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THERAPY IN PRACTICE

Management of Juvenile Idiopathic Arthritis: A Clinical Guide

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Abstract Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood. The outcome in patients with JIA has markedly improved with the advent of biologic drugs. Although early aggressive therapy with biologics seems to be very effective, this approach leads to overtreatment in patients who would respond to classic disease-modifying anti-rheumatic drugs. Therefore, methotrexate remains first-line long-term therapy for most children with polyarticular JIA. Tumor necrosis factor-α inhibitors have shown tremendous benefit in children with refractory non-systemic JIA. Similar effects have been observed with interleukin-1 and interleukin-6 blockade in patients with systemic JIA. Correct choice and timely use of available medications to achieve early and sustained remission with as few side effects as possible remain challenges for the treating physician. In this review, a practical, clinically oriented guide to the management of JIA is provided, focusing on pharmacological treatment with non-steroidal anti-inflammatory drugs, intra-articular and systemic corticosteroids, disease-modifying anti-rheumatic drugs, and biologic agents. In addition, issues regarding treatment failure, early aggressive treatment, and drug tapering are discussed, with alternative treatment options being suggested.

Key Points

Intra-articular steroids are suggested as first-line treatment for oligoarticular juvenile idiopathic arthritis (JIA) to avoid side effects of systemic medications and as adjunctive treatment to disease-modifying anti-rheumatic drugs and biologics. Although they are highly effective anti-inflammatory drugs, the relapse rate is high.

Methotrexate should be used as first-line treatment in polyarticular JIA. The expected rate of remission on medication is around 70 %, but compliance may be a problem and should be regularly checked.

Biologics should be used in refractory JIA. Anti–tumor necrosis factor-α agents are the biologics of first choice in non-systemic JIA, and interleukin-1 and interleukin-6 blockers are the first choice in systemic JIA.

In cases of treatment failure with biologics, there are several treatment options, including increasing the dosage of the drug, switching to another drug targeting the same cytokine, or switching to a drug targeting another cytokine.

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1 Introduction

Juvenile idiopathic arthritis (JIA) is the most common chronic rheumatic disease of childhood, characterized by chronic joint inflammation of unknown etiology and beginning before the age of 16 years [1]. Joint inflammation can manifest with joint pain, a reduced range of

motion, effusion, or warm skin over the joint, and it is arbitrarily defined as chronic when it persists for more than 6 weeks. In the last two decades, introduction of several new drugs combined with old therapies has significantly improved the long-term outcome of children with JIA [2–8]. The aim of this review is to provide a practical, clinically oriented guide to the management of JIA, focusing on pharmacological therapies. Non-pharmacological interventions—such as physical therapy and psychosocial support, which are also essential parts of the management of children with JIA—are beyond the scope of this review.

The current classification of JIA recognizes seven distinct categories, including systemic JIA (SJIA), oligoarthritis, rheumatoid factor (RF)–negative polyarthritis, RF-positive polyarthritis, juvenile psoriatic arthritis (JPsA), enthesitis-related arthritis (ERA), and undifferentiated arthritis [1]. In all JIA subtypes, non-steroidal anti-inflammatory drugs (NSAIDs) and intra-articular steroids (IASs) are used either as first-line treatment or in addition to disease-modifying anti-rheumatic drugs (DMARDs). In this review, the role of NSAIDs and IASs is discussed in the "General Medication Usage" section, followed by sections on the use of DMARDs and biologics in specific JIA categories. The concepts of "treat to target" and early aggressive treatment are presented, followed by current experience and recommendations for drug tapering and withdrawal.

This clinical guide is based on the results of clinical studies in JIA treatment, published recommendations [9, 10], and the personal experience of the authors (Fig. 1).

2 General Medication Usage

NSAIDs and IASs are used in all JIA categories, either as induction treatment or as adjunctive treatment in patients who have signs of inflammation despite use of other medications. Unfortunately, they allow stable and long-lasting remission only in a minority of patients with JIA.

2.1 Non-steroidal Anti-inflammatory Drugs

Symptoms of arthritis have negative impacts on the quality of life; therefore, anti-inflammatory treatment should be offered to all patients with arthritis, even within the first 6 weeks of the disease. Naproxen has been shown to reduce inflammation in patients with JIA; the response rate according to the American College of Rheumatology (ACR) Pediatric 30 criteria (ACR Pedi 30, defined as at least 30 % improvement from baseline in three of any six variables in the core set of criteria, with no more than one of the remaining variables worsening by >30 %) improved from 64 to 74 % from month 3 to month 12. However, the ACR Pedi 70 response rates were low (29 % at month 3 and 50 % at month 12) [11]. According to the current recommendations, NSAIDs are considered the agents of first choice for controlling joint and tendon sheath inflammation in patients with all JIA categories [12, 13]. In the 2011 ACR recommendations, NSAIDs were suggested mainly as adjunctive treatment. NSAIDs were suggested as brief-course monotherapy only in patients without poor prognostic factors and with low or moderate disease activity [9]. In the Australian and German recommendations, use of NSAIDs was generally advised, but no specific descriptions of their role in JIA treatment were provided [14, 15]. NSAIDs were not included in the consensus treatment plans for new-onset polyarticular JIA developed by the Childhood Arthritis and Rheumatology Research Alliance (CARRA) [16].

Although they are very effective in reducing symptoms in patients with reactive arthritis, they generally do not have a major role in the long-term treatment of JIA and, in particular, they do not halt progression of radiographic changes.

In our practice, sustained remission in JIA is only rarely achieved on monotherapy with NSAIDs, which are generally not used for long-term therapy. NSAIDs are commonly prescribed as initial therapy in patients during the process of exclusion of other etiologies of arthritis, while the patient awaits application of IAS treatment, and for up to 8 weeks after an IAS injection until the follow-up outpatient clinic visit (Table 1).

Patients with severe disease at onset that involves the cervical spine or hip joint and/or demonstrates radiographic bone damage should be treated early with systemic steroids, DMARDs, and/or biologics, without awaiting a clinical response to NSAID monotherapy.

2.1.1 Adverse Effects of Non-steroidal Anti-inflammatory Drugs

The most common adverse effects are gastritis and tubulointerstitial nephritis. Although the frequency of gastrointestinal complaints and gastritis with NSAIDs seems to be lower in children than in adults, proton-pump inhibitors should be considered in children receiving long-term NSAID treatment. Kidney and liver function should be evaluated 1 month after the introduction of treatment and every 3 months thereafter.

2.2 Intra-articular Steroids

Long-term remission in patients with JIA is rarely achieved and maintained with NSAID monotherapy. Most patients

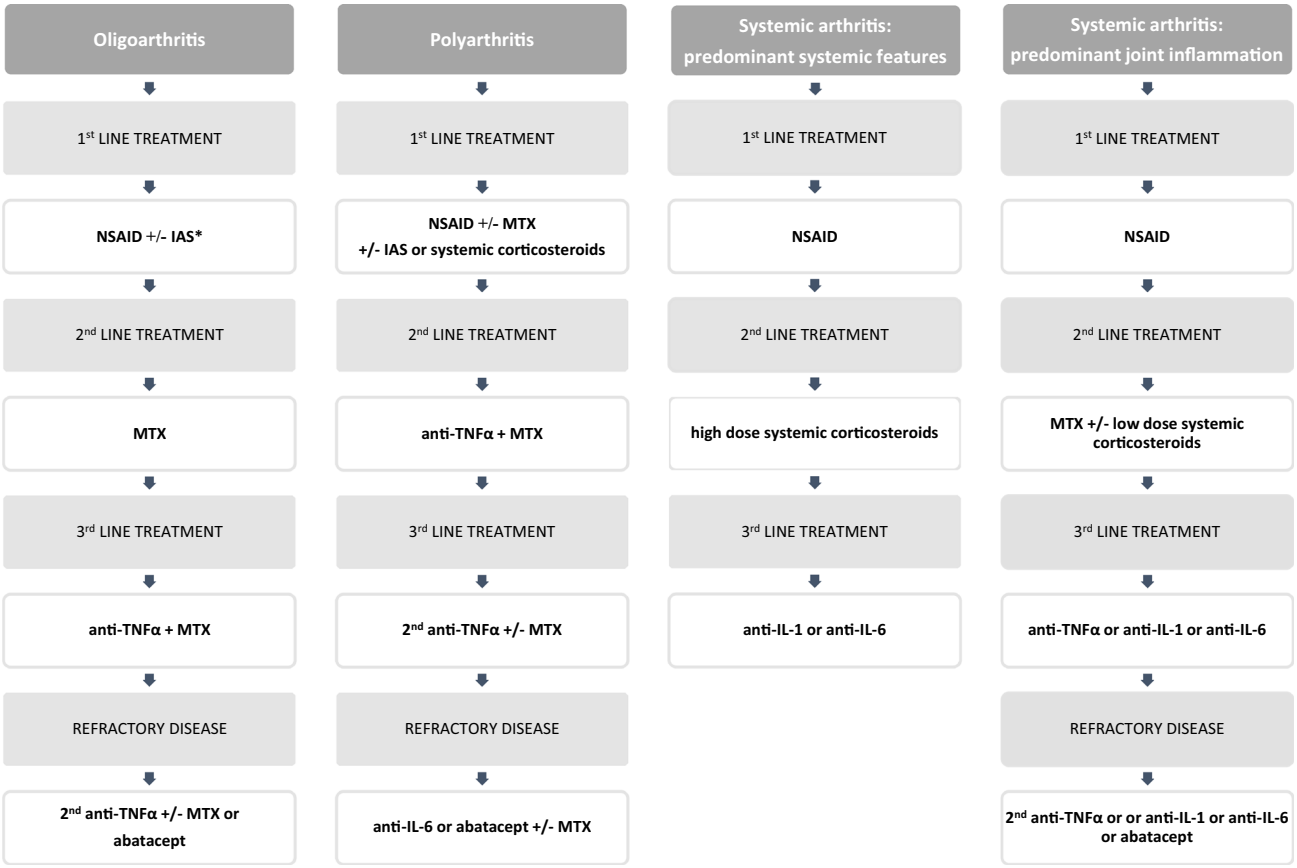

Fig. 1 Flow chart for general treatment of patients with juvenile idiopathic arthritis; see text for details. *Asterisk* indicates an intra-articular steroid (IAS) can be used as adjunctive treatment for arthritis that persists despite methotrexate (MTX) or biologic treatment. *anti-IL-1* biologic drug that binds interleukin-1, *anti-IL-6* biologic drug that binds interleukin-6, *anti-TNFα* biologic drug that binds tumor necrosis factor-α, *NSAID* non-steroidal anti-inflammatory drug

Table 1 Daily dosages and administration intervals for the most commonly used non-steroidal anti-inflammatory drugs (NSAIDs)

NSAID	Daily dosage (mg/kg BW)	Administration interval
Naproxen	15	BID
Ibuprofen	30	TID
Diclofenac	2	TID
Meloxicam	0.125	OD
Indomethacin[a]	1–3	TID–QID

BID daily dose divided into two equal parts, *BW* body weight, *OD* once daily, *QID* daily dose divided into four equal parts, *TID* - daily dose divided into three equal parts

[a] Used mainly for enthesitis-related arthritis and systemic juvenile idiopathic arthritis

require additional treatment, and this decision is based primarily on the number of affected joints. In patients with a small number of affected joints, IASs are the preferred treatment to avoid side effects of systemic medications.

Although IAS injections effectively suppress inflammation in injected joints, long-term disease remission after IAS injections depends on the disease course. Different biomarkers in synovial fluid (matrix metalloproteinase [MMP]-3, interleukin [IL]-6, and IL-10) have been found to be associated with the response to IASs. Higher levels of serum IL-6 predicted a shorter time to relapse, and higher levels of serum IL-10 predicted a longer duration of the IAS effect [17].

Different corticosteroids are used for IAS therapy, with a preference for long-acting corticosteroids. Triamcinolone hexacetonide (TH) and triamcinolone acetonide (TA) are most widely used. Although pharmacokinetic studies have shown that the biological effects of TA are equivalent to those of TH, TH was shown to be more effective than TA even when TA was given at higher dosages. The reported relapse rate in knees, ankles, and wrists injected with TA was 54 % versus only a 15 % relapse rate in joints injected with TH [18]. The percentage of joints with lasting remission was also higher with TH than with TA (80 versus

47 % after 12 months, and 64 versus 32 % after 24 months) [18].

Given the literature data and clinical experience, IAS therapy appears to be efficient and safe for arthritis in various joints. Full remission of joint inflammation after IAS treatment has been achieved in 58–82 % of large joints, including knees, ankles, hips, wrists, shoulders, and elbows [19, 20]. Similar response rates after IAS treatment have been observed also in the temporomandibular joint, with complete resolution of pain and a significantly increased range of movement in 77 and 43 % of patients, respectively [21]. Moreover, IASs have been shown to reduce JIA disease activity evaluated by different scores [22].

Discontinuation of all oral medications after IAS treatment can be accomplished in up to 74 % of patients with oligoarticular JIA, while correction of joint contracture and reduction of leg-length discrepancies can be achieved in most injected joints. IASs are similarly effective in patients with a Baker's cyst or tenosynovitis. Infections and other serious complications after IAS therapy are exceptional [19].

In our practice, treatment with IAS TH (Table 2) is used as first-line treatment if there are up to five affected joints. IASs are also used as adjunctive treatment in patients with arthritis persisting in a few joints despite treatment with DMARDs or biologics.

In contrast to the slow resolution of arthritis seen with methotrexate (MTX) and leflunomide (4–6 weeks; see below), absence of inflammation can already be observed a few days after an IAS injection. Therefore, in patients with contractures or radiological damage, IAS injections are frequently administered concomitantly with introduction of a DMARD to stop the progression of damage in joints immediately, even before the DMARD begins to take effect.

Table 2 Suggested doses of triamcinolone hexacetonide for intra-articular joint injection[a]

BW (kg)	Joint	Dose (mg)
<20	Shoulder, knee, hip	20
	Elbow, wrist, ankle, subtalar	10
20–40	Shoulder, knee, hip	30
	Elbow, wrist, ankle, subtalar	15
>40	Shoulder, knee, hip	40
	Elbow, wrist, ankle, subtalar	20
	Fingers[b,c], toes[b,c], tendon sheaths[b]	5–10
	Temporomandibular joint	10

BW body weight

[a] For triamcinolone acetonide, double the dose of triamcinolone hexacetonide

[b] The drug should be mixed with lidocaine 1:1

[c] An alternative treatment for fingers and toes is methylprednisolone acetate 5–10 mg (mixed with lidocaine 1:1)

The procedure may be performed with or without ultrasound guidance and under general anesthesia, conscious sedation, or local anesthesia alone. The choice of sedation or anesthesia should be tailored to the patient's needs. The sedation can be administered by an anesthesiologist or by a physician who has undergone a specialized sedation course [23].

In our practice, general anesthesia is rarely used for IAS therapy. It is mainly reserved for patients in whom we expect difficulties with conscious sedation or those who have experienced complications during previous procedures. Different medications are used for conscious sedation in younger children, including ketamine [19], propofol [19], nitrous oxide [24], and midazolam [23]. Eutectic lidocaine/prilocaine cream (EMLA®) and subcutaneous lidocaine are most frequently used for local anesthesia [23].

Our practice is to sedate children under the age of 6 years with midazolam 0.1–0.2 mg/kg and ketamine 0.8 mg/kg intravenously. Older children receive oral midazolam 3.25–7.5 mg half an hour before the procedure and EMLA® at least 1 hour before the procedure. Since the depth of the analgesic effect of EMLA® is less than the depth of the synovial membrane, additional local anesthetic (lidocaine) is applied during the procedure [23]. The decision on the type of anesthesia is always personalized according to each individual patient.

The effect of IAS treatment can be permanent, but in JIA, joint inflammation may recur after the medication disappears from the joint. In the case of an arthritis relapse, the IAS injection can be repeated, but not more frequently than every 3 months and three times per year.

2.2.1 *Adverse Effects of Intra-articular Steroids*

Sometimes, local adverse effects are observed after IAS treatment, including skin hypopigmentation or atrophy at the site of the injection or—extremely rarely—a joint infection. Changes in the patella are observed even more rarely.

In one study [20], femoral head necrosis following hip IAS treatment was observed in two of 67 patients, both of whom were also receiving long-term systemic corticosteroids. No necrosis occurred in 30 children who did not receive systemic corticosteroids.

2.2.2 *Exceptions to Intra-articular Steroids*

There are some exceptions to treatment with IASs. First, to prevent joint infection, IAS treatment should not be given if there are any signs of infection on the skin overlying the joint. Second, in cases of accompanying chronic uveitis

that does not respond to local treatment, systemic treatment for both uveitis and arthritis is usually indicated even if only a small number of joints are inflamed. Third, systemic treatment should also be considered in patients with cervical spine or hip arthritis, and in patients with destructive arthritis and poor prognostic features (erosions, joint-space narrowing, positive RF, or anti–cyclic citrullinated peptide [anti-CCP] antibodies).

3 Oligoarticular and Polyarticular Juvenile Idiopathic Arthritis

In oligoarthritis that persists despite IAS therapy and in polyarticular disease, systemic DMARDs represent first-line long-term treatment.

3.1 Disease-Modifying Anti-rheumatic Drugs

3.1.1 Methotrexate

MTX is widely known as a folic acid analog and an inhibitor of several different enzymes in the folate pathway. Its immunomodulatory and anti-inflammatory actions are believed to be mediated through release of endogenous adenosine, especially locally at the site of inflammation [25]. MTX is the cornerstone of initial treatment in polyarticular JIA [9, 14–16]. Because of its high efficacy and safety, it is the most commonly prescribed DMARD in JIA, as well as in various other rheumatic diseases of childhood [26].

The standard effective dosages of MTX in JIA are 10–15 mg/m^2/week [9, 14–16]. Further increases in the MTX dosage have not been associated with additional therapeutic benefit [27]. The bioavailability of MTX is about 15 % higher after subcutaneous administration than after oral administration, but pain associated with subcutaneous injections is a significant drawback, particularly in younger patients [28]. Nevertheless, parenteral administration should be considered in patients with a poor response or significant gastrointestinal toxicity after orally administered MTX.

MTX is an efficient drug, with 65–90 % of patients successfully responding to treatment [27, 29]. In a large, international, randomized trial, which included 595 children with polyarticular JIA, the ACR Pedi 30 response rate after 6 months of treatment with MTX was 72 %, and the ACR Pedi 70 response rate was 38 %. More than 60 % of non-responders achieved an ACR Pedi 30 response after an increase in the MTX dosage [27]. MTX also significantly improved a wide range of health-related quality-of-life components, particularly in the physical domains [30]. In our cohort of 119 JIA patients treated with MTX, 74 % achieved at least a 30 % improvement in the Juvenile Arthritis Disease Activity Score (JADAS)-71 (which includes a complete 71-joint count) after 6 months of treatment, and 70 % of patients achieved the state of inactive disease in a median time of 5.9 months.

In our practice, we generally start with oral MTX in a dosage of 10 mg/m^2/week. If the patient tolerates the drug well and arthritis persists, the dosage is increased to 15 mg/m^2/week and applied subcutaneously to achieve maximum efficacy. MTX is a slow-acting drug, displaying its full therapeutic effect in 6–8 weeks, which needs to be taken into account when efficacy is being assessed [31].

3.1.1.1 Adverse Effects of Methotrexate MTX is generally safe and well tolerated in children, but gastrointestinal complaints are quite common and can result in intolerance of MTX in a significant number of children [25, 26, 32]. It is possible to administer an anti-emetic drug, such as ondansetron, before administering MTX, although antiemetics are rather ineffective in reducing these symptoms [32]. Hepatic fibrosis is extremely rare in children, but transient elevation of liver transaminase levels occurs in 10–20 % of patients [25, 26]. The transaminase levels usually normalize after a short interval off treatment. In order to minimize gastrointestinal and hepatic adverse effects, folic acid may be added in a dosage of 1 mg once daily [33]. MTX does not significantly affect immune function, and severe infections are very uncommon with low-dose MTX. Currently, it is recommended that MTX therapy be interrupted in cases of severe infections [31]. MTX is teratogenic, and it is necessary to use contraception while taking the drug and for 3–6 months after discontinuation [25].

3.1.1.2 Monitoring In our practice, we exclude active tuberculosis by a chest X-ray and Mantoux testing or an interferon (IFN)-γ release assay before the start of MTX treatment. While immunization with inactivated vaccines can be performed during MTX treatment, live attenuated vaccines are best given before the treatment is started. There have been published case series of safe vaccinations with live attenuated vaccines in patients with JIA receiving MTX as well as biologics [34–36]. If exposure to varicella is documented and the anti-varicella titer is either non-protective or unknown, we generally suggest prophylaxis with varicella hyperimmunoglobulin within 72 hours and treatment with acyclovir if the patient develops varicella, especially in the presence of concomitant corticosteroid treatment [31].

Testing of serum creatinine and liver enzyme levels and a complete blood count are recommended prior to initiation of MTX.

In general, laboratory tests are recommended 1 month after initiation of MTX and then approximately 1–2 months after any subsequent increase in the MTX dosage. Repeated measurements of serum creatinine and liver enzyme levels and a complete blood count are recommended approximately every 3–4 months for patients who are receiving a stable dosage of MTX and have no recent history of abnormal laboratory test results [9]. It is our practice to perform more frequent monitoring in the first month of treatment and each time the MTX dosage is increased, or if the patient experiences febrile illness. In cases of elevated liver enzyme levels, one dose of MTX can be omitted and the liver enzyme levels can be rechecked. If liver enzyme levels remain elevated at >3 times the upper limit of normal after a decrease in the dosage, discontinuation of MTX is recommended [9].

3.1.2 Leflunomide

Leflunomide is another DMARD to be considered for use in polyarticular JIA. In a controlled study of 86 patients with JIA, 68 % of those taking leflunomide and 89 % of those taking MTX achieve an ACR Pedi 30 response. The response rates seen with leflunomide were significantly inferior to those seen with MTX [29]. In a group of 27 patients with JIA who either achieved a suboptimal response to MTX or were intolerant of MTX, 52 % achieved an ACR Pedi 30 response after 26 weeks of leflunomide, which means that this drug could represent a good second-line treatment option [15, 37]. In the CARRA consensus plan, both MTX and leflunomide represent equal choices for the first DMARD [16]. However, in our practice, we prefer MTX to leflunomide as the first choice. Leflunomide is used as an alternative only in cases of intolerance of MTX and mild disease. In refractory disease, biologics are preferred as the second choice.

3.1.2.1 Adverse Effects of Leflunomide The frequencies of adverse events (AEs) are comparable between MTX and leflunomide [29]. Leflunomide is a teratogenic drug, and it is necessary to use contraception during treatment [29]. Laboratory parameter monitoring for adverse effects is, in general, the same for leflunomide as for MTX [9].

3.2 Systemic Steroids

As MTX and leflunomide are slow-acting drugs, induction therapy with IASs, oral corticosteroids, or—rarely—parenteral corticosteroids can be used [33, 38]. In our practice, patients with severe disease receive bridging therapy with prednisolone 0.25–0.5 mg/kg/day for up to 2 weeks and then progressively taper and discontinue prednisolone in approximately 6–8 weeks.

3.2.1 Side Effects of Corticosteroids

Corticosteroid therapy has many short-term and long-term adverse effects, including weight gain, acne, striae rubrae, infections, hypertension, osteoporosis, gastritis, avascular bone necrosis, hyperglycemia, cataracts, and growth suppression, which can sometimes be very severe and irreversible [6].

During the course of therapy with systemic corticosteroids, calcium and vitamin D supplementation, as well as protein-pump inhibitor therapy, are added in order to prevent adverse effects of the corticosteroids.

3.3 Biologic Agents

Some children either do not respond to or are intolerant of IASs or DMARDs. In these children, treatment with biologics is indicated. Elucidation of signaling proteins involved in synovial inflammation has led to development of monoclonal antibodies directed against pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α, IL-6, and IL-17. TNF-α plays a fundamental role in synovial inflammation through activation of cytokine and chemokine expression, expression of endothelial cell adhesion molecules, promotion of angiogenesis, suppression of regulatory T cells, and induction of pain. Similarly, IL-6 drives local leukocyte activation and autoantibody production, and mediates systemic effects that promote acute-phase responses, anemia, cognitive dysfunction, and lipid-metabolism dysregulation [39]. To our knowledge, the response to biologics in relation to serum levels of cytokines—namely, TNF-α and IL-6—has not been studied yet. However, in our clinical practice, we have observed just such a correlation, though this needs to be further tested.

3.3.1 Tumor Necrosis Factor-α Inhibitors

TNF-α inhibitor therapy (etanercept, adalimumab, infliximab) is usually used as the first biologic treatment in refractory oligoarticular or polyarticular JIA.

Etanercept is a fusion protein of the TNF-α receptor and the constant end of the immunoglobulin (Ig) G1 antibody, which binds to soluble TNF-α. It is given subcutaneously once weekly in a dose of 0.8 mg/kg of body weight (BW). In the first clinical trial of use of etanercept in polyarticular JIA, published in 2000, 74 % of children receiving subcutaneous etanercept 0.4 mg twice weekly during the 3-month open-label phase showed an ACR Pedi 30 response [40]. In the double-blind withdrawal phase, the median time to disease flares within the placebo group was 28 days compared with >116 days in the etanercept group ($P < 0.001$), confirming the superior efficacy of the drug

[40]. During long-term open-label extension treatment with etanercept, an ACR Pedi 70 response or greater was achieved by 61 % of patients, according to the last observation [2].

Combined treatment with etanercept and MTX could improve the efficacy of the biologic drug. ACR Pedi 30/50/70 responses were observed in 81/74/62 % of 376 patients, respectively, in the combined etanercept and MTX group, and in 70/63/45 % of 55 patients, respectively, in the etanercept monotherapy group [41].

Data from a German registry show that almost one half of patients treated with etanercept ± MTX achieved the criteria for inactive disease, and one quarter achieved remission on medication. For the inactive disease state and remission on medication, good prognostic factors were a shorter disease duration, a weekly dosage of at least 0.8 mg/kg, a lower active joint count, and a lower Childhood Health Assessment Questionnaire score at baseline. Concomitant administration of MTX raised the relative chance of achieving inactive disease, especially in patients with seronegative polyarthritis [42].

In a Dutch registry, ACR Pedi 30 responses were observed in 77 % of patients in the first 3 months of treatment with etanercept. One half of all patients met the remission criteria. In 29 % patients, no other second-line agents were needed. The rate of serious AEs (SAEs) was low [43].

Adalimumab is a fully human monoclonal antibody, which binds both soluble and transmembrane TNF-α. It is given subcutaneously every other week. The recommended dose of adalimumab for patients aged 2–12 years with polyarticular JIA is 24 mg/m^2 of body surface area up to a maximum single dose of 20 mg for patients aged 2–4 years, and up to a maximum single dose of 40 mg for patients aged 4–12 years.

Adalimumab was studied in 171 patients with active polyarticular JIA that had not responded adequately to treatment with NSAIDs. The patients either had not previously been treated with MTX or had previously been treated with MTX but had experienced AEs or an inadequate response. Patients in this trial were stratified according to concomitant treatment with MTX. After 16 weeks of open-label treatment with adalimumab ± MTX, 74 % of patients receiving adalimumab alone versus 94 % of patients receiving both adalimumab and MTX achieved an ACR Pedi 30 response [3]. In the double-blind withdrawal phase, disease flares occurred in 43 % of patients receiving adalimumab alone (versus 71 % of patients in the respective placebo group) and in 37 % of those receiving adalimumab together with MTX (versus 65 % of patients in the respective placebo group). This study showed the efficacy of adalimumab in JIA either as monotherapy or in combination with MTX [3]. Sustained efficacy of adalimumab was demonstrated also during the long-term, open-label extension phase after 104 weeks of treatment [3].

In patients treated with adalimumab who were included in the German registry, ACR Pedi 30/50/70/90 scores were achieved in 63/61/49/34 % of biologic-naive patients, respectively, at 6 months of treatment [44].

Infliximab, a chimeric monoclonal antibody directed against TNF-α, is given intravenously every 4 weeks in a dose of 3–10 mg/kg BW. The drug is not registered for use in JIA in Europe. In a large, randomized, double-blind, placebo-controlled study of infliximab in children with persistent polyarticular JIA, the primary endpoint of a significant difference between infliximab-treated and placebo-treated patients at 3 months was not reached. The long-term superiority of infliximab to placebo was not studied, since all children received infliximab after the first 3 months of the study. Nevertheless, the drug was shown to be effective in the long-term study extension, and by week 52, ACR Pedi 50 and ACR Pedi 70 responses had been achieved in 69 and 52 % of patients, respectively [45].

In a 3-year, open-label extension study of infliximab plus MTX, ACR Pedi 30/50/70/90 responses at week 204 were achieved in 44/40/33/24 % of patients, respectively, with inactive disease status being achieved in 13 % of patients [46].

In real-life clinical experience, the efficacy of infliximab seems to be comparable to that of other anti-TNF-α drugs, but infusion reactions and inefficiency due to development of anti-drug antibodies are not uncommon [47]. In our practice, infliximab in combination with pulsed steroids is used particularly in JIA patients with atlantoaxial arthritis and in patients with uveitis resistant to DMARDs.

As data from studies show better disease control in patients who receive combined treatment with anti-TNF-α and MTX, MTX is usually continued in our patients during treatment with a biologic drug whenever it is tolerated. From the literature in adults, it seems that the occurrence of antibody formation is significantly less frequent when adalimumab or infliximab is combined with MTX. Antibody development with neutralization of the drug seems to be less of a problem with etanercept. Although the combined therapy is more effective, the probability of adverse effects is higher.

In patients with uveitis, adalimumab and infliximab are preferred to etanercept, as monoclonal antibody TNF-α inhibitors appear to be superior to etanercept in treatment of chronic uveitis [48–50].

Golimumab, another TNF-α inhibitor, has recently received a positive opinion from the European Medicines Agency's Committee for Medicinal Products for Human Use (CHMP) for the treatment of polyarticular JIA. The

CHMP decision was based on the GO-KIDS study (ClinicalTrials.gov study ID NCT01230827), which has not yet been published in full. If approved, golimumab will be another TNF-α inhibitor available for the treatment of patients with active polyarticular JIA.

3.3.2 Other Biologic Drugs

In addition to anti-TNF-α biologic drugs, the anti-IL-6 monoclonal antibody tocilizumab has been studied in polyarticular JIA with an insufficient response to DMARD therapy. Tocilizumab is given as an intravenous infusion every other week in patients with systemic JIA. In patients with polyarticular JIA over the age of 2 years and weighing more than 30 kg, the dosage is 8 mg/kg once every 4 weeks, and in patients weighing less than 30 kg, the dosage is 10 mg/kg once every 4 weeks.

In a study of tocilizumab as a first-line biologic drug in polyarticular JIA with an insufficient response to MTX, a significant improvement was observed. JIA flares occurred in 48 % of patients receiving placebo and in 26 % of those receiving tocilizumab. At the end of the second phase, 65 % and 45 % of patients receiving tocilizumab achieved ACR Pedi 70 and ACR Pedi 90 responses, respectively [8].

3.3.3 Safety of Biologic Therapy

Biologic therapy has tremendously improved the quality of life of many patients with JIA resistant to DMARDs; however, it is important to have longitudinal, multinational registries, such as PharmaChild, to detect risks of rare, severe side effects.

3.3.3.1 Etanercept During long-term treatment with etanercept, the overall rate of SAEs (0.12 per patient-year) did not increase. The rate of infections remained low. No cases of tuberculosis, opportunistic infections, malignancies, lymphomas, SLE, demyelinating disorders, or deaths were reported [2].

Data from the German JIA registry show, in total, 25 infectious and 23 non-infectious SAEs, including three malignancies, that occurred in patients receiving etanercept ± MTX, and one infectious and three non-infectious SAEs that occurred in those receiving etanercept monotherapy [41].

3.3.3.2 Adalimumab During treatment with adalimumab, SAEs considered possibly related to the study drug occurred in 14 patients (in six of 171 patients during the open-label phase, in one patient during the double-blind phase, and in seven of 128 patients during the open-label extension phase). Of these 14 SAEs, seven were serious infections (one case each of bronchopneumonia, herpes simplex virus infection, pharyngitis, pneumonia, and unspecified viral infection, and two cases of herpes zoster virus infection). Nine patients during the open-label phase, no patients during the double-blind phase, and three patients during the open-label extension phase discontinued treatment because of AEs. No deaths, malignant conditions, opportunistic infections, tuberculosis cases, demyelinating diseases, or lupus-like reactions were reported during the study period [3].

Forty-eight of 289 patients in the German JIA registry who were treated with adalimumab experienced 222 AEs. Eleven were reported as serious (2.5 per 100 patient-years). No malignancies were observed during adalimumab exposure [44].

3.3.3.3 Infliximab Infusion reactions are rather common during treatment with infliximab and were observed in 32 % of patients in one trial, with a higher incidence in patients who tested positive for antibodies to infliximab [46].

3.3.4 Treatment options after failure of the first biologic drug

In patients with an inadequate response to or intolerance of the first biologic drug, there are several further treatment options. First, the dosage of the medication can be increased. Second, the patient can be switched to another anti-TNF-α biologic drug. Finally, the patient can be switched to a medication with a different mechanism, such as an anti-IL-6 biologic drug (tocilizumab) or a selective T-cell co-stimulation modulator (abatacept). All three options have shown beneficial effects in individual patients, but direct comparison data are not available in the literature.

The anti-IL-1 drug anakinra was not found to be effective in reducing the frequency of disease flares in comparison with placebo in a study of polyarticular JIA [51].

Some children relapse after achieving an inactive disease state or remission, because the dosage of the medication has not been increased with the growth of the child. In these patients, the dosage should be increased accordingly.

There are anecdotal reports of beneficial effects of high-dose biologic drugs in refractory or highly active JIA patients. For example, high doses of infliximab (10–20 mg/kg) in children have been reported to result in statistically significant improvements in the active joint count and the physician global assessment of disease activity. The frequency of side effects was similar to that seen with low-dose treatment; there were nine SAEs (9.5/100 patient-years)—seven of which were potentially related to the therapy—and six infusion reactions (0.5 %), none constituting anaphylaxis [52].

An important feature of all biologics is their potential to be immunogenic and to induce formation of anti-biologic-

drug antibodies. Anti-biologic-drug antibodies have been associated with significantly decreased serum concentrations of biologic drugs and treatment failure [47, 53]. Monitoring of serum drug concentrations and detection of anti-biologic-drug antibodies could therefore be considered especially in patients who fail biologic treatment. Non-responding patients whose sera show the presence of anti-biologic-drug antibodies and/or low serum drug concentrations may benefit from a switch to a different biologic drug.

4 Enthesitis-Related Arthritis/Juvenile Spondyloarthropathies

A group of related rheumatic diseases, which begin prior to 16 years of age and are strongly associated with human leukocyte antigen (HLA)-B27, are named juvenile spondyloarthropathies (JSpA). According to the current International League of Associations for Rheumatology (ILAR) classification, most patients with JSpA are classified as having ERA, JPsA, or undifferentiated arthritis [54, 55]. Additional conditions that share similar pathogenic features, such as reactive arthritis and inflammatory bowel disease–related arthropathy, are not included in the current ILAR classification [56, 57].

There is convincing evidence that TNF-α plays a pivotal role in the pathophysiology of spondyloarthropathy. In recent years, an additional inflammation axis, IL-23/IL-17, has been shown to highly contribute to the pathogenesis as well [54, 55]. Currently, there are no published recommendations for the treatment of JSpA.

4.1 Non-steroidal Anti-inflammatory Drugs

The first-line treatments for JSpA are NSAIDs, which are used to reduce inflammation and provide symptom relief in the axial and peripheral joints. If there is a lack of a clinical response within 2 weeks with the usual dosages (10–15 mg/kg/day of naproxen in two divided doses, or indomethacin 1–3 mg/kg/day in 3–4 divided doses), it is unlikely that NSAID therapy will be effective.

4.2 Disease-Modifying Anti-rheumatic Drugs

DMARDs have not been evaluated in clinical trials in patients with JSpA or ERA. The ACR recommendations for the management of JIA suggest use of MTX as the first-line agent in patients with active peripheral arthritis. However, for patients with ERA, sulfasalazine is the preferred choice instead of MTX. This recommendation is based on clinical experience and data from adult patients with ankylosing spondylitis (AS) [56, 57].

In a study of the efficacy and safety of sulfasalazine in 21 children with JSpA and 15 children with JIA, a shorter time to remission was observed in the patients with JSpA (5 months) than in those with JIA (25 months), but there was no difference in response rates between the two groups. Remission was achieved in 39 % and clinical improvement in 25 % of children with either JSpA or JIA [57].

In adult patients with AS treated with sulfasalazine, a recent Cochrane review concluded that even though there had been significant benefits in reducing the erythrocyte sedimentation rate and easing spinal stiffness in previous studies, there was currently not enough evidence to support long-term treatment of AS with sulfasalazine [58].

4.3 Biologic Drugs

Several studies in adult populations have showed that traditional DMARDs are insufficient for axial disease and that sulfasalazine is effective only in peripheral arthritis [54, 56, 57]. It has been shown in several observational studies that TNF-α inhibitors are beneficial in JSpA, which is consistent with the results of multiple clinical trials in adults with spondyloarthropathy. In addition to having important influences on the symptoms and course of the axial disease, TNF-α inhibitors appear to induce responses in two important therapeutic targets in JSpA—peripheral arthritis and enthesitis.

In the presence of low axial disease activity and lack of radiographic damage in patients with ERA, TNF-α inhibitors should be used when initial DMARD therapy (most commonly, sulfasalazine) is ineffective. Anti-TNF-α therapy should be used earlier in moderate or highly active axial disease with established radiographic damage, such as erosions or joint-space narrowing. In patients with peripheral arthritis without active sacroiliitis, TNF-α inhibitors are usually used only if 3–6 months of treatment with DMARDs has been ineffective.

An observational study published in 2004 showed significant and sustained efficacy of etanercept in eight patients with ERA, with reductions in morning stiffness, active joint counts, and erythrocyte sedimentation rates [59]. Moreover, in a group of ten HLA-B27-positive patients with refractory JSpA, rapid remission of the disease was achieved in all patients within 6 weeks and was sustained during 1-year follow-up in the eight patients treated with infliximab and in the two treated with etanercept [60]. In a prospective observational study, 16 patients with JSpA that was refractory to conventional treatment were treated with infliximab (10 patients) or etanercept (6 patients) with a mean follow-up of 7.2 years, and clinical remission at 6 months was achieved in 13 of the 16 patients (83 %). After a median of 3.5 years, 38 %

of patients showed a flare of arthritis. The patients showed progression of sacroiliitis despite treatment [61]. In 22 patients with ERA selected from the Dutch Arthritis and Biologicals in Children registry, treatment with anti-TNF-α agents was effective and safe, but a sustained disease-free state was not achieved, and no patient could successfully discontinue the TNF-inhibiting therapy [62]. The effectiveness of subcutaneous etanercept 0.8 mg/kg once weekly was studied in 122 JIA patients, including 38 patients with ERA. The primary endpoint of an ACR Pedi 30 response at 12 weeks was achieved in 83 % of patients with ERA, and inactive disease was achieved in 17 % of ERA patients [63]. Another TNF-α inhibitor, adalimumab, also showed good clinical effectiveness, with reductions in signs and symptoms at 12 weeks of treatment in patients with ERA and sustained efficacy for up to 52 weeks [64].

Several biologics other than TNF-α inhibitors (such as abatacept, tocilizumab, and rituximab) that have been effective in other forms of JIA have not proven to be effective in pediatric and adult patients with spondyloarthropathy. However, anti-IL-17 and anti-IL-23 agents could represent promising alternatives for the treatment of JSpA patients in the near future, since they have both shown good efficacy in adult patients with AS [65, 66].

5 Systemic Arthritis

SJIA differs from other JIA subtypes in several aspects. High spiking daily fevers accompanied by an evanescent rash, serositis, generalized lymphadenopathy, and hepatosplenomegaly are characteristic features of SJIA that are not seen in other JIA subtypes [67]. Chronic arthritis can have a very severe and devastating course in SJIA. Systemic signs of the disease are sometimes more easy to control than chronic arthritis, which can be unresponsive to various treatment approaches [6]. The most severe complication of SJIA is macrophage activation syndrome (MAS)—a life-threatening condition, which develops during the course of the disease in up to 10 % of patients with SJIA. Diagnostic evaluation of a patient with fever and arthritis requires a multidisciplinary approach. Any underlying infections or malignant diseases should be thoroughly investigated and excluded before the diagnosis of SJIA is established.

5.1 Non-steroidal Anti-inflammatory Drugs

As in other JIA subtypes, the preferred first-choice drugs are NSAIDs. Ibuprofen 30 mg/kg/day in three divided doses or naproxen 20 mg/kg/day in two divided doses is frequently used as initial therapy to control fever and arthritis. Another frequently used NSAID is indomethacin, with a suggested dose of 1–3 mg/kg. There are no clear recommendations on how long NSAID treatment should continue in SJIA, but, as a common rule, a minimum of a 1-week trial of a NSAID should be given before it is deemed to have failed. If the patient is not too ill, a second NSAID trial should be attempted. In general, lymphadenopathy, hepatosplenomegaly, and rash alone do not justify an increase in treatment.

5.2 Corticosteroids

If fever lasts for more than 14 days with no clear response to NSAIDs, a systemic corticosteroid (e.g., prednisone or prednisolone in a dosage of 1–2 mg/kg/day orally, often as two or three divided doses) is introduced. In addition to uncontrolled fever, other indications for introduction of systemic corticosteroid therapy include symptomatic serositis, severe anemia, or an unusual presentation with major organ involvement. Low to moderate dosages of prednisone (0.5–1 mg/kg/day) are usually sufficient to control serositis. Pulse intravenous methylprednisolone in a dosage of 30 mg/kg/day for 3 days can be considered in patients with severe flares or myocarditis with congestive heart failure, to achieve a rapid response.

Depending on the severity of the disease flare, corticosteroid tapering begins after 2–4 weeks [9, 38]. To avoid side effects, corticosteroid therapy should be tapered soon after initial achievement of disease control, and it is usually stopped at 6–8 weeks.

Because of the side effects of long-term steroids and the quite impressive rates of response to biologic agents specifically in SJIA, there is a tendency to consider biologic therapy earlier in the disease course of SJIA. However, in many countries, SJIA patients are still first treated with high-dose steroids, and biologic agents are started only when steroids cannot be tapered after several weeks or after an insufficient response to steroid therapy has been observed.

5.3 Biologic Agents

If the disease is not inactive after initial treatment with NSAID and corticosteroids, further treatment depends on the presence of persistent arthritis and systemic signs. When arthritis persists without systemic signs, the treatment approach follows the same principles as those used for management of arthritis in other forms of JIA, as discussed above [9].

MTX has little or no effect on systemic signs of the disease, and the same is also true for anti-TNF-α agents. Among 45 patients with SJIA who were treated with anti-TNF-α agents, only 24 % experienced remission, and only 13 % experienced a sustained benefit [68].

When systemic signs persist during corticosteroid tapering, biologic therapy is indicated to control inflammation (Table 3). The two main cytokines involved in the pathogenesis of SJIA are IL-1 and IL-6, so treatment with an IL-1 inhibitor (anakinra or canakinumab) or an IL-6 inhibitor (tocilizumab) is highly effective [6]. The biologic drugs that are most commonly used in the treatment of SJIA are listed in Table 3.

Anakinra competitively inhibits IL-1 type I receptors and neutralizes the biological activity of both IL-1α and IL-1β. Use of anakinra is currently indicated in refractory SJIA patients with persistent systemic signs of the disease in spite of corticosteroid therapy [6, 9, 69–71]. The first study showing an excellent response to treatment with anakinra (in 10 of 21 patients with SJIA) was published in 2008 [69]. A larger retrospective study including 46 patients with SJIA showed that a complete clinical response was achieved in about 60 % of patients treated with anakinra. Of note, ten children in this report received anakinra as monotherapy without corticosteroids, and 80 % of these patients had a complete response [71]. The efficacy of anakinra in SJIA was also confirmed in a small, randomized, placebo-controlled study [72]. The first prospective study in which anakinra was used as first-line therapy (before the use of systemic corticosteroids), in 20 consecutive patients with SJIA, showed an excellent response in nearly all patients during the first 3 months of treatment [7]. After 1 year, 17 of the 20 patients (85 %) had clinically inactive disease. Thirteen of these patients met the criteria for inactive disease while receiving monotherapy with anakinra, while seven patients needed additional immunosuppressive therapy because of persistent disease activity. Although there has been extensive experience with anakinra in SJIA worldwide, this drug is still not officially registered for use in SJIA in Europe and the USA.

Recently, a new anti-IL-1 drug—canakinumab—has shown effectiveness in SJIA. Canakinumab is a human monoclonal antibody, which neutralizes the biological activity of IL-1β but not IL-1α. It has been approved for use as monotherapy or in combination with MTX for the treatment of patients with SJIA who are at least 2 years old, have active disease, and have responded inadequately to previous therapy with NSAIDs or systemic corticosteroids [73]. Two randomized trials have shown the efficacy of canakinumab in SJIA with active systemic features [5]. In the first trial, patients were randomized to receive a single subcutaneous dose of canakinumab or placebo. At day 15, significantly more patients in the canakinumab group than in the placebo group had achieved an ACR Pedi 30 response (84 versus 10 %). In the second trial, patients who had a response were randomly assigned to receive continued treatment with canakinumab or placebo, and it was found that 74 % of patients in the canakinumab group had no flare, whereas only 25 % of patients in the placebo group had no flare. The average dosage of corticosteroids was significantly reduced in canakinumab-treated patients, and in 33 % of them, corticosteroids were discontinued. Rilonacept is the third anti-IL-1 agent that has shown efficacy comparable to that of anakinra and canakinumab in patients with SJIA [74]; however, it is not yet registered for use in SJIA in Europe.

Another biologic treatment in patients with SJIA and persistent systemic signs is tocilizumab, which is directed against IL-6. The efficacy and safety of tocilizumab has been proven in several studies, and the drug can be used alone or together with MTX in children older than 2 years [6, 75]. In 2005, the first published report showed prompt clinical and laboratory parameter responses in 10 of 11 children with SJIA who were treated with tocilizumab [76]. Later, the efficacy was confirmed in a randomized, placebo-controlled trial and a long-term, open-label extension [77, 78]. Within 3 months, 70 % of children receiving tocilizumab improved clinically by at least 70 %, in comparison with only 8 % of those receiving placebo [79].

A recent study using French registry data showed that some patients with SJIA might achieve remission with canakinumab or tocilizumab as second-line or even third-line biologic therapy [80]. With the first biologic drug, inactive disease was achieved in 26 of 51 patients treated with anakinra, 7 of 10 treated with canakinumab, 1 of 12 treated with etanercept, and 2 patients treated with

Table 3 Doses, routes of administration, and administration intervals for the most commonly used biologic drugs for the treatment of systemic juvenile idiopathic arthritis

Biologic drug	Mechanism of action	Dose (mg/kg BW)	Route of administration	Administration interval
Anakinra	Recombinant IL-1R antagonist, blocks IL-1α and IL-1β	1–2	Subcutaneous	Daily
Canakinumab	Monoclonal antibody, blocks IL-1β	2–4[a]	Subcutaneous	Every 4 weeks
Tocilizumab	Monoclonal antibody, blocks IL-6R	8–12[b]	Intravenous	Every 2 weeks

BW body weight *IL* interleukin, *R* receptor

[a] For patients with BW ≥ 15 kg and ≤ 40 kg: 2 mg/kg BW; for patients with BW ≥ 7.5 kg and < 15 kg: 4 mg/kg BW

[b] For patients older than 2 years: 8 mg/kg BW; for patients with BW < 30 kg: 12 mg/kg BW

tocilizumab. Switching of biologic drugs was common and resulted in an inactive disease state in a further 13 patients (6 treated with canakinumab and 7 treated with tocilizumab). Given the published data, it appears that introduction of an anti-IL-1 or anti-IL-6 inhibitor instead of an anti-TNF-α agent as the first-line biologic therapy in patients with SJIA significantly increases the chance of these patients achieving remission.

5.3.1 *Adverse Effects of Biologics in Systemic Juvenile Idiopathic Arthritis*

The numbers of patients with SJIA treated with biologics so far are smaller than the numbers of patients with non-systemic JIA treated with anti-TNF-α therapy; therefore, longitudinal international registries, such as PharmaChild, are even more important in providing information on rare, severe side effects.

Fortunately, side effects of biologic therapy are rare—the main concern is infections. In a retrospective French cohort study, there were no cases of cancer or death. For anakinra and canakinumab, mainly infections were reported, and tociluzumab was associated with Crohn's disease, infusion reactions, cutaneous vasculitis, and toxidermia in one case each [80].

It should be noted that early recognition of infection during treatment with tocilizumab is difficult, because it reduces C-reactive protein (CRP) levels through its effects on the liver.

6 Early Aggressive Therapy for Juvenile Idiopathic Arthritis and the Treat-To-Target Strategy

In recent years, early aggressive treatment of JIA has been advocated, which has resulted in substantial proportions (up to 40 %) of patients achieving clinically inactive disease by 6 months and clinical remission on medication within 12 months of treatment [81].

Additional observations that have provided further evidence in favor of early aggressive treatment are rapidly instituted catch-up growth, improvements in bone mineralization and body composition, and clinical control of disease activity with etanercept in MTX-refractory polyarticular JIA [82].

Although early aggressive therapy for JIA has been proven to be effective, it should be noted that many patients would have achieved remission even with less aggressive and possibly less toxic and less expensive treatment. Currently, there are no reliable prognostic markers of an insufficient response to or intolerance of DMARDs or biologics in JIA. Nevertheless, growing evidence suggests that single nucleotide polymorphisms (SNPs) in metabolic pathways contribute to inter-individual differences in the response to MTX and biologics. Associations have been found with inefficacy of MTX and intolerance of MTX in rheumatoid arthritis, as well as in JIA [32, 83–85]. In our cohort of 119 JIA patients treated with MTX, specific SNPs were associated with switching to biologic therapy.

Recent therapeutic advances have made inactive disease and low disease activity an achievable goal in most patients. This has led to implementation of a treat-to-target strategy aimed at achieving and maintaining tight disease control, with treatment escalation if a target score is not achieved or is lost [86]. Although these treat-to-target strategies are really interesting from both clinical and scientific points of view, they need to be replicated/validated before they can be generally implemented in clinical practice.

7 Drug Tapering and Withdrawal

Many patients treated with DMARDs or biologics achieve clinically inactive disease and remission on medication, meaning they have no clinical and laboratory signs of disease. According to published data, approximately two thirds of patients relapse after stopping biologic therapy [87].

At present, there are no uniform drug withdrawal protocols, including lowering of the drug dose or prolonging the intervals between applications.

If a patient achieves sustained remission on MTX therapy, there are no clear guidelines on how and when to discontinue treatment. The flare rate after MTX withdrawal remains high—up to 40–50 % in the first year after treatment discontinuation [88, 89]. Recently, attention has been focused on whether longer treatment after remission reduces the flare rate. Several studies have demonstrated comparable flare rates when MTX was discontinued after 3.8 months versus 12.6 months, or after 6 months versus 12 months [88]. At our center, we usually start MTX tapering after 1 year of continuously inactive disease, following a scheme of gradual discontinuation over approximately 9 months. In the first 3 months of the tapering period, MTX is administered once every 2 weeks; in the next 3 months, it is administered once every 3 weeks; in the last 3 months, it is administered once every 4 weeks. If there are any signs of a disease flare, the patient is again administered a full MTX dose every week.

In a study of etanercept tapering with lowering of the dosage in 31 patients with JIA, the dosage was first halved to 0.4 mg/kg/week. During the second year, the dosage of etanercept was further lowered to 0.4 mg/kg/month.

DMARDs were allowed in this study. Four patients experienced disease flares during the first year, but no further flares were observed during the second year. A logistic regression model indicated no differences in sex, age at disease initiation, disease duration, subtypes, DMARDs, HLA-B27, etanercept treatment duration, and scores on magnetic resonance imaging (MRI) between patients with remission and those experiencing flares [90].

The optimal period of tapering is still not known, and more studies on drug withdrawal are needed before a particular protocol can be advised.

According to our experience, most patients receiving biologic agents have not experienced flares during the tapering period, but flares have occurred shortly after cessation of the treatment when the biologic drug was metabolized and excreted. The currently ongoing PREVENT-JIA study has a primary aim of identifying patients at risk of flares after withdrawal of treatment, according to serum levels of biomarkers.

7.1 Continued Low Dosages/Longer Administration Intervals

As there is a high percentage of relapses after discontinuation of DMARDs and biologics, continued treatment with lower dosages or prolonged intervals between applications might be a better alternative.

Continuing combination therapy at a reduced dosage resulted in better disease control than switching to MTX alone or placebo in patients with early rheumatoid arthritis who had a remission while receiving full-dose etanercept plus MTX therapy [91].

8 Conclusions

This review presents current knowledge on the treatment of JIA, based on published studies and recommendations, as well as our personal clinical experience. The general principles of successful JIA management include prompt establishment of the correct diagnosis, early recognition of active disease, and achieving as well as maintaining control of inflammation, with the goal of preventing joint injury. The application of these strategies requires more rapid and sustained control of synovitis by early introduction of DMARDs and biologic agents, which has resulted in significant improvements in the functional and radiographic outcomes of JIA patients.

Compliance with Ethical Standards

Conflict of interest Tadej Avčin declares speakers bureau (AbbVie, Pfizer, Octapharma) and advisory board (Bristol-Myers Squibb, Octapharma). Štefan Blazina, Gašper Markelj, Mojca Zajc Avramovič and Nataša Toplak have no conflicts of interest that are relevant to the content of this review.

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References

1. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol. 2004;31:390–2.
2. Lovell DJ, Reiff A, Ilowite NT, Wallace CA, Chon Y, Lin SL, et al. Safety and efficacy of up to eight years of continuous etanercept therapy in patients with juvenile rheumatoid arthritis. Arthritis Rheum. 2008;58:1496–504.
3. Lovell DJ, Ruperto N, Goodman S, Reiff A, Jung L, Jarosova K, et al. Adalimumab with or without methotrexate in juvenile rheumatoid arthritis. N Engl J Med. 2008;359:810–20.
4. Giannini EH, Ilowite NT, Lovell DJ, Wallace CA, Rabinovich CE, Reiff A, et al. Long-term safety and effectiveness of etanercept in children with selected categories of juvenile idiopathic arthritis. Arthritis Rheum. 2009;60:2794–804.
5. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012;367:2396–406.
6. Beukelman T. Treatment advances in systemic juvenile idiopathic arthritis. F1000Prime Rep. 2014;6:21.
7. Vastert SJ, de Jager W, Noordman BJ, Holzinger D, Kuis W, Prakken BJ, et al. Effectiveness of first-line treatment with recombinant interleukin-1 receptor antagonist in steroid-naive patients with new-onset systemic juvenile idiopathic arthritis: results of a prospective cohort study. Arthritis Rheumatol. 2014;66:1034–43.
8. Brunner HI, Ruperto N, Zuber Z, Keane C, Harari O, Kenwright A, et al. Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial. Ann Rheum Dis. 2015;74:1110–7.
9. Beukelman T, Patkar NM, Saag KG, Tolleson-Rinehart S, Cron RQ, DeWitt EM, et al. 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: initiation and safety monitoring of therapeutic agents for the treatment of arthritis and systemic features. Arthritis Care Res. 2011;63:465–82.
10. Ringold S, Weiss PF, Beukelman T, et al. 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. Arthritis Rheum. 2013;65:2499–512.
11. Ruperto N, Nikishina I, Pachanov ED, Shachbazian Y, Prieur AM, Mouy R, et al. A randomized, double-blind clinical trial of two doses of meloxicam compared with naproxen in children with juvenile idiopathic arthritis: short- and long-term efficacy and safety results. Arthritis Rheum. 2005;52:563–72.
12. Hull RG. Guidelines for management of childhood arthritis. Rheumatology. 2001;40:1309–12.
13. Ilowite NT. Current treatment of juvenile rheumatoid arthritis. Pediatrics. 2002;109:109–15.
14. Munro J, National Health and Medical Research Council, et al. Clinical guideline for the diagnosis and management of juvenile

idiopathic arthritis. Melbourne: Royal Australian College of General Practitioners; 2009.
15. Dueckers G, Guellac N, Arbogast M, Dannecker G, Foeldvari I, Frosch M, et al. Evidence and consensus based GKJR guidelines for the treatment of juvenile idiopathic arthritis. Clin Immunol. 2012;142:176–93.
16. Ringold S, Weiss PF, Colbert RA, DeWitt EM, Lee T, Onel K, et al. Childhood Arthritis and Rheumatology Research Alliance consensus treatment plans for new-onset polyarticular juvenile idiopathic arthritis. Arthritis Care Res. 2014;66:1063–72.
17. Cattalini M, Maduskuie V, Fawcett PT, Brescia AM, Rosé CD. Predicting duration of beneficial effect of joint injection among children with chronic arthritis by measuring biomarker concentration in synovial fluid at the time of injection. Clin Exp Rheumatol. 2008;26:1153–60.
18. Zulian F, Martini G, Gobber D, Plebani M, Zacchello F, Manners P. Triamcinolone acetonide and hexacetonide intra-articular treatment of symmetrical joints in juvenile idiopathic arthritis: a double-blind trial. Rheumatology. 2004;43:1288–91.
19. Padeh S, Passwell JH. Intraarticular corticosteroid injection in the management of children with chronic arthritis. Arthritis Rheum. 1998;41:1210–4.
20. Neidel J, Boehnke M, Küster RM. The efficacy and safety of intraarticular corticosteroid therapy for coxitis in juvenile rheumatoid arthritis. Arthritis Rheum. 2002;46:1620–8.
21. Arabshahi B, Dewitt EM, Cahill AM, Kaye RD, Baskin KM, Towbin RB, et al. Utility of corticosteroid injection for temporomandibular arthritis in children with juvenile idiopathic arthritis. Arthritis Rheum. 2005;52:3563–9.
22. Brown GT, Wright FV, Lang BA, Birdi N, Oen K, Stephens D, et al. Clinical responsiveness of self-report functional assessment measures for children with juvenile idiopathic arthritis undergoing intraarticular corticosteroid injections. Arthritis Care Res. 2005;53:897–904.
23. Oren-Ziv A, Hoppenstein D, Shles A, Uziel Y. Sedation methods for intra-articular corticosteroid injections in juvenile idiopathic arthritis: a review. Pediatr. Rheumatol. 2015;13:28.
24. Uziel Y, Chapnick G, Rothschild M, Tauber T, Press J, Harel L, et al. Nitrous oxide sedation for intra-articular injection in juvenile idiopathic arthritis. Pediatr Rheumatol Online J. 2008;6:1.
25. Braun J, Rau R. An update on methotrexate. Curr Opin Rheumatol. 2009;21:216–23.
26. Hashkes PJ, Laxer RM. Update on the medical treatment of juvenile idiopathic arthritis. Curr Rheumatol Rep. 2006;8:450–8.
27. Ruperto N, Murray KJ, Gerloni V, Wulffraat N, De Oliveira SKF, Falcini F, et al. A randomized trial of parenteral methotrexate comparing an intermediate dose with a higher dose in children with juvenile idiopathic arthritis who failed to respond to standard doses of methotrexate. Arthritis Rheum. 2004;50:2191–201.
28. Jundt JW, Browne BA, Fiocco GP, Steele AD, Mock D. A comparison of low dose methotrexate bioavailability: oral solution, oral tablet, subcutaneous and intramuscular dosing. J Rheumatol. 1993;20:1845–9.
29. Silverman E, Mouy R, Spiegel L, Jung LK, Saurenmann RK, Lahdenne P, et al. Leflunomide or methotrexate for juvenile rheumatoid arthritis. N Engl J Med. 2005;352:1655–66.
30. Céspedes-Cruz A, Gutiérrez-Suárez R, Pistorio A, Ravelli A, Loy A, Murray KJ, et al. Methotrexate improves the health-related quality of life of children with juvenile idiopathic arthritis. Ann Rheum Dis. 2008;67:309–14.
31. Gutiérrez-Suárez R, Burgos-Vargas R. The use of methotrexate in children with rheumatic diseases. Clin Exp Rheumatol. 2010;28:S122–7.
32. Bulatovic M, Heijstek MW, Van Dijkhuizen EHP, Wulffraat NM, Pluijm SMF, de Jonge R. Prediction of clinical non-response to methotrexate treatment in juvenile idiopathic arthritis. Ann Rheum Dis. 2012;71:1484–9.
33. Ravelli A, Martini A. Juvenile idiopathic arthritis. Lancet. 2007;369:767–78.
34. Toplak N, Avčin T. Long-term safety and efficacy of varicella vaccination in children with juvenile idiopathic arthritis treated with biologic therapy. Vaccine. 2015;33:4056–9.
35. Pileggi GS, de Souza CBS, Ferriani VPL. Safety and immunogenicity of varicella vaccine in patients with juvenile rheumatic diseases receiving methotrexate and corticosteroids. Arthritis Care Res. 2010;62:1034–9.
36. Heijstek MW, Kamphuis S, Armbrust W, Swart J, Gorter S, de Vries LD, et al. Effects of the live attenuated measles–mumps–rubella booster vaccination on disease activity in patients with juvenile idiopathic arthritis: a randomized trial. JAMA. 2013;309:2449–56.
37. Silverman E, Spiegel L, Hawkins D, Petty R, Goldsmith D, Schanberg L, et al. Long-term open-label preliminary study of the safety and efficacy of leflunomide in patients with polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum. 2005;52:554–62.
38. Malattia C, Martini A. Glucocorticoids in juvenile idiopathic arthritis. Ann NY Acad Sci. 2014;1318:65–70.
39. McInnes IB, Schett G. The pathogenesis of rheumatoid arthritis. N Engl J Med. 2011;36:5–8.
40. Lovell DJ, Giannini EH, Reiff A, Cawkwell GD, Silverman ED, Nocton JJ, et al. Etanercept in children with polyarticular juvenile rheumatoid arthritis. N Engl J Med. 2000;342:763–9.
41. Horneff G, De Bock F, Foeldvari I, Girschick HJ, Michels H, Moebius D, et al. Safety and efficacy of combination of etanercept and methotrexate compared to treatment with etanercept only in patients with juvenile idiopathic arthritis (JIA): preliminary data from the German JIA Registry. Ann Rheum Dis. 2009;68:519–25.
42. Papsdorf V, Horneff G. Complete control of disease activity and remission induced by treatment with etanercept in juvenile idiopathic arthritis. Rheumatology. 2011;50:214–21.
43. Prince FHM, Twilt M, ten Cate R, van Rossum MAJ, Armbrust W, Hoppenreijs EPAH, et al. Long-term follow-up on effectiveness and safety of etanercept in juvenile idiopathic arthritis: the Dutch national register. Ann Rheum Dis. 2009;68:635–41.
44. Schmeling H, Minden K, Foeldvari I, Ganser G, Hospach T, Horneff G. Efficacy and safety of adalimumab as the first and second biologic agent in juvenile idiopathic arthritis: the German Biologics JIA Registry. Arthritis Rheumatol. 2014;66:2580–9.
45. Ruperto N, Lovell DJ, Cuttica R, Wilkinson N, Woo P, Espada G, et al. A randomized, placebo-controlled trial of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis. Arthritis Rheum. 2007;56:3096–106.
46. Ruperto N, Lovell DJ, Cuttica R, Woo P, Meiorin S, Wouters C, et al. Long-term efficacy and safety of infliximab plus methotrexate for the treatment of polyarticular-course juvenile rheumatoid arthritis: findings from an open-label treatment extension. Ann Rheum Dis. 2010;69:718–22.
47. Kosmač M, Avčin T, Toplak N, Simonini G, Cimaz R. Curin Šerbec V. Exploring the binding sites of anti-infliximab antibodies in pediatric patients with rheumatic diseases treated with infliximab. Pediatr Res. 2011;69:243–8.
48. Anink J, Otten MH, Gorter SL, Prince FHM, van Rossum MAJ, van den Berg JM, et al. Treatment choices of paediatric rheumatologists for juvenile idiopathic arthritis: etanercept or adalimumab? Rheumatology. 2013;52:1674–9.
49. Simonini G, Druce K, Cimaz R, Macfarlane GJ, Jones GT. Current evidence of anti–tumor necrosis factor α treatment efficacy in childhood chronic uveitis: a systematic review and meta-

analysis approach of individual drugs. Arthritis Care Res. 2014;66:1073–84.
50. Kearsley-Fleet L, Davies R, Baildam E, Beresford MW, Foster HE, Southwood TR, et al. Factors associated with choice of biologic among children with juvenile idiopathic arthritis: results from two UK paediatric biologic registers. Rheumatology. doi:10.1093/rheumatology/kev429 **(Epub 2016 Jan 4)**.
51. Ilowite N, Porras O, Reiff A, Rudge S, Punaro M, Martin A, et al. Anakinra in the treatment of polyarticular-course juvenile rheumatoid arthritis: safety and preliminary efficacy results of a randomized multicenter study. Clin Rheumatol. 2009;28:129–37.
52. Tambralli A, Beukelman T, Weiser P, Atkinson TP, Cron RQ, Stoll ML. High doses of infliximab in the management of juvenile idiopathic arthritis. J Rheumatol. 2013;40:1749–55.
53. Bartelds GM, Krieckaert CLM, Nurmohamed MT, van Schouwenburg PA, Lems WF, Twisk JWR, et al. Development of antidrug antibodies against adalimumab and association with disease activity and treatment failure during long-term follow-up. JAMA. 2011;305:1460–8.
54. Gmuca S, Weiss PF. Juvenile spondyloarthritis. Curr Opin Rheumatol. 2015;27:364–72.
55. Burgos-Vargas R. The assessment of the spondyloarthritis international society concept and criteria for the classification of axial spondyloarthritis and peripheral spondyloarthritis: a critical appraisal for the pediatric rheumatologist. Pediatr Rheumatol Online J. 2012;10:14.
56. Aggarwal A, Misra DP. Enthesitis-related arthritis. Clin Rheumatol. 2015;34:1839–46.
57. Huang JL, Chen LC. Sulphasalazine in the treatment of children with chronic arthritis. Clin. Rheumatol. 1998;17:359–63.
58. Chen J, Lin S, Liu C. Sulfasalazine for ankylosing spondylitis. Cochrane Database of Syst Rev. 2014;(11):CD004800. doi:10.1002/14651858.CD004800.pub3.
59. Henrickson M, Reiff A. Prolonged efficacy of etanercept in refractory enthesitis-related arthritis. J Rheumatol. 2004;31:2055–61.
60. Tse SML, Burgos-Vargas R, Laxer RM. Anti-tumor necrosis factor alpha blockade in the treatment of juvenile spondylarthropathy. Arthritis Rheum. 2005;52:2103–8.
61. Hugle B, Burgos-Vargas R, Inman RD, O'Shea F, Laxer RM, Stimec J, et al. Long-term outcome of anti-tumor necrosis factor alpha blockade in the treatment of juvenile spondyloarthritis. Clin Exp Rheumatol. 2014;32:424–31.
62. Otten MH, Prince FHM, Twilt M, Ten Cate R, Armbrust W, Hoppenreijs EPAH, et al. Tumor necrosis factor–blocking agents for children with enthesitis-related arthritis—data from the Dutch Arthritis and Biologicals in Children Register, 1999–2010. J Rheumatol. 2011;38:2258–63.
63. Horneff G, Burgos-Vargas R, Constantin T, Foeldvari I, Vojinovic J, Chasnyk VG, et al. Efficacy and safety of open-label etanercept on extended oligoarticular juvenile idiopathic arthritis, enthesitis-related arthritis and psoriatic arthritis: part 1 (week 12) of the CLIPPER study. Ann Rheum Dis. 2014;73:1114–22.
64. Burgos-Vargas R, Tse SML, Horneff G, Pangan AL, Kalabic J, Goss S, et al. A randomized, double-blind, placebo-controlled multicenter study of adalimumab in pediatric patients with enthesitis-related arthritis. Arthritis Care Res. 2015;67:1503–12.
65. Horneff G, Fitter S, Foeldvari I, Minden K, Kuemmerle-Deschner J, Tzaribacev N, et al. Double-blind, placebo-controlled randomized trial with adalimumab for treatment of juvenile onset ankylosing spondylitis (JoAS): significant short term improvement. Arthritis Res Ther. 2012;14:230.
66. Poddubnyy D, Hermann K-GA, Callhoff J, Listing J, Sieper J. Ustekinumab for the treatment of patients with active ankylosing spondylitis: results of a 28-week, prospective, open-label, proof-of-concept study (TOPAS). Ann Rheum Dis. 2014;73:817–23.
67. Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. Lancet. 2011;377:2138–49.
68. Russo RAG, Katsicas MM. Clinical remission in patients with systemic juvenile idiopathic arthritis treated with anti-tumor necrosis factor agents. J Rheumatol. 2009;36:1078–82.
69. Gattorno M, Piccini A, Lasigliè D, Tassi S, Brisca G, Carta S, et al. The pattern of response to anti-interleukin-1 treatment distinguishes two subsets of patients with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum. 2008;58:1505–15.
70. Zeft A, Hollister R, LaFleur B, Sampath P, Soep J, McNally B, et al. Anakinra for systemic juvenile arthritis: the Rocky Mountain experience. J Clin Rheumatol. 2009;15:161–4.
71. Nigrovic PA, Mannion M, Prince FHM, Zeft A, Rabinovich CE, van Rossum MAJ, et al. Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: report of forty-six patients from an international multicenter series. Arthritis Rheum. 2011;63:545–55.
72. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). Ann Rheum Dis. 2011;70:747–54.
73. Hoy SM. Canakinumab: a review of its use in the management of systemic juvenile idiopathic arthritis. BioDrugs. 2015;29:133–42.
74. Ilowite NT, Prather K, Lokhnygina Y, Schanberg LE, Elder M, Milojevic D, et al. Randomized, double-blind, placebo-controlled trial of the efficacy and safety of rilonacept in the treatment of systemic juvenile idiopathic arthritis. Arthritis Rheumatol. 2014;66:2570–9.
75. Barone P, Pignataro R, Garozzo MT, Leonardi S. IL-6 blockers in systemic onset juvenile idiopathic arthritis. Immunotherapy. 2016;8:79–87.
76. Yokota S, Miyamae T, Imagawa T, Iwata N, Katakura S, Mori M, et al. Therapeutic efficacy of humanized recombinant anti-interleukin-6 receptor antibody in children with systemic-onset juvenile idiopathic arthritis. Arthritis Rheum. 2005;52:818–25.
77. Yokota S, Imagawa T, Mori M, Miyamae T, Aihara Y, Takei S, et al. Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. Lancet. 2008;371:998–1006.
78. Yokota S, Imagawa T, Mori M, Miyamae T, Takei S, Iwata N, et al. Long-term treatment of systemic juvenile idiopathic arthritis with tocilizumab: results of an open-label extension study in Japan. Ann Rheum Dis. 2013;72:627–8.
79. De Benedetti F, Brunner HI, Ruperto N, Kenwright A, Wright S, Calvo I, et al. Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. N Engl J Med. 2012;367:2385–95.
80. Woerner A, Uettwiller F, Melki I, Mouy R, Wouters C, Bader-Meunier B, et al. Biological treatment in systemic juvenile idiopathic arthritis: achievement of inactive disease or clinical remission on a first, second or third biological agent. RMD Open. 2015;1:1–9.
81. Wallace CA, Giannini EH, Spalding SJ, Hashkes PJ, O'Neil KM, Zeft AS, et al; Childhood Arthritis and Rheumatology Research Alliance. Trial of early aggressive therapy in polyarticular juvenile idiopathic arthritis. Arthritis Rheum. 2012;64:2012–21.
82. Billiau AD, Loop M, Le PQ, Berthet F, Philippet P, Kasran A, et al. Etanercept improves linear growth and bone mass acquisition in MTX-resistant polyarticular-course juvenile idiopathic arthritis. Rheumatology. 2010;49:1550–8.
83. Malik F, Ranganathan P. Methotrexate pharmacogenetics in rheumatoid arthritis: a status report. Pharmacogenomics. 2013;14:305–14.
84. de Rotte MCFJ, Bulatovic M, Heijstek MW, Jansen G, Heil SG, van Schaik RHN, et al. ABCB1 and ABCC3 gene polymorphisms are associated with first-year response to methotrexate in juvenile idiopathic arthritis. J Rheumatol. 2012;39:2032–40.

85. Albers HM, Wessels JAM, van der Straaten RJHM, Brinkman DMC, Suijlekom-Smit LWA, Kamphuis SSM, et al. Time to treatment as an important factor for the response to methotrexate in juvenile idiopathic arthritis. Arthritis Rheum. 2009;61:46–51.
86. Consolaro A, Schiappapietra B, Dalprà S, Calandra S, Martini A, Ravelli A. Optimisation of disease assessments in juvenile idiopathic arthritis. Clin Exp Rheumatol. 2014;32(Suppl 85): S126–30.
87. Baszis K, Garbutt J, Toib D, Mao J, King A, White A, et al. Clinical outcomes after withdrawal of anti-tumor necrosis factor α therapy in patients with juvenile idiopathic arthritis: a twelve-year experience. Arthritis Rheum. 2011;63:3163–8.
88. Verazza S, Negro G, Marafon D, Consolaro A, Martini A, Ravelli A. Possible discontinuation of therapies after clinical remission in juvenile idiopathic arthritis. Clin Exp Rheumatol. 2013;31(Suppl. 78):S98–101.
89. Chang CY, Meyer RML, Reiff AO. Impact of medication withdrawal method on flare-free survival in patients with juvenile idiopathic arthritis on combination therapy. Arthritis Care Res. 2015;67:658–66.
90. Cai Y, Liu X, Zhang W, Xu J, Cao L. Clinical trial of etanercept tapering in juvenile idiopathic arthritis during remission. Rheumatol Int. 2013;33:2277–82.
91. Emery P, Hammoudeh M, FitzGerald O, Combe B, Martin-Mola E, Buch MH, et al. Sustained remission with etanercept tapering in early rheumatoid arthritis. N Engl J Med. 2014;371:1781–92.