis, uveitis	a, b, c, d, e
Seropositive polyarthritis [†]	Low-grade fever, tenosynovitis, rheumatoid nodules	a, b, c, e
Persistent oligoarthritis [‡] Extended oligoarthritis [§]	Chronic uveitis	a, b, c, d, e
Enthesitis-related arthritis	Enthesitis, acute uveitis	a, d, e
Psoriatic arthritis	Psoriasis, uveitis	b, c
Unclassified JIA	Variable	NA

Specific exclusion criteria are considered:
a: Psoriasis, or psoriasis in first-degree relatives;
b: HLA-B27⁺, male and older than 6 years;
c: Ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, Reiter's syndrome in patients or first-degree relatives;
d: Rheumatoid factor repeatedly detected at least 3 months apart;
e: Systemic symptoms.
[†]Affecting at least five joints during the first 6 months of the illness.
[‡]Affecting a maximum of four joints during the first 6 months of the illness.
[§]Affecting a maximum of four joints during the first 6 months of the illness and at least five joints thereafter.
JIA: Juvenile idiopathic arthritis; NA: Not applicable.
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rate, number of active joint and number of joints with limited range of motion. A clinical response on treatment on the PedACR30 level is defined as improvement of at least 30% in at least three of the six listed criteria without worsening of more than 30% in no more than one of the remaining criteria. For the PedACR50 and 70 level, improvement of at least 50 or 70% of at least three criteria is required, respectively.

Methotrexate has been studied in controlled clinical trials and emerged to be the most common first-line DMARD treatment according to several national treatment guidelines [8–12].

Other DMARDs, such as gold salts, penicillamine, sulfasalazine, the antimalarial drugs hydroxychloroquine and chloroquine, and the immunosuppressants azathioprine and cyclosporin A, are currently rarely used for treatment of JIA [13]. Combination treatment using sulfasalazine, antimalarials or cyclosporine A together with methotrexate are sometimes considered but data for these strategies are scarce. Since these drugs have been used for decades despite the lack of controlled trials performed in juvenile arthritis simply because of their efficacy in adult rheumatoid arthritis they will not be discussed in details. Methotrexate and leflunomide as well as sulfasalazine in HLA-B27-associated arthritis are the only exceptions with evidence for the use in JIA [14–16].

■ Methotrexate

In children with JIA, methotrexate is approved for the therapy of refractory, severe and active polyarticular arthritis. A dose of 10–15 mg/m² is applied once weekly orally or subcutaneously. No difference in bioavailability has been found between oral and intramuscular administration at a dosage of 10 mg/m²/week and subcutaneous application at a dosage of 15 mg/m²/week in children with acute lymphoblastic leukemia or rheumatoid arthritis patients, respectively [17,18]. Bioavailability of oral methotrexate shows marked interindividual variation but may not be significantly affected by the presence of foods in adult patients with rheumatoid arthritis [19]. There is no proof of a postulated higher efficacy and tolerability of parenteral application [20]. At dosages >15 mg/m²/week parenteral application is recommended, because bioavailability and tolerability are supposed to be better.

Application of folic acid 24 h after application of methotrexate may be able to reduce the rate of side effects without affecting efficacy as shown in a randomized controlled trial in adults [21]. In patients failing to improve on low to medium dosages, a controlled trial with two higher dosages showed a dose-dependent increase of efficacy up to a weekly dosage of 20 mg/m² while a further increase of dosage up to 30 mg/m² did not increase efficacy [10]. *Post hoc* analyses of the trial demonstrated that ANA negativity, a high

Childhood Health Assessment Questionnaire (CHAQ) disability index before initiation of treatment and the presence of right and left wrist activity were predictors of poor response to methotrexate in polyarticular course JIA [22].

Efficacy of methotrexate treatment on systemic JIA as well as extended oligoarticular JIA was analyzed in a further clinical trial. In the extended oligoarticular arthritis group, methotrexate treatment produced significant improvement. In systemic JIA, a trend to beneficial effects was observed on arthritis only, but not against systemic symptoms [9].

Finally, strategies when and how to stop methotrexate in JIA patients achieving remission already have been proposed [23]. Weaning methotrexate after a duration of remission of 12 months on treatment was not superior to a duration of 6 months after achieving remission. Furthermore, the biomarker S100 MRP A8/A14 turned out to be a valuable prognostic marker with a higher relapse rate in patients with higher blood levels at the time of discontinuation of treatment.

■ Leflunomide

In a double-blind active controlled study in polyarticular JIA, patients receiving an effective concentration of leflunomide showed an efficacy comparable to methotrexate treatment. Younger children were underdosed in this study and did not reach therapeutical blood levels [14]. Based on this experience, children up to a bodyweight of 20 kg receive 10 mg daily, those with a bodyweight between 20 and 40 kg receive 15 mg daily (respectively, 10 mg and 20 mg alternating), and those with a bodyweight of 40 kg or more received 20 mg daily. Despite treatment with either methotrexate or leflunomide, a persistence of approximately 50% of symptoms was observed in both groups of this study, indicating a limited response of polyarticular JIA in numerous patients. Furthermore, leflunomide is still not approved for treatment of JIA and therefore may only be used as an off-label candidate in patients who had been refractory to methotrexate or have been treated with those biologics already licensed for polyarticular JIA. Therefore, clinical experience with leflunomide is rare. Data on combination treatment of leflunomide and methotrexate or TNF inhibitors in JIA are insufficient for a recommendation.

■ Sulfasalazine

Sulfasalazine showed some efficacy in treatment of JIA, especially in HLA-B27-associated arthritis. In a clinical trial on polyarticular JIA, the effect

of sulfasalazine on joint tenderness, joint swelling, joint score and laboratory parameters was only marginally significant [24,25]. Combination of sulfasalazine together with methotrexate and antimalarials have shown no superiority over methotrexate alone and turned out to be markedly inferior to a combination regimen including TNF inhibitors [26]. Therefore, currently there is no evidence supporting such a combination for treatment of polyarticular JIA.

In patients with enthesitis-related arthritis (ERA) a placebo-controlled double-blind study demonstrated an advantage of sulfasalazine over placebo [15]. It may therefore be used in ERA patients failing intra-articular corticosteroids and NSAIDs. Currently, it is the only approved drug for patients of this JIA category so far as the disease pattern is oligoarticular. In polyarticular ERA patients sulfasalazine is a therapeutic alternative or amendment to methotrexate. Sulfasalazine is not approved for the treatment of JIA in patients under the age of 6 years and it should not be used for treatment of systemic arthritis.

Biologics

Conventional therapy with methotrexate, leflunomide or sulfasalazine is often not successful in ameliorating disease, especially in patients with polyarticular and systemic-onset JIA [3,27]. Extrapolating data of the only randomized trial with two active comparators, approximately 50% of the clinical disease activity persists despite prolonged treatment [14]. This warrants more efficient treatment for those patients who did not reach remission.

■ Inhibition of TNF- α

A decade ago, as new biological treatment option, anti-TNF- α therapy has shown success in polyarticular JIA patients. Neutralization of TNF- α has beneficial effects in rheumatoid arthritis, ankylosing spondylitis, Crohn's disease and a number of further inflammatory conditions. Three different monoclonal antibodies, the chimeric antibody infliximab, the human antibodies adalimumab and golimumab, a soluble TNF receptor fusion protein etanercept and the pegylated anti-TNF antibody F(ab)2 fragment certolizumab have been studied and approved for at least rheumatoid arthritis. They all bind to TNF- α and antagonize its effects, although there seem to be some differences since adalimumab, golimumab and infliximab proved to be valuable in chronic inflammatory bowel disease while etanercept is not. Monoclonal antibodies

bind their target not only when it is free in the serum like etanercept, but also when it is bound to the cell surface, which may be one explanation. Furthermore, they differ in their binding affinity to TNF- α and in their biological plasma half-life, which is 4–5 days for etanercept, 8–10 days for infliximab and 12–14 days for adalimumab, respectively. Accordingly, the application intervals are different: etanercept 3–7 days, infliximab 28–56 days and adalimumab 7–14 days. Etanercept, adalimumab, golimumab and certolizumab can be self-injected subcutaneously at home. Due to possible infusion reactions infliximab has to be administered under clinical monitoring. Etanercept and adalimumab have been approved for treatment in children with JIA by the US FDA and the EMA while infliximab is approved in children for treatment of Crohn's disease only.

■ Etanercept

Etanercept has now been used in the treatment of active polyarticular juvenile arthritis in patients aged at least 4 years for 10 years, after it was proven to be greatly beneficial in a single randomized controlled study [28]. It is a TNF receptor immunoglobulin-fusion protein, which binds both TNF- α and TNF- β (lymphotoxin- α) with high affinity. In a single placebo controlled trial with 69 children with polyarticular disease who were refractory to previous treatment, etanercept proved to be effective. Efficacy seemed to last over a period of up to 8 years [29,30].

Patients in the pilot study were continually treated and followed up over more than 8 years, with a very high adherence rate. A total of 63% of patients with continuous treatment reached clinical remission under treatment, while 82% of patients were able to discontinue treatment with corticosteroids or could reduce the dose below 5 mg/day prednisone equivalent [30]. The results of the open long-term follow-up study emphasize the high and sustained efficacy of treatment of polyarticular JIA with etanercept.

The rate of adverse effects and serious infections was low, even with prolonged treatment. These observations in a few patients correspond with data from the German etanercept long-term register, in which data of more than 1350 patients are recorded [31,32]. In this collective, 92% of patients were treated with etanercept for at least 1 year, 78% for at least 2 years and 66% for at least 4 years. The high adherence rate to this therapy suggests a favorable balance of efficacy and tolerability. Reported adverse events, for example local skin reactions, were

generally mild and transient. Of special interest are the occurrence of infectious diseases, other autoimmune diseases (e.g., demyelinating diseases, uveitis) or demasking of other autoimmune diseases (e.g., Crohn's disease), as well as new manifestations of malignancy and especially lymphoma. However, so far there is no apparent association between the occurrence of malignancies and treatment with etanercept while biologics naive JIA patients had a higher incidence of malignancies and especially lymphoma compared with controls [33–35].

The therapeutic goal 'remission', meaning an 'inactive disease' [36], is reached after 2 years of treatment in approximately half of the Registry patients [37]. A condition of 'inactive disease' is reached more frequently in patients who started therapy earlier, initially showed a lower active joint count with a lower disability indicated by the Childhood Health Assessment Questionnaire score, received at least the recommend weekly dosage of 0.8 mg/kg biweekly or received a combination of etanercept and methotrexate, while patients with systemic-onset JIA or seropositive polyarthritis reached this condition less frequently.

Etanercept is administered subcutaneously in a dose of 0.4 mg/kg (maximum dose 25 mg) twice weekly. In the USA a weekly dose of 0.8 mg/kg in one or two single doses is approved. Two retrospective analyses with JIA patients who received a single application per week (once weekly) were published. In patients who switched to a once-weekly application no loss of efficacy was observed [38,39]. In addition, a prospective Phase IV study demonstrated safety and efficacy of once weekly application of etanercept with a dose of 0.8 mg/kg/week (maximum dose 50 mg/week) [40].

■ Adalimumab

Adalimumab is a human monoclonal anti-TNF antibody. Adalimumab is approved in patients over 4 years old with polyarticular JIA either as monotherapy or in combination with methotrexate. In an open phase of a controlled clinical withdrawal trial of adalimumab for the treatment of JIA 171 patients were initially treated with adalimumab (24 mg/m² every other week subcutaneously) [41]. A total of 84 of these patients continued a previous treatment with methotrexate. 88, 80 and 59% of patients on monotherapy and 95, 92 and 82% of patients on a combination with methotrexate showed a response according to PedACR 30, 50 and 70 criteria, respectively. In the subsequent placebo-controlled phase of the

trial disease flares were significantly less frequent in the adalimumab group. Thus, adalimumab demonstrated efficacy in treating polyarticular JIA. In the open long-term extension phase a dosage of 24 mg/m² every other week was used. However, a change to a fixed dose of 20 mg every other week in children with a bodyweight below 30 kg and 40 mg every other week in children with a bodyweight of 30 kg or more did not result in a change of efficacy or tolerability [42]. No tuberculosis, other opportunistic infections or malignancies were observed in this patient cohort while data on larger patient numbers are lacking so far.

Adalimumab seems valuable not only for treatment of arthritis but also for chronic recurrent anterior uveitis, which emerged in approximately 20% of JIA patients especially in oligoarticular JIA, seronegative polyarthritis and juvenile psoriasis arthritis [43].

In an open trial 16 of 18 patients with uveitis who had all failed systemic steroids, cyclosporine, methotrexate, leflunomide, etanercept or infliximab had good responses to adalimumab [44]. In another retrospective study on 20 patients with chronic uveitis of whom 19 previously were treated with infliximab or etanercept seven showed improved activity, one worsening while in 12 there was no change in the activity of uveitis [45]. These studies suggest that adalimumab is a potential treatment option in JIA-associated uveitis. So far only open uncontrolled trials have indicated clinical usefulness while controlled trials are still ongoing.

■ Infliximab

Infliximab is a chimeric murine–human monoclonal anti-TNF antibody marketed first for treatment of rheumatoid arthritis in the late 90s of the last century. It is still not approved for treatment of JIA. In a controlled, randomized, double-blind trial with infliximab 3 mg/kg bodyweight on weeks 0, 2, 6, 14 in combination with methotrexate compared with placebo and methotrexate there was no difference in effectiveness between treatment arms at end point. At 14 weeks, a higher proportion of patients randomized to infliximab 3 mg/kg had a PedACR30 response when compared with the placebo group. Patients initially treated with placebo later on received infliximab in a dose of 6 mg/kg bodyweight. By week 52, clinical response meeting the PedACR50 and 70 criteria were reached by 70% and 52% of the patients respectively. The frequency of serious adverse effects, especially infusion reactions, was

significantly higher in the 3 mg/kg group than in the group who received placebo first and then infliximab 6 mg/kg. The detection of antibodies against infliximab was significantly associated with the occurrence of infusion reactions in the group with a dose of 3 mg/kg [46].

The long-term efficacy and safety of infliximab was analyzed in an open-label extension (52–204 weeks) study in 78 of 122 of the initial patient cohort, representing only 64% of initial patients [47]. The initial dose of infliximab of 3 mg/kg could be increased in <1.5 mg/kg steps every 8 weeks. 42 patients discontinued infliximab prematurely (34%), most often by withdrawing consent, lack of efficacy or patient/physician/sponsor requirement. Infusion reactions occurred in 32% patients, with a higher incidence in patients who tested positive for antibodies to infliximab. The proportion of patients who achieved a PedACR30/50/70/90 response or an inactive disease at week 204 was 44, 40, 33, 24 and 13%. In summary, in this 4-year extension study infliximab was found to be safe and effective with a high dropout rate [47].

However, according to retrospective case collections and open case series, efficacy of infliximab seems to be comparable to etanercept [48]. Tolerability is apparently limited owing to higher risk of infections, including reactivation of tuberculosis, when compared with treatment with etanercept [49]. Incompatibility reactions during infusion are not rare and probably related to the development of human anti-chimeric antibodies. Infliximab is applied as intravenous infusion in a clinical setting with availability of emergency treatment. Dosages of 3–6 mg/kg bodyweight and infusion intervals of 4 to 8 weeks have been studied but higher dosages and shorter intervals may be preferred. Infliximab should only be used in combination with methotrexate to prevent the development of anti-chimeric antibodies, which may interfere with tolerability and efficacy of treatment. Infliximab may have a special role in JIA patients with uveitis or in patients who are not compliant to subcutaneous therapy.

■ Golimumab & certolizumab

In rheumatoid arthritis, certolizumab, pegol and golimumab have comparable efficacy and safety profiles compared with previously approved TNF antagonists. Certolizumab pegol, a PEGylated Fab fragment of a humanized anti-TNF antibody, was tested in Phase III trials in Crohn's disease and in rheumatoid arthritis [50,51]. Certolizumab pegol does not possess a Fc-region. Therefore, cell-mediated cytotoxicity

is not possible. This could possibly result in a decreased risk for infectious diseases compared with full TNF-antibodies. However, it may be of value for treatment during pregnancy, since without a Fc-fragment it will not cross the placental border.

Golimumab is a completely humanized monoclonal anti-TNF antibody for subcutaneous application binding both soluble and membrane bound forms of TNF- α [52]. So far it is studied and approved for the treatment of rheumatoid arthritis and adult ankylosing spondylitis while a controlled multicenter trial in JIA (GoKids) is still ongoing (ClinicalTrials.gov Identifier NCT01230827) [101].

Inhibition of IL-1

IL-1 β , a proinflammatory cytokine produced by monocytes/macrophages and dendritic cells, induces the expression of numerous proinflammatory genes, among them the one coding for cyclooxygenase (COX)2, which is important in rheumatic inflammation processes including fever. IL-1 seems to be a major mediator of the inflammatory cascade especially important in systemic onset JIA. Systemic-onset JIA patients' mononuclear cells spontaneously produce large amounts of IL-1 and patients' sera could provoke IL-1 synthesis in cultures of mononuclear cells from healthy controls, making this cytokine an interesting target for therapy of this disease. Currently, three different biologic inhibitors of the IL-1 β pathway are available: anakinra, an IL-1 receptor antagonist, canakinumab, a human IL-1 β antibody, and rilonacept, an IL-1 receptor fusion protein.

■ Anakinra (IL-1 receptor antagonist)

Apart from lacking glycosylation and an additional methionine residue, anakinra is identical to the physiological IL-1 receptor antagonist, which constitutes a to date unique form of regulation of cell activation. It binds competitively to the IL-1 receptor without inducing a stimulatory signal. In a placebo-controlled trial in patients with polyarticular JIA no benefit of treatment with anakinra over placebo was demonstrated [53]. However, the effectiveness of anakinra in systemic-onset JIA patients was superior to those with other categories of JIA.

In a case collection 35 patients (20 with juvenile, 15 with adult-onset Still's disease) were treated with anakinra at a dosage of 1–2 mg/kg (maximum 100 mg) daily subcutaneous [54]. At initiation of treatment, fever was present in 45% of the juvenile patients and 87% of adults. All patients had active arthritis and were initially

treated with corticosteroids, methotrexate, TNF inhibitors and thalidomide. Of the 20 patients with systemic-onset JIA, 15 (75%) improved. Systemic symptoms (fever, rash) disappeared in 14 of 15 cases. The corticosteroid dose was reduced in 50% of patients. 11 of the 15 adult patients (73%) showed a response with an at least 50% reduction of measures of disease activity after 17.5 (11–27) months. Two patients discontinued therapy because of severe skin reactions, two due to infection.

In patients with systemic-onset JIA the use of anakinra was then analyzed in a placebo-controlled multicenter trial resulting in an immediate and beneficial effect on systemic manifestations of the disease (e.g., fever, rash) as well as on joint inflammation [55]. After 1 month on anakinra eight of 12 patients but only one of 12 patients upon placebo showed a response according to PedACR criteria. In the second month ten patients of the placebo group switched to treatment with anakinra. A total of nine of these ten patients showed a response according to PedACR criteria. The tolerability was similar in the anakinra and placebo group. Five patients discontinued from the study in the first year of treatment because of intolerance or secondary treatment failure.

In a report of 46 patients from an international multicenter series anakinra was used as a first-line disease-modifying therapy in systemic-onset JIA. Anakinra was used as monotherapy in ten patients. Fever and rash resolved very rapidly in >95% of patients and C-reactive protein (CRP), a marker for active disease and ferritin normalized within 1 month in >80%. Active arthritis resolved less frequently and less rapidly. Complete response to initial therapy was observed in 59% of patients, while another 39% exhibited a partial response. Inactive disease was achieved in eight of ten patients on anakinra monotherapy. Anakinra was discontinued in one patient for lack of response [56].

Although anakinra seems to be effective in systemic-onset JIA, there are patients who are anakinra-resistant. Several case series described a sustained improvement in approximately 50% of cases. A differential treatment effect was seen in an other open-label study with 22 patients with systemic-onset JIA with anakinra in a starting dose of 1 mg/kg [57]. At baseline, 17 patients had fever and 12 had skin rashes. Ten patients showed a dramatic therapeutic success, usually in the first week. All these patients were able to end the comedication completely and be treated solely with anakinra. A total of 11 patients had not or only temporarily

responded. Increased dosages of up to 4 mg were also ineffective. The systemic symptoms were mostly well controlled during therapy, while joint inflammation and CRP/erythrocyte sedimentation rate (ESR) increases occurred during relapse. Patients with a good response initially had fewer active joints ($p = 0.02$) and higher neutrophil counts ($p = 0.02$). Besides local reactions, no major side effects were observed. Two patients showed a macrophage activation syndrome (MAS). It has been suggested that the arthritis improved significantly less than the systemic symptoms of the disease [58]. In a subgroup of patients blocking of IL-1 signalling had a dramatic effect on clinical symptoms and acute phase markers, while in others treatment partially or completely failed, indicating that there may be more than IL-1 driven pathways of immune activation of importance in systemic-onset JIA.

Treatment with anakinra as a first steroid sparing treatment has recently been proposed in the US guidelines [59]. Anakinra has very good results in the short term, but these may not be sustained in the long term and a further downside is that it has to be injected daily. Furthermore, anakinra injections may be painful and lead to injection site reactions. Guidelines suggest that if systemic features are prominent anakinra has the preference, but if arthritis is prominent etanercept may be a good option also [59].

Anakinra is approved for the treatment of rheumatoid arthritis but not for the treatment of systemic JIA. It is used in a daily dose of 1–2 mg/kg bodyweight subcutaneously. In the course of treatment an increase of the dosage seems necessary to sustain the efficacy of therapy [56]. Treatment is limited especially due to, in some cases, considerable local injection site reactions, which may require stopping medication. Furthermore, the risk of infections seems increased. According to experiences in adult RA patients this also limits combination treatment with anakinra and TNF- α inhibitors [60]. The mode of application, the limited response rate and the side effect profile limits a widespread recommendation for anakinra for treatment of systemic-onset JIA but the experience with anakinra as a proof of concept is encouraging further study of IL-1 inhibitors in systemic-onset JIA.

■ Rilonacept

Rilonacept is an IL-1R/IL1RacP/Fc-fusion protein with a prolonged plasma half-life compared with anakinra. It blocks soluble IL-1 β , thereby preventing binding of IL-1 β to its cell bound receptor.

In an open-label phase of a randomized controlled double-blind study in nine patients with systemic arthritis aged 5–18 years it demonstrated an impressive effect [61]. After 2 weeks 55% of patients and after 4 weeks 78% of patients treated with a dose of 2.2 mg/kg bodyweight showed a response according to the PedACR50 criteria. At inclusion feverish patients showed an immediate disappearance of fever. A substantial reduction of the number of affected joints (-43% after 2 and -57% after 4 weeks), the restriction of physical activity (measured by the CHAQ, -48% after 2 and -78% after 4 weeks) and laboratory parameters (CRP, -48% after 2 weeks and -78% after 4 weeks) was achieved. Tolerability was acceptable, but for a further recommendation a controlled trial on larger patient cohorts with a longer follow-up is needed.

The long-term treatment of 23 patients aged 5–20 years with rilonacept in an open-label extension study resulted in an impressive improvement of the mean values of all six PedACR core set criteria [62]. After 6 months, 87/78/61% of patients and after 24 months 70/70/57% reached the PedACR30/50/70. Fever and/or skin rashes present at the beginning of treatment were no longer observed. Leukocytosis, thrombocytosis, anemia and fibrinogen improved significantly. A previously increased CRP became almost normal in all patients. In three patients a total of six serious adverse events were recorded, including MAS (two), pulmonary fibrosis (one), anemia (one) and relapse (two). Deaths, malignancies or serious infections did not occur. Rilonacept is so far not approved for the treatment of JIA.

■ Canakinumab

Canakinumab, a human IL-1 β antibody with prolonged plasma half-life, binds selectively to IL-1 β without interfering with IL-1RA. It is administered as a subcutaneous injection once monthly. Its efficacy in the treatment of IL-1-dependent genetic fever syndromes makes canakinumab an interesting option for use in systemic arthritis [63]. So far data of a Phase II trial with a dosage escalation are available. In an open-label study, 23 children and adolescents (age 4–19 years) received a single injection of canakinumab subcutaneously at a dosage escalating from 0.5 to 9 mg/kg [64]. A new dose was administered at the time the disease flared. Previously, there was a comparable high disease activity (median baseline physician and parent/patient global assessment of disease activity, 68.5 and 67.0 mm on a 100 mm visual analog scale, CHAQ disability index of 2.1 of a maximum of 3, active joint count 6.2, CRP 136 mg/l)

despite an intolerably high median prednisone equivalent dose of 0.33 mg/kg. 13 of 22 (59%) patients showed an immediate response, reaching at least a PedACR50 on day 15. Inactive disease was achieved in four patients (18%). 17 of 23 patients were previously treated with anakinra. 6 of 11 nonresponders to anakinra achieved at least a PedACR50 on day 15 after a single dose of canakinumab. The best baseline predictor of improvement was the number of active joints. The median number of active joints in nonresponders was 33.5 but only nine in responders. The median time to re-recognizable disease activity was 56 (95% CI: 32–100), 60 (38–95) and 90 (45–181) days for doses <3 mg/kg, 3 mg/kg and >3 mg/kg, with a probability of relapse within 1 month from 19% (95% CI: 6–41), 17% (95% CI: 6–34) and 7% (95% CI: 1–23). The injections were well tolerated. Adverse events were mild to moderate in severity and consisted mainly as infections and gastrointestinal disorders. Three serious adverse events occurred. Canakinumab thus appears effective in the treatment of systemic JIA, a placebo-controlled double-blind study with monthly subcutaneous injections of canakinumab is currently underway.

Inhibition of IL-6

Numerous clinical and laboratory characteristics of systemic JIA can be attributed to the direct influence of IL-6: acute phase reaction, leucocytosis, thrombocytosis, hypergammaglobulinemia, hepatosplenomegaly, osteoporosis and growth delay. IL-6 is a pleiotropic cytokine with proinflammatory effects on numerous cells, among them B-lymphocytes, T-lymphocytes, hematopoietic stem cells and also hepatocytes and osteoclasts. It is also synthesized by numerous different cell types: lymphocytes, monocytes, fibroblasts, synoviocytes and endothelial cells. In B-lymphocytes IL-6 induces the activation and maturation to antibody-producing plasma cells. CRP as well as serum amyloid A are produced under the influence of IL-6. Plasma concentration of IL-6 correlates with disease activity and decreases under effective treatment.

■ Tocilizumab

Tocilizumab is a humanized antibody against the IL-6 receptor, which blocks the formation of a complex of IL-6 and IL-6 receptor. Bioactivity of IL-6 can be inhibited by the antibody tocilizumab.

In a pilot study, patients with active refractory systemic JIA received a single infusion of 2, 4 or 8 mg/kg. Within 48 h improvements in

all 18 children were detected and lasted up to 4–8 weeks. 11 patients (61%) achieved an ACR JRA30 response [65].

In a dose escalating study with repeated application of tocilizumab 11 patients with active refractory systemic JIA initially received up to three infusions at a dose of 2 mg/kg every 14 days. In the absence of treatment success, the dose was increased to 4 mg and finally to 8 mg/kg each for up to three more infusions. Finally, three patients required infusions with a maximum of 2 mg/kg, five patients received a maximum of 4 mg/kg and three patients 8 mg/kg. Ten of the 11 children showed immediate improvement with a response to the PedACR50 criteria, 7% by the PedACR70 criteria. All patients showed an improvement in episodes of fever and arthritis. The medical laboratory parameters CRP, ESR acceleration, hemoglobin and platelet counts returned to normal during therapy.

In addition to uncomplicated infections, in these open-label studies no clinical side effects were observed, but there was a rise in cholesterol and alanine aminotransferase, as well as a decrease in gammaglobulins [66]. Discontinuations were not necessary as serious adverse events did not occur.

One double-blind placebo-controlled study on 56 Japanese systemic juvenile idiopathic arthritis patients aged 2–19 years has been performed. During the open-label 12-week initial phase of this placebo-controlled, double-blind trial patients were treated with tocilizumab 8 mg/kg every other week over 6 weeks. 91% of patients showed a PedACR30 response. An immediate control of fever, leukocytosis, thrombocytosis, CRP and ESR elevation could be demonstrated. Patients having at least a PedARP30 and low CRP of less than 5 mg/l were randomized to either receive placebo or to continue tocilizumab treatment for 12 weeks. In this placebo-controlled phase, in the placebo group disease flares were significantly more frequent. 83% of patients in the placebo group but in only 20% of patients in the tocilizumab group reach the primary end point of a flare of the disease. At the end of the double-blind phase only four (17%) patients in the placebo group but 16 (80%) in the tocilizumab group had at least reached the PedACR30 criteria + low CRP ($p < 0.0001$) [67].

In the open-label wash in phase of the study there were two serious adverse events, an anaphylactic reaction in a patient without anti-tocilizumab antibodies of the IgE-type and gastrointestinal bleeding in the other patient. In

the double-blind phase of the study, one infectious mononucleosis with a significant increase in transaminases and leukopenia occurred and one patient in the placebo group had a herpes zoster. The number of nonserious adverse events with tocilizumab was similar to that of the placebo group. However, safety assessment is limited while all patients previously had entered the open-label wash in phase of the trial and had been exposed to the drug. No opportunistic infections or deaths occurred. A MAS was not observed.

■ Long-term studies with tocilizumab in systemic-onset JIA

Overall, 128 patients from several Phase II and Phase III studies participated in an open label extension study to examine the long-term tolerance and safety. Here, all patients received tocilizumab 8 mg/kg intravenously every 2 weeks. The mean duration of therapy was 78 weeks. In 14 patients, the therapy was terminated prematurely, in eight cases on grounds of incompatibility, in five patients due to IgE antibodies to tocilizumab and one patient because of ineffectiveness. Adverse events occurred in 120 patients (94%), resulting in a rate of 787 per 100 patient-years. Serious adverse events and serious infections occurred at a rate of 37 and 14.5 per 100 patient-years. The most common events were diarrhea (3.8/100 patient-years) and pneumonia (3.4/100 patient-years). MAS, anaphylaxis (n = 2), cardiac amyloidosis, a duodenal wall or gastrointestinal bleeding all led to discontinuation of therapy. Two patients died, one of MAS and one of cardiac amyloidosis. Opportunistic infections, tuberculosis, or the new onset of autoimmune disease were not observed. Sustained remission of the disease after treatment with tocilizumab was reported in four patients [68].

In the global double-blind placebo-controlled TENDER trial 120 patients with active systemic onset JIA (aged 2–17 years) with a previous inadequate response to NSAIDs and corticosteroids were randomly assigned in a 2:1 ratio to receive tocilizumab every 2 weeks (8 mg/kg for patients >30 kg bodyweight; 12 mg/kg for patients <30 kg) or placebo [69].

Significantly more tocilizumab patients reached the primary end point of a PedACR30 response plus absence of fever (85 vs 24%; $p < 0.0001$). Additionally, significantly more patients on tocilizumab than controls achieved a PedACR50/70/90 response at week 12 compared with controls. Of the patients who had fever, anemia or thrombocytosis at baseline, significantly

more tocilizumab patients than controls had no fever, had normal hemoglobin levels and normal platelet counts at week 12. The response rate was not influenced by the number of affected joints, nor by the presence of fever at initiation of treatment. Pretreatment with anakinra had no negative impact on the effectiveness of tocilizumab, while patients with no prior TNF inhibitor therapy had a slightly better response than those who have been exposed to TNF antagonists. The combination with methotrexate had no effect on the efficacy of tocilizumab in this trial. Serious adverse events were rare: angioedema, urticaria, varicella infection and bacterial arthritis resolved without sequelae. According to these results tocilizumab seems highly effective in treating systemic-onset JIA.

In polyarticular JIA patients, tocilizumab has been tested in an open-label trial with 19 patients [70]. While all but one patient responded to at least the PedCAR30 criteria, the data gained by an open-label design allow a limited assessment only. As a consequence of the successful trial in Japanese children tocilizumab was approved for the treatment of systemic and polyarticular JIA in Japan in 2008. The global placebo-controlled CHERISH trial in polyarticular JIA patient with and without prior exposure to TNF inhibitors is ongoing.

Inhibition of T-cell costimulation

■ Abatacept

Abatacept is a CTLA4–IgFC γ fusion protein with long plasma half-time for therapeutic use. The mechanism of action of abatacept is significantly different from that of other biologics. For stimulation of T cells an interaction of the T-cell receptor (TCR) with the HLA class 2 antigen of the antigen-presenting cell (APC) is crucial, as well as an interaction between accessory membrane antigens. By interaction between CD28 on T cells and CD80 and CD86 on APCs, the T cell is stimulated. The CTLA4 antigen on T cells may also enter into an interaction with CD80/CD86, resulting in anergy or even apoptosis. Abatacept binds to CD80/CD86 on APCs, thereby preventing T-cell activation.

In a double-blind randomized placebo-controlled study, 190 patients with polyarticular JIA were initially treated with abatacept for 4 months at a dose of 10 mg/kg monthly [71]. After 4 months, 123 of 170 remaining patients showed a response to the PedACR30 criteria. 76% of patients not previously treated with TNF inhibitors achieved a response according to the PedACR30, 60% a PedACR50 and 36%

a PedACR70 response. 13% achieved clinical remission (inactive disease). Patients who have previously been exposed to TNF inhibitors had a significantly less frequent response to therapy (PedACR30/50/70 in 39/25/11%). The response rate to therapy was comparable in all JIA categories. In the following placebo-controlled double-blind phase, significantly more patients in the placebo group had disease flares compared with patients receiving abatacept. 33% of placebo patients but only 20% of abatacept patients in the 6-month study period had a relapse ($p = 0.0003$). The PedACR50 response rate increased until the end of the 6-month controlled phase to nearly 80% of patients receiving abatacept, with over 50% of patients showing a PedACR70 response [71].

The tolerability of abatacept was good. There were comparable numbers of adverse events on abatacept to those on placebo. One case of acute lymphatic leukemia was observed in a patient who at inclusion already had a conspicuous blood count. In the double-blind phase, no serious adverse events was observed. 12 patients experienced new antinuclear antibodies, and antibodies to dsDNA occurred in nine patients. Clinically, there were no cases of lupus.

Abatacept is applied intravenously in a dosage of 10 mg/kg biweekly at weeks 0, 2, 4 and then every 4 weeks. In contrast to TNF antagonists, clinical effects of abatacept set in with a delay and usually increase with continuation of therapy over several months [72].

Abatacept has been approved for treatment of JIA patients of 6 years or older with polyarticular arthritis in patients refractory or intolerant to TNF inhibitors although this subgroup of patients responded to a much lesser extend to treatment than biologic naive patients.

B-cell depletion

Rituximab is a chimeric anti-CD20 antibody that specifically binds and destroys CD20 positive B cells, leading to several months or longer B-cell depletion. Rituximab is a well established therapeutic option in adult rheumatoid arthritis. It has so far not been regularly studied in JIA. While some case reports and series have described beneficial effects in so far nonresponsive patients there was only one study with a larger number of patients [73–76]. In this open study 50 children with refractory JIA (39 systemic and 11 with polyarticular JIA) aged 2.3–19 years were treated with rituximab [77]. The majority of patients previously failed on IL-1 inhibitors and TNF- α blockers. A decrease in disease activity

was observed within 6–8 weeks, with a decline in systemic and articular manifestations as well as laboratory parameters of inflammation. The interpretation of the results is limited by the uncontrolled character of the study and by the indeterminable effect of concomitant treatment including high dosage intravenous corticosteroids. Adverse events, infections, leukopenia and neutropenia have been described in several patients. Furthermore, as pointed out in a survey on children exposed to rituximab, long-lasting B-cell depletion is not uncommon and hypogammaglobulinemia may necessitate immunoglobulin replacement [78]. This observation is contrary to experience in adulthood. The incomplete maturation of the immune system may limit B-cell depletion as an irreversible form of therapy in childhood to exceptional indications.

Therapeutic algorithm in JIA

The choice of initial therapy of JIA is made on the basis of clinical presentation, the activity of the disease, the JIA category and the approval situation (TABLE 2). For initial treatment NSAIDs and intra-articular corticosteroids are available (FIGURE 1). Symptomatic treatment is often started on a suspected diagnosis of JIA while establishing the diagnosis of chronic arthritis requires duration of symptoms for at least 6 weeks.

In case of a seropositive or seronegative polyarthritis (with or without detection of rheumatoid factor) an effective therapy should be started as soon as possible because of the unfavorable prognosis. The goal of treatment is a complete control of inflammation (remission). First evidence has been published that there may be a 'window of opportunity', which meant that success rate is higher in patients who received an early treatment [22]. Since establishing the diagnosis of JIA requires a persistent disease for at least 6 weeks, a potentially effective therapy should be started soon thereafter. It consists of a combination treatment of an NSAID, oral and intra-articular corticosteroids, and a DMARD. Methotrexate is currently the only approved drug suitable for 'first-line' treatment of polyarticular JIA, for which scientific evidence of efficacy exists. A recognizable effect of methotrexate therapy can be expected at 3 months of treatment. Usually, efficacy increases further over the next 3–6 months and may get stronger thereafter. If the response to treatment is insufficient, the dose can be increased up to 20 mg/m²/week or 0.5 mg/kg/week, respectively [10]. In case of significant limitation of physical activity due to pain or stiffness, low-dosed oral corticosteroids can be used for

Table 2. Current treatment option for juvenile arthritides with biologics.

Principle of activity	Generic name	Trade name	Evidence	Dosage and treatment interval	Approval situation in childhood
TNF- α -blockade	Etanercept	Enbrel®	Placebo-controlled study	0.4 mg/kg s.c. 2 weeks, maximum 25 mg or 0.8 mg/kg/week, maximum 50 mg/week	Juvenile polyarthritis over 4 years of age (EU), over 2 years of age (US) Psoriasis over 6 years of age (EU)
	Adalimumab	Humira®	Placebo-controlled study	40 mg s.c./2 weeks	Juvenile polyarthritis over 4 years of age
	Infliximab	Remicade®	Placebo-controlled study	5 mg/kg i.v. 4–8 weeks [†]	Crohn's disease (specific indications, over 6 years of age)
	Golimumab [†]	Simponi®	None		None
	Certolizumab [†]	Cimzia®	None		None
IL-1-blockade	Anakinra	Kineret®	Placebo-controlled study	1–4 mg/kg/day s.c.	None
	Rilonacept	Arcalyst®	Placebo-controlled study	2–4 mg/kg/2 weeks i.v.	Muckle-Wells syndrome/CAPS US only
	Canakinumab [†]	Ilaris®	Open study	4 mg/kg/4 weeks s.c.	Muckle-Wells syndrome/CAPS over 4 years of age
IL-6-blockade	Tocilizumab	Actemra® (Japan)	Placebo-controlled study (systemic JIA)	8–12 mg/kg/2 weeks i.v. (systemic JIA)	Systemic and poly-JIA since 2008 in Japan only
		Roactemra® (EU)		8 mg/kg/4 weeks i.v. (poly-JIA)	Systemic JIA in US and EU expected in June 2011
Blockade of T-cell costimulation	Abatacept	Orencia®	Placebo-controlled study	10 mg/kg/4 weeks i.v. [‡]	Juvenile polyarthritis over 6 years of age in TNF-unresponsive or intolerant patients
B-cell depletion	Rituximab [†]	MabtheRA®	Case series	2–4 courses of approximately 375 mg/m ² up to 1000 mg i.v.	None

[†]To date, no controlled clinical trials in JIA patients have been published.
[‡]Initial dosing at weeks 0 and 2.
CAPS: Cryopyrin associated periodic fever syndrome; i.v.: Intravenous; JIA: Juvenile idiopathic arthritis; Poly-JIA: Polyarticular JIA; s.c.: Subcutaneous.
Reproduced with permission from [84].

'therapeutic bridging'. Particularly active joints can be injected with triamcinolonehexacetone. Inefficiency or intolerability of treatment is an indication for modification of treatment or additional therapy.

Etanercept, approved from the age of 4 years in the EU and the age of 2 years in the USA, and adalimumab, approved from the age of 4 years are currently the only drugs available in this situation. After starting TNF antagonists a rapid response can be expected within weeks [28]. Efficacy should be assessed after 3 months at the latest.

If the response is insufficient, treatment should be modified. Monotherapy with etanercept or adalimumab can be supplemented with methotrexate, if it has been tolerated well before. Switching to a different TNF antagonist is another option [79]. In cases with a history of uveitis adalimumab may be preferred over etanercept since it has shown efficacy in a number of open-label studies [44,45]. Maintaining methotrexate when etanercept is chosen is an alternative since it may prevent uveitis flares as

recently pointed out in an observational study [80].

Abatacept is an approved alternative therapy for nonresponders to TNF inhibitors while tocilizumab is approved in Japan only. The use of infliximab (combination with methotrexate is obligatory) or a combination of etanercept and leflunomide can be attempted; however, it is off-label and scientific evidence is scarce.

Apart from ocular involvement, the prognosis of persistent oligoarthritis is relatively favorable. Therefore, therapy with DMARDs or TNF antagonists is initiated with caution. If arthritis is refractory to NSAIDs and repeated joint injections or in case of extended oligoarthritis, patients can be treated in the same way as polyarthritis patients.

Patients with ERA presenting with oligoarthritis are treated accordingly. Sulfasalazine is a justifiable alternative to methotrexate in these patients. In case of a polyarticular course of disease patients are treated in analogy to the algorithm for polyarthritis. A favorable response to TNF antagonist can be expected according to uncontrolled data [32].

Since so far there have no controlled trials with biologics performed in juvenile psoriatic arthritis patients, it is treated according to the number of affected joints as polyarticular or oligoarticular JIA. Psoriasis in childhood itself rarely is an indication for systemic immunosuppressants or TNF inhibitors. However, a welcomed response of skin manifestations to methotrexate as well as TNF inhibitors can be expected [81]. Beneficial effects of etanercept in juvenile psoriatic arthritis have been described [82]. In a large cohort of JIA patients documented in the German registry, of all JIA categories patients with psoriatic arthritis were most likely to gain inactive disease upon treatment with etanercept [37]. Besides beneficial effects of etanercept on psoriasis, the primary occurrence of psoriasis, especially of palmoplantar pustulosis, upon treatment with TNF inhibitors has been described [27]. Simply switching TNF inhibitors can resolve this problem.

Among all JIA subtypes systemic-onset JIA is considered especially problematic as to success of treatment and prognosis. Initially, fever and other systemic symptoms have to be managed. In mild cases treatment with NSAIDs (ibuprofen, indometacin or naproxen) alone can be tried. High doses of corticosteroids (prednisone,

prednisolone, methylprednisolone in a dosage of 2 mg/kg/day in three single doses) are indicated, if the fever does not resolve quickly. After 2 weeks of high-dose treatment, weekly tapering of the dosage may be tried by no more than 25% of the previous dose. Dosages below 1 mg/kg per day may be administered as a single dose. If disease is resistant to this treatment or relapses during tapering of corticosteroids, additional treatment is necessary. In case of prominent joint involvement patients can be treated according to recommendations for polyarthritis/oligoarthritis. Treatment with methotrexate may improve the arthritis without significant changes of systemic features [9]. If systemic symptoms are still ongoing, the use of anakinra is an option [55,56]. In patients with prominent systemic manifestations, anakinra also can be used as primary drug in patient in whom steroids have to be avoided. In Japan, tocilizumab is an approved treatment for resistant systemic JIA. It will become available in 2011 in the EU and USA and will be useful for treatment of systemic and articular manifestations. Alternatives, such as the IL-1 inhibitors rilonacept and canakinumab, are presently not approved. B-cell depletion with rituximab may be tried in patients with refractory disease [77].

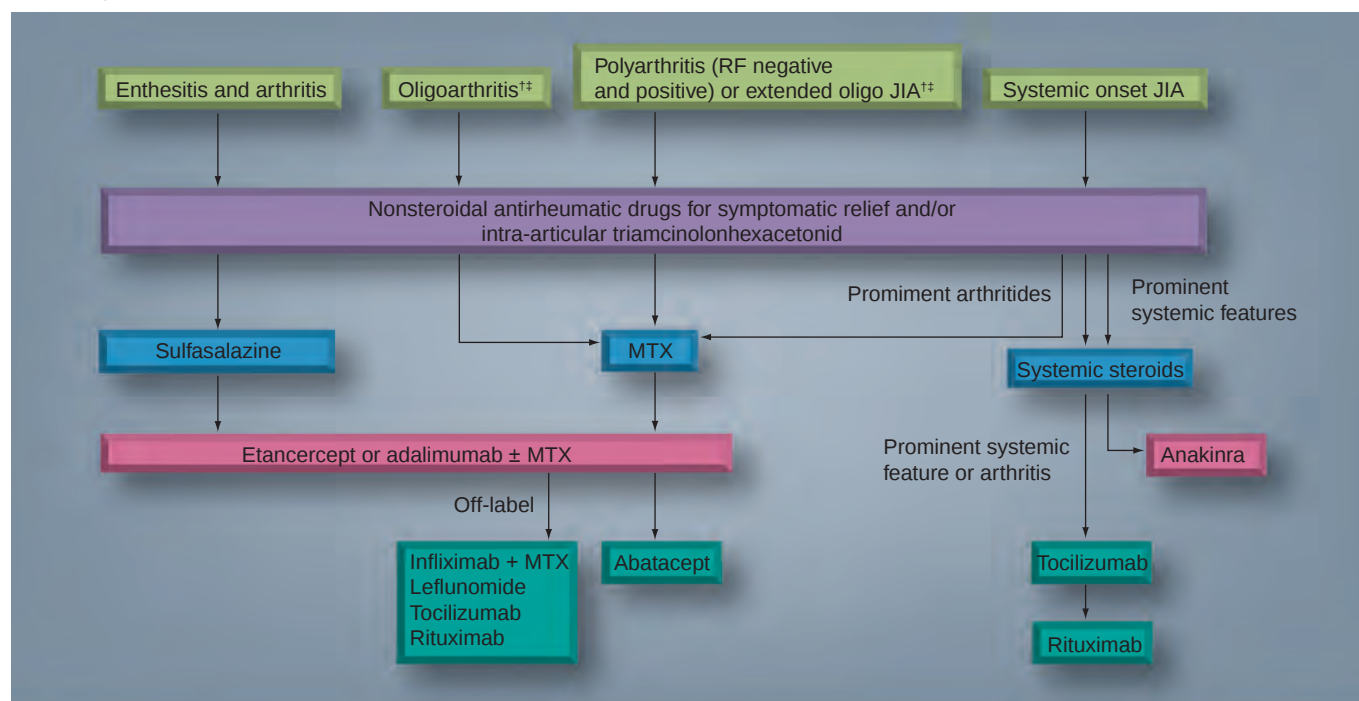


Figure 1. Proposed algorithm for treatment of juvenile idiopathic arthritis. Details are listed in the text. Before off-label treatment is considered, approved drugs have to be tried according to the local legal situation.

[†]Oligoarthritis defined by the involvement of up to four joints in the first 6 months of the disease may extend to polyarticular JIA but is still labeled as (extended) oligoarthritis.

^{*}Psoriasis arthritis is treated according to the joint manifestations as oligoarthritis or polyarthritis.

JIA: Juvenile idiopathic arthritis; MTX: Methotrexate; RF: Rheumatoid factor.

Conclusion

In the prebiologic era JIA was associated with significant morbidity, leading to functional disability, growth defects and ocular damage. In the last decade several biologic response modifiers have been introduced targeting pro-inflammatory cytokines like TNF- α , IL-1 and IL-6 and inhibiting T-cell costimulation or inducing B-cell depletion. Several treatment strategies have already been analysed by randomized controlled trials and for some of them long-term observational studies have provided data on long-term safety and efficacy. This progress enables pediatric rheumatologists to design a treatment strategy for each individual patient according to the extent and severity of the arthritides and extra-articular manifestations. These developments raise the hope that in numerous patients remission or residual disease not affecting the development of the child can be reached to markedly improve long-term functional outcomes of patients with JIA.

Future perspective

The development of new drugs and the obligation to also perform studies in children who suffer from similar clinical conditions as adults are clearly the origin of the progress in treatment of children with rheumatic diseases. The rarity of most of the

rheumatic diseases in childhood has prevented such developments in pediatric rheumatology for decades. The developments to be reached in the next 5–10 years will enable pediatric rheumatologists to treat the vast majority of their patients according to evidence-based guidelines.

Each entire JIA subcategory aims to describe a distinct disease with a particular pathogenesis, clinical course and prognosis. Therapeutic experiences with cytokine inhibitors have for example triggered the discussion about the ILAR classification of JIA. For instance, it is suggested that within systemic JIA there are different diseases depending on their response to anti-IL1 or anti-TNF.

For those patients with a less beneficial prognosis strategies for early and effective treatment will have to be developed. These will be guided by a distinct risk profile, which might be recognizable by progress in proteomics and genomics and individualize therapeutic strategies by identifying those treatment with the highest likelihood of success. Treatment intensity will be guided by new biomarkers indicating residual disease, which will also prevent overtreatment. For those patients with a beneficial prognosis there is a chance for remission of the disease and strategies for a withdrawal of medical treatment have to be developed.

Executive summary

- Due to improvement in the therapeutic options more categories of juvenile idiopathic arthritis (JIA) have become treatable.
- First evidence has been presented for a 'window of opportunity' giving preference to an early institution of an effective drug therapy.
- Methotrexate followed by TNF inhibitors are recommended for polyarticular JIA according to controlled trials and long-term treatment experience.
- At least for methotrexate it has been shown that in patients reaching remission on drug for at least 6 months duration, discontinuation is an option not inferior to a prolongation of treatment for 12 months.
- Discontinuation of methotrexate treatment in patients with stable clinical inactive disease may be guided by biomarkers.
- In resistant systemic-onset JIA patients with ongoing systemic activity, inhibitors of IL-1 or IL-6 are considered to be superior while in those patients with prominent arthritis TNF inhibitors are still a valuable option.
- Abatacept is an approved option for JIA patients refractory to treatment with TNF inhibitors, while B-cell depletion with rituximab as an off-label alternative is restricted to exceptional patients with resistant and intolerable disease activity.

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Website

- 101 A Study of the Safety and Efficacy of CNTO 148 (Golimumab) in Children With Juvenile Idiopathic Arthritis (JIA) and Multiple Joint Involvement Who Have Poor Response to Methotrexate (GO KIDS)
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Treatment options with biologics for juvenile idiopathic arthritis

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Activity evaluation: where 1 is strongly disagree and 5 is strongly agree.

	1	2	3	4	5
The activity supported the learning objectives.					
The material was organized clearly for learning to occur.					
The content learned from this activity will impact my practice.					
The activity was presented objectively and free of commercial bias.					

1. A 5-year-old boy presents with a new diagnosis of juvenile idiopathic arthritis (JIA) with polyarthritis. Which of the following disease-modifying antirheumatic drugs (DMARDs) is indicated as a first-line agent for this patient?

- ☐ A Sulfasalazine
- ☐ B Leflunomide
- ☐ C Infliximab
- ☐ D Methotrexate

2. The patient has a poor response to primary therapy. Which of the following medications is most appropriate to recommend now?

- ☐ A Anakinra
- ☐ B Rituximab
- ☐ C Abatacept
- ☐ D Etanercept

3. The patient develops uveitis. Which of the following DMARDs may be particularly effective for patients with JIA and uveitis?

- ☐ A Anakinra
- ☐ B Adalimumab
- ☐ C Etanercept
- ☐ D Tocilizumab

4. Two years later, you see this patient's 4-year-old sister who has developed JIA with prominent systemic features despite initial treatment with corticosteroids. Which of the following DMARDs might be the best choice for her?

- ☐ A Anakinra
- ☐ B Rilonacept
- ☐ C Tocilizumab
- ☐ D Abatacept