Portuguese recommendations for the use of biological therapies in children and adolescents with Juvenile Idiopathic Arthritis - December 2011 update

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ABSTRACT

Objective: To update the Portuguese recommendations in order to assist the rational and safe prescribing of biological therapies in children and adolescents with Juvenile Idiopathic Arthritis (JIA) as more evidence and experience with these drugs are available.

Methods: The recommendations were formulated by Rheumatologists and Pediatricians, with experience in Pediatric Rheumatology, based on literature evidence and consensus opinion. The evidence was sought through a MEDLINE search. The retrieved results were discussed and a set of recommendations proposed. All propositions were extensively debated and the final recommendations formulated.

Results: A consensus was achieved regarding the eligibility, response criteria, maintenance of biologic therapy, and procedures in case of non-response. Also, specific recommendations concerning safety procedures before and while on biologic therapies were formulated.

Conclusions: Thirteen recommendations for guidance biological therapy in children and adolescents with JIA were developed using both evidence-based and expert consensus. These recommendations will be updated as more evidence becomes available and more biological therapies are licensed.

Keywords: Juvenile Idiopathic Arthritis, Children, Guidelines, Biological therapies, Portugal

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is the most common rheumatic disease of childhood, affecting 1/1000 children. JIA includes a heterogeneous group of arthritis of unknown cause that begins before 16 years-old. According to the disease onset seven subtypes can be identified[1]. Beyond the first 6 months the disease may follow a different clinical pattern and while some cases are mild and self-limited, others are severe, persist into adulthood and cause significant morbidity, imposing a considerable societal burden[2].

Biologic agents represent a great advance in the treatment of JIA patients, but their use is associated with some adverse effects and considerable costs. In 2007 we published national recommendations for the use of biologics in JIA aiming to improve the medical practice and guarantee their safest and most effective use in children and adolescents[3]. These recommendations are now revised as new data and greater daily experience are available. There are currently four biologics licensed for the treatment of JIA: etanercept (after 2 years-old), abatacept (after 6 years-old), adalimumab (after 4 years-old) and tocilizumab (after 2 years-old). Other biological options are under evaluation and some are often prescribed off-label. For practical purposes we have differentiated two major indications for the use of biologics: 1) active arthritis and 2) systemic features.

METHODS

The recommendations were elaborated by the Pediatric Rheumatology Working Group of the Portuguese Society of Rheumatology and the Rheumatology Section of the Portuguese Society of Pediatrics. A steering committee composed by 13 physicians (7 Rheumatologists and 6 Pediatricians) with experience in the management of JIA patients defined the relevant questions regarding initiation, monitoring and maintenance of biological treatment, as well as safety procedures befo-

re starting and while on active treatment. Subsequently, a comprehensive literature search was performed using primarily MEDLINE. The results of the retrieved evidence were discussed and a set of recommendations was proposed. All propositions were then extensively debated among rheumatologists and pediatricians and final recommendations formulated.

RECOMMENDATIONS

The general principles of the present recommendations establish that biological therapies should only be started in patients with a definitive diagnosis of JIA and active disease despite correct standard treatment. Maintenance of treatment requires that a clinical response is achieved. Before starting and while on biologics, safety procedures must be assured and there must be no contra-indications.

CRITERIA FOR STARTING BIOLOGIC THERAPY

DIAGNOSIS

RECOMMENDATION 1: Biological therapy should only be initiated and managed by physicians with experience in the diagnosis and treatment of JIA. A definitive diagnosis of JIA is required.

JIA can be diagnosed if arthritis in one or more joints persists for at least 6 weeks and after excluding other known conditions[1]. Former European League Against Rheumatism (EULAR) and American College of Rheumatology (ACR) classification criteria have been replaced by the International League Against Rheumatism (ILAR) criteria[1] which are intended at classifying all forms of childhood arthritis into 7 homogeneous, mutually exclusive categories of JIA: systemic arthritis (sJIA), oligoarthritis (oJIA), polyarthritis (pJIA) rheumatoid factor (RF) positive, polyarthritis RF negative, enthesitis related arthritis (ERA), juvenile psoriatic arthritis (jPsA) and undifferentiated arthritis. Beyond the first six months oJIA can be further classified in persistent oJIA (if still less than 5 joints are involved) or extended oligoarticular (eoJIA) (if involvement of ≥5 joints occurs). In the case of sJIA systemic features may persist or the disease may evolve into a polyarthritis. Although the strict application of the ILAR criteria received some criticism[4,5], this remains the most widely used classification. The diagnosis of JIA should be made by a rheumatologist or a pediatrician with experience in rheumatic diseases of childhood. Initiation of biological therapy should only be undertaken by a consultant who regularly sees children and young people with JIA and who runs specialized pediatric rheumatology clinics according to the Portuguese law. Children starting biologics should be registered in the national register for rheumatic diseases from the Portuguese Society of Rheumatology, the Reuma.pt[6].

ACTIVE DISEASE CANDIDATE TO BIOLOGICAL THERAPY

RECOMMENDATION 2: Active arthritis is eligible for treatment with biologics when 5 or more active joints are present on two separate occasions at least 3 months apart, despite standard treatment. The decision to initiate a biologic earlier or in patients with fewer active joints, enthesitis or systemic manifestations should be made on an individual basis and taking into account prognostic features, functional status and drug side effects.

A) Definition of active disease

Joint disease: During the last decade, a variety of instruments have been used for measuring disease activity, all of them comprise the active joint count. Active joints are defined by the presence of swelling (not due to deformity) or limitation of motion with pain, tenderness or both[7]. The total joint count includes 75 joints: 35 peripheral joints at each side of the body, cervical, thoracic, lumbar spine and sacroiliac joints. Enthesitis is a common feature of ERA subtype and this manifestation should also be adequately captured. Recently, a composite score named Juvenile Arthritis Disease Activity Score (JADAS) was found to be a valid instrument for assessment of disease activity[8]. JADAS includes the active joint count, physician global assessment of disease activity (PhGA), parent/patient global assessment (PtGA) of well-being and erythrocyte sedimentation rate (ESR).

Systemic features: There are currently no measures of disease activity available for sJIA. However, the following domains were found to be the most important to evaluate systemic features: systemic symptoms (fever, rash, splenomegaly, lymphadenopathy) and inflammatory markers – raised ESR and C-reactive protein (CRP)[9].

B) Poor prognostic criteria

Published evidence demonstrates that clinical subtype, disease activity and duration, and response to treatment, all influence the prognosis[10-14]. Children with

persistent oJIA have a substantially better outcome than those with either sJIA or pJIA with regard to remission, disability and structural damage[15,16]. However, when considering prognosis following the onset of JIA, it is important to consider the predictive role of the individual disease features rather than relying on disease subtype alone. Greater severity and extension of arthritis at onset, symmetric disease, early hip or wrist involvement, the presence of RF, early age at onset, female gender, family history of rheumatic disease and prolonged active disease were the best predictors of a poor outcome[10-13]. *Bartoli et al* also showed that achievement of a good response to methotrexate (MTX) therapy at 6 months predicts a more favorable long-term outcome[14]. With the aim of covering and scoring all forms of long-term articular and extra-articular morbidity in patients with JIA, *Viola* et al created a damage assessment tool – the Juvenile Arthritis Damage Index (JADI)[17]. The JADI has been demonstrated to correlate with parameters of disease activity, different levels of functional disability and radiographic damage of joints.

FAILURE TO STANDARD TREATMENT

RECOMMENDATION 3: Biological therapy can be started in active polyarthritis despite the use of NSAIDs, intra-articular corticosteroid injections (if indicated) and synthetic DMARDs, including MTX in a standard effective dose for at least 3 months, unless contraindicated or not tolerated.

Sustained severe systemic features regardless of concurrent therapy (systemic corticosteroids with or without DMARDs) also constitute an indication for treatment with biologics.

Patients with active uveitis despite corticosteroids and immunossupressants or requiring long term corticosteroids or presenting severe side effects related to these medications are also eligible for biological therapy.

A flowchart depicting the general treatment strategy for active JIA is shown in Figure 1.

Intra-articular corticosteroid (IAC) injections represent one of the greatest advances and stands as the first line treatment option in oJIA. IAC are also useful in other JIA subtypes, especially when a rapid resolution

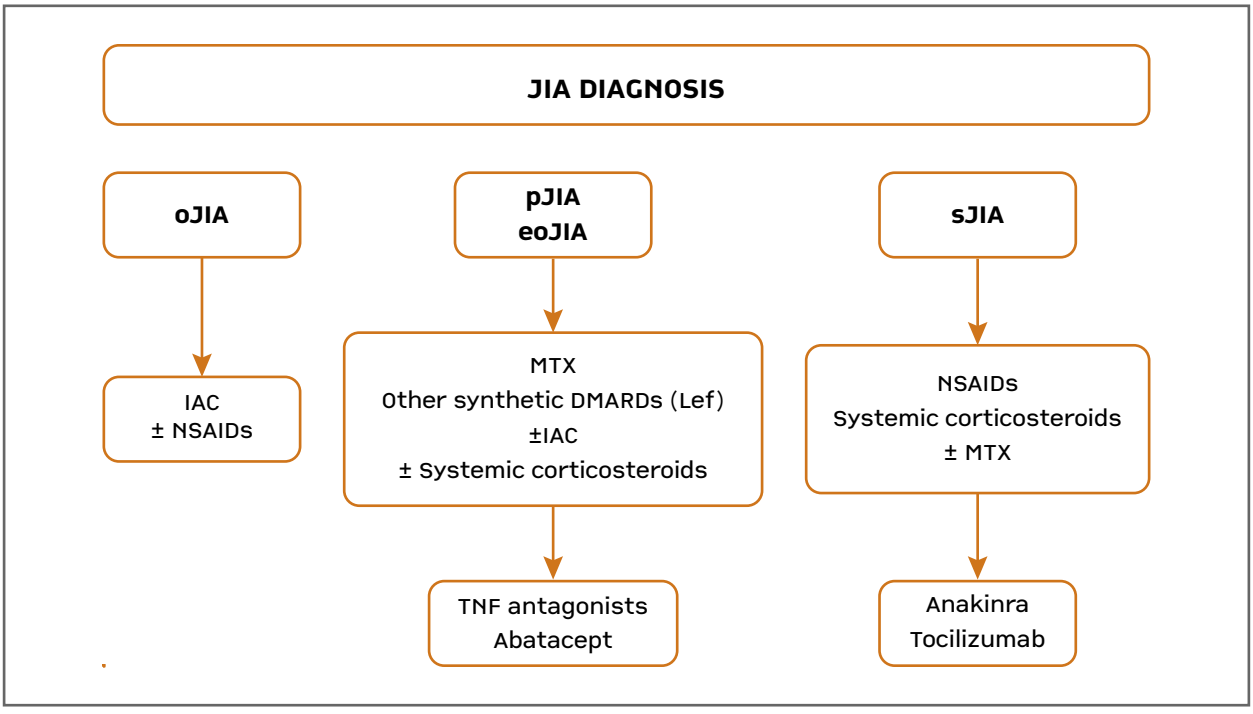

FIGURE 1. Schematic approach to the treatment of juvenile idiopathic arthritis

JIA – Juvenile idiopathic arthrtis; oJIA – oligoarthritis; pJIA – polyarthritis; eoJIA – extended oligoarthritis; sJIA – systemic arthritis; IAC – intra-articular corticosteroids; NSAIDs – non-steroidal anti-inflammatory drugs; MTX – methotrexate; DMARDs – disease modifying anti-rheumatic drugs; Lef – leflunomide

TABLE I. INDICATIONS FOR JOINT INJECTION OF CORTICOSTEROIDS IN JIA PATIENTS

Oligoarthritis	Inadequate response to NSAIDs or toxicity Alternative to long-term NSAIDs and/or before starting DMARDs Flexion contractures Limb length discrepancies Muscle atrophy Treatment of arthritis relapse in patients on DMARDs
Polyarthritis	Multiple intra-articular injections as "bridge therapy" in order to accelerate recover while waiting the maximum effect of DMARDs and in alternative to systemic corticosteroids Treatment of persistently active joints despite the use of synthetic or biologic DMARDs Treatment of arthritis relapse in patients on DMARDs

NSAIDs – non-steroidal anti-inflammatory drugs; DMARDs – disease modifying anti-rheumatic drugs

of the clinical manifestations is required[18-23] (Table I). Intra-articular injections can be performed in almost every joint, including the hip and the temporo-mandibular joints[18-23], but an adequate analgesia and/or sedation of the child and sterile technique must be assured[20,21,24]. The early use of IAC makes the return to normal daily activities faster and reduces the risk of limb length discrepancy in oJIA patients[19]. Triamcinolone hexacetonide (TH) should be the first choice given its efficacy and safety profile[18-23]. However, in the case of hand and feet small joints or tenosynovitis, and having in mind the risk of subcutaneous tissue atrophy, less potent corticosteroids are sometimes preferred[19]. A long-lasting (beyond 12 months) sustained remission can be achieved in one half to two thirds of the patients with oJIA[19,20,22,23] and durable results are also obtained in pJIA RF negative with intra-articular TH[22]. Intermediate results were observed in other subtypes of JIA[19,20,22]. Clinical and laboratory predictors of response to IAC are outlined in Table II. Repeated joint injections seem to have a similar efficacy to the first one[22]. However, it is unclear how repeated injections affect the remission rate or duration. The occurrence of adverse events is rare and includes most frequently atrophy of the subcutaneous fat tissue and hypopigmentation[19-23]. Systemic effects, such as transient suppression of cortisol release, especially in younger children and when multiple joints are injected simultaneously, are rare[19,24]. However, planed surgery should be postponed for some days and in children with diabetes an adjustment in insulin dosage might be needed[19,24]. Ultrasound guided injections are more accurate and can be very useful for joints with difficult access[25].

Systemic corticosteroids provide rapid and potent anti-inflammatory effect, although there is no evidence of disease modifying effect in JIA[26]. On the other hand, long-term corticosteroids should be avoided in children because of the high incidence of side effects, particularly growth retardation[27] and osteoporosis[28]. The main indications for systemic steroids are: 1) sJIA with severe systemic features and/or the macrophage activation syndrome (MAS), 2) pJIA – as bridging therapy until other medications become effective and 3) chronic uveitis – as bridging therapy until other medications become effective[19].

Systemic corticosteroids in combination with Disease Modifying Anti-Rheumatic Drugs (DMARDs) such as MTX have been the mainstay of sJIA treatment. Corticosteroids are used during the acute phase of the illness for patients with high fever, severe anemia or significant symptomatic serositis[29], in some cases in dosages as high as 1-2 mg/kg/day (maximum 60 mg/day). Pulse therapy with methylprednisolone is an alternative to oral corticosteroids and has been used to treat refractory systemic features of sJIA and MAS[30,31]. The goal is to achieve a strong anti-inflammatory effect and reduce daily dosage of oral steroids and related toxicity, although there are no controlled studies showing fewer adverse effects[32]. One controlled study showed that the use of intravenous mini-pulses of corticosteroids in the first week of sJIA treatment resulted in lower daily and lower cumulative doses at 6 months, when compared with initial oral corticosteroids[33]. Established protocols of pulse therapy consist of methylprednisolone 10-30 mg/kg per pulse (1 gram maximum), administered as single pulses 1 month apart (or repeated as clinical circumstances warrant), 3 pul-

TABLE II. CHARACTERISTICS ASSOCIATED WITH THE OUTCOME AFTER IAC INJECTION

Better outcome	Worse outcome
oJIA	sJIA
Upper limbs and knee joints	Hip and ankle involvement
Only one joint injected	Several joints injected in one session
Younger age	pJIA RF+
Recent disease onset	ANA negative
Positive ANA	High percentage of neutrophils in synovial fluid
pJIA RF- under therapy with DMARDs (MTX and/or biologics)	

IAC – intra-articular corticosteroids; oJIA – oligoarthritis; sJIA – systemic arthritis; pJIA -polyarthritis; RF – rheumatoid factor; ANA – antinuclear antibodies; DMARDs – disease modifying anti-rheumatic drugs; MTX – methotrexate

TABLE III. GENERAL PRINCIPLES FOR MINIMIZING CORTICOSTEROID TOXICITY

- Use short-acting or intermediate-acting corticosteroids
- Use the lowest necessary dose and the shorter duration of treatment
- Once-a-day early morning administration is preferable
- Monitor body weight, height, blood pressure, blood and/or urine glucose and serum lipids
- Monitor ocular pressure and development of cataract
- After long term steroid administration withdraw carefully
- Supplement with calcium and vitamin D
- Encourage physical activity

Corticosteroids should be tapered gradually to avoid adrenal insufficiency or disease reactivation. In high doses (60 mg/day) reductions of 10 mg are usually well tolerated; at low doses (10 mg/day) reductions of 1-2 mg may be necessary. Although daily administration is more effective than administration of the same total dose every other day, corticosteroids can be tapered every other day in order to achieve an alternate day regimen

ses given on 3 consecutive days, or 3 pulses on alternate days each month[34]. Methylprednisolone must be diluted in 100-200 ml of 5% dextrose or normal saline and infused over a period of 1-3 hours under cardiovascular monitoring during the infusion and for a time thereafter. Careful attention must be given to electrolyte and fluid balance, and to the potential for cardiac arrhythmia or acute hypertension[35].

Every effort must be made to minimize the dosage and duration of corticosteroid therapy (Table III). Whenever possible, the dose should be kept below 0.5 mg/kg/day of prednisolone (or its equivalent) and the duration of therapy should be less than six months. Recent experience suggests that IL-1 inhibitors (anakinra and canakinumab) and IL-6 receptor antagonist (tocilizumab) could be the most appropriate disease modifying agents for long-term sJIA management, as well as for induction of early remission, before severe damage due to arthritis or side effects of corticosteroids occur. There is some evidence that the early use of IL-1 blockade might result in long-term sustained remission[36,37], thus preventing the occurrence of crippling arthritis.

In pJIA corticosteroids should be used in low doses and limited to patients with extreme pain and functional impairment, while awaiting the effects of DMARDs, or during an acute flare[38]. Low dose corticosteroids (prednisolone 0.1-0.2 mg/kg/day) can be used as a bridging agent. A short course of oral prednisolone (0.5 to 2 mg/kg) may be required for very active disease[39,40]. Once improvement is achieved, steroids should be tapered as quick as possible and stopped or used in the lowest dose that controls symptoms. With the early introduction of synthetic and biologic DMARDs, systemic corticosteroids have little place in JIA treatment, as they hardly ever contribute to the induction of remission and are associated with severe side effects.

Disease modifying anti-rheumatic drugs (DMARDs) – The efficacy of MTX in controlling the signs and symptoms of JIA is well established although most of the evidence comes from uncontrolled clinical trials[41]. In an attempt to determine in which subtype of JIA MTX is more effective, investigators from UK undertook a randomized controlled trial (RCT) and concluded that MTX produced significant improvement in patients with eoJIA, but was much less effective in patients with sJIA[42]. Ravelli *et al* determined that the extended oligoarticular subtype was the best predictor of short-

term clinical response[43]. More recently PRINTO published the analysis of a MTX trial in pJIA[44] and concluded that longer disease duration, absence of ANA, higher disability and presence of wrist activity was significantly associated with a poorer response at 6--month. MTX is sometimes used in ERA, but there are no consistent reports of its efficacy in this group of children[45]. Moreover, anecdotal reports suggest that MTX is less effective in ERA than in other types of JIA[46]. No RCTs have been conducted in JPsA. In inflammatory bowel disease arthropathies MTX results in improvement of both GI and joint symptoms[47-49]. Studies on the management of uveitis in children with JIA concluded that MTX was very effective[50,51]. MTX may also slow the radiologic progression[52], although the available data is scarce. Standard effective doses of MTX in children with JIA are 10 to 15mg/m^2/wk. Improvement is generally seen by about 6 to 8 weeks on effective doses, but may take 6 months[53]. Children seem to tolerate much higher doses than adults, and some series have described using 20 to 25 mg/m^2/wk in children with resistant disease with relative safety in the short--term[54]. Parenteral MTX administration should be considered in children who have a poor clinical response to orally administered MTX, develop significant GI intolerance or are apparently needing a dose greater than 10-15mg/m^2/wk[55]. However, a RCT failed to demonstrate the superior efficacy of parenteral 30 mg/m^2/wk versus 15 mg/m^2/wk[56].

Until now no firm conclusions can be drawn about the optimal strategy for MTX withdrawal when remission is achieved. Stopping MTX may result in disease flare in more than 50% of patients, or even in a higher rate in younger children[57,58]. In JIA patients in remission, a 12-month vs. 6-month MTX gradual withdrawal did not reduce the relapse rate[59].

Although MTX is associated with several potential toxicities, the documented overall frequency and severity of adverse events in children with arthritis is low[60,61]. The most frequent are abdominal discomfort and nausea, reported in 12% of children[60]. Transaminases elevation, occurring in about 9% of children with JIA treated with MTX[60], are usually transient and resolve with either discontinuation or lowering the dose[61,62]. Stomatitis or oral ulcers are reported in about 3% of children[60]. Although MTX may potentially increase the risk for serious infections, these complications are infrequently reported in JIA patients. The issue of whether MTX treatment is an independent risk factor for various malignancies is controversial and remains unsettled. Several cases of Hodgkin lymphoma[63,64] and non-Hodgkin lymphoma[65,66] have been reported in children with JIA treated with MTX. Regarding routine folate supplementation it seems that low--dose (1 mg/day) folic acid does not have any detrimental effect on disease control[67] and confers a beneficial effect in terms of GI and mucosal toxicities related to MTX[53]. Recommendations for optimal laboratory monitoring intervals for complete blood count, liver enzyme levels, and serum creatinine levels for the follow up of JIA patients receiving MTX is based on duration of therapy: <3 months 2-4wk intervals; 3-6 months 8-12wk interval and > 6 months 12wk interval[53].

Treatment with other DMARDs is not as well established as with MTX. Leflunomide, a pyrimidine synthesis inhibitor, has been shown to be effective in pJIA. A randomized controlled trial compared the use of leflunomide (5 to 20mg daily based on weight cutoff values) and oral MTX (0.5mg/kg/wk) in 94 patients with active pJIA. Although the ACR Pedi 30 response was higher in the MTX group at week 16, in the extended phase there were similar ACR Pedi 30, 50 and 70 responses between the two groups. The frequency of adverse events was also similar in both groups[68]. In an open label study of 27 patients with pJIA who had either failed to respond or were intolerant to MTX, the majority (52%) reached the ACR Pedi 30 response by week 26. This response was maintained in 53% of the patients that entered the extended phase (up to 30 months)[69]. The most common adverse reactions were diarrhea, anorexia, abdominal pain, gastritis and elevated serum transaminases. Other reported side effects include rash, allergic reactions, headache, elevated blood pressure and reversible alopecia. Weight loss and hypophosphatemia are less common. Leflunomide is also a known teratogen.

Sulfasalazine can be used in ERA following glucocorticoid joint injections or a trial of non-steroidal anti--inflammatory drugs (NSAIDs). It is also commonly used in arthritis associated with inflammatory bowel disease in a daily dosage of 40-60 mg/kg/day. A few controlled trials showed efficacy, particularly in the above mentioned JIA subtypes, with acceptable short term safety profiles. Adverse events included rashes, gastrointestinal symptoms and leukopenia[39,70,71].

Treatment with thalidomide is only supported by case series. The largest of these included 13 children with severe, refractory sJIA, 10 of which achieved an ACR Pedi 50 response or better[72,73]. Nevertheless, it is

not recommended as first line therapy. Side effects included sedation, somnolence and neutropenia. Besides the teratogenic effect, permanent peripheral neuropathy is a concern with long term use.

Cyclosporin A and other calcineurin inhibitors have no documented efficacy in arthritis with or without systemic features. Yet, cyclosporin A can be useful in the control of chronic uveitis associated with JIA and is part of the approach to MAS treatment[74].

There is scarce information on combined DMARD therapy in JIA[75], and as such its usage was classified as uncertain in the recent ACR recommendations[18].

STARTING BIOLOGICAL THERAPY

RECOMMENDATION 4 – The choice of the biologic agent must take into consideration the JIA subtype, children's age, individual risk evaluation and drug label.

Tumor Necrosis Factor (TNF) inhibitors – TNF is a key cytokine in the physiopathological pathway of multiple inflammatory rheumatic diseases, JIA included[76].

Etanercept was the first biologic licensed for JIA. It is a genetically engineered fusion protein consisting of two identical chains of the recombinant extracellular human TNF-receptor p75 monomer fused with the Fc domain of the human IgG1. It effectively binds TNF and lymphotoxin alpha and inhibits their activity[77,78]. In most countries, etanercept is licensed and recommended for children with polyarticular course JIA after failure to the maximum tolerated MTX dosage. First studies were done on monotherapy but about three quarters of JIA patients who start etanercept therapy use MTX as a concomitant drug[79]. Etanercept is slowly absorbed after subcutaneous (SC) injection. In adults it reaches its peak about 50 hours after injection and has a half-life of 115 hours[80]. In JIA patients, the limited data that is available suggests that the clearance of etanercept is slightly reduced in children ages 4 to 8 years (<23kg)[80]. The efficacy and safety of etanercept in JIA was first assessed in a double-blind, randomized controlled withdrawal trial published by Lovell *et al*[7]. Subtypes included sJIA with polyarticular involvement, pJIA and eoJIA. All patients included had an active polyarticular course and the study was conducted in two phases. First, all patients received 0.4 mg/kg (maximum 25 mg per dose) of SC etanercept, twice weekly. In the second phase, patients with clinical improvement at day 90, according to the ACR Pedi 30 criteria, were randomized to remain on etanercept or receive placebo for four months and assessed for disease flare. At the end of the open-label part of the study, 51 of the 69 patients (74%) had had response to etanercept treatment. Etanercept was clearly superior to placebo. In the double-blind phase of the study, significantly more who received placebo withdrew because of disease flare (81%), as compared with patients who received etanercept (28%). The median time to disease flare was also shorter in the placebo arm. In the double-blind study, there were no significant differences between the two treatment groups in the frequency of adverse events. All patients on etanercept at the end of the 7-month clinical trial were observed in an open label extension study. Sustained effectiveness was shown after 2, 4 and 8 years of etanercept therapy. Authors concluded that treatment with etanercept led to significant improvement in patients with active pJIA and was well tolerated by pediatric patients. Short and long-term observational studies and case series also confirmed that the efficacy and safety of etanercept extends beyond trial conditions to everyday clinical practice[79,81,82].

However, some questions remained to be answered. The first one is related to the optimal dosing. Initially the recommended dosing regimen for etanercept in JIA patients was 0.4 mg/kg (maximum 25 mg) twice weekly[83]. But eventually, studies in rheumatoid arthritis and ankylosing spondylitis demonstrated that once weekly double dose SC administration could be as effective as the twice a week dosing schedule. Yim et al[80] developed a pharmacokinetic computational model that showed equivalent concentrations of etanercept with the administration of 0.8 mg/kg SC once weekly and 0.4mg/kg SC twice weekly in children. Three clinical studies, one from Netherlands[84,85], and two from Germany[86,87] also confirmed the efficacy and safety of the once weekly 0.8 mg/ kg SC dose. Concomitant therapy is also an issue. Giannini et al[88] compared patients who received MTX alone (n=197), with patients who received etanercept in combination with MTX (n=294) and in monotherapy (n=103). They concluded that both treatments with etanercept alone and etanercept plus MTX have an acceptable safety and effectiveness profile in patients with sJIA, pJIA RF+, pJIA RF- and eoJIA. Other questions are still under debate, namely the optimal timing for starting etanercept therapy, discontinuation in the context of long standing remission, efficacy in extra-articular manifestations and long-term safety concerns, like lymphoma. It has been suggested that starting etanercept earlier in the disease course would be beneficial, especially for sJIA

patients. However, a study of sJIA patients in the USA did not show significant differences in disease duration between responders and nonresponders[89]. Data on etanercept suspension is scarce. Most studies with biological therapies reported flares after treatment interruption. However, due to safety reasons Summary of Product Characteristics and practical recommendations suggest to stop biological drug after 2 or 3 years of symptoms remission. Although etanercept was initially licensed in Europe for use in JIA patients from the age of 4 years, this approval was recently extended to the age of 2 years, a change supported by a report from the German registry, which included 25 JIA patients under 4 years old[90]. A relatively large proportion of these patients had sJIA (60%). No differences in effectiveness were shown between groups under and above 4 years old. In young children only 2 adverse events and no severe adverse events were reported. Also, other anecdotal reports did not show complications when treating children younger than 4 years with etanercept[79,86,91,92]. Etanercept use in JIA associated uveitis, sJIA and MAS has been also reported. Several reports described newly onset or flaring of JIA associated uveitis during etanercept therapy[93,94]. However, a large survey study, as well as a large chart review study, showed that there was no significant increase in uveitis in patients on etanercept compared to patients not taking etanercept[95,96]. Also, severity of uveitis did not seem to be influenced by etanercept. There are also reports on the therapeutic effect of etanercept on uveitis. A small prospective study in 16 uveitis events treated with etanercept showed a statistically significant improvement in 63%[97]. Increase of etanercept dose did not show an additional positive effect. A double-blind RCT of 12 patients did not document differences in uveitis between placebo and etanercept treated groups, but power was low[98]. Etanercept may benefit certain patients with JIA associated uveitis, but appears to be more effective for treating arthritis than uveitis. Several studies (but not head-to-head RCT) suggested a better effect of infliximab and adalimumab on active uveitis[99-102].

Etanercept has been used for the treatment of the systemic symptoms accompanying sJIA, but it is more efficacious in controlling arthritis than systemic features. Also, patients with sJIA have a propensity to develop MAS. This is a potentially fatal hemophagocytic syndrome, which can be triggered by medication or infection[103,104]. Etanercept has been described either as treatment or as a trigger for the development of MAS. Ramanan *et al* [25] described a patient with sJIA who developed MAS after 4 doses of etanercept. Kimura *et al*[89] reported two patients who developed MAS after 12 and 25 months of etanercept use, during a disease flare. On the other hand, several case reports describe sJIA patients with therapy-resistant MAS, who were successfully treated with etanercept[105,106]. In fact, more knowledge on the pathogenesis of MAS is needed to better understand the potential role of candidate therapies. Long-term safety issues are mainly related with lymphomas and neoplasms. An increase in malignancies has been historically a possible long-term effect of etanercept and other TNF-blocking agents. The United States Food and Drug Administration has given out a warning in 2008 about the possible association between the use of TNF blockers and the development of lymphoma and other cancers in children and young adults. In 2009 they reported their analysis of TNF blockers and concluded that there is an increased risk of lymphoma and other cancers associated with the use of these drugs in children and adolescents[107]. In total, FDA claims to have found 14 cases of malignancies in JIA patients using TNF-alpha blocking therapies. Not enough details were given to report differences in JIA subtype. No dose association was found. The background incidence of malignancy in JIA patients is not well defined. Most of the patients were under other immunosuppressant medications. The strength of the association between etanercept use and the risk of developing a malignancy in JIA patients should be subjected to further investigation.

Adalimumab is a anti-TNF fully human monoclonal antibody administered in 40mg SC doses every two weeks to children above 12 years-old, and in a dose of 24 mg/m^2 (maximum 40 mg) every two weeks in children aged 4-12 years-old.

Efficacy and safety was proven in a randomized, placebo-controlled, double-blind clinical trial[108]. Based on the results from this trial adalimumab was the second biologic licensed for JIA in children above 4 years-old, as monotherapy or in combination with MTX. In the open phase of the 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). A total of 85 patients continued previous treatment with MTX. Seventy-four percent of patients on adalimumab monotherapy (64 out of 86) and 94% of those receiving concomitant MTX (80 out of 85) had an ACR Pedi 30 response at week 16 and were eligible for double-

blind treatment. In the subsequent placebo-controlled phase of the trial, disease flares were significantly less frequent in the adalimumab group. At 48 weeks, the percentages of patients treated with concomitant MTX who had ACR Pedi 30, 50, 70, or 90 responses were significantly greater than those receiving adalimumab monotherapy or placebo. Response rates were sustained after 104 weeks of treatment. Serious adverse events possibly related to adalimumab occurred in 14 patients. Thus, adalimumab demonstrated efficacy in treating pJIA. 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. No tuberculosis, other opportunistic infections or malignancies were observed in this patient cohort. Long-term safety data on larger cohorts is being collected.

Adalimumab seems also efficacious in the treatment of chronic recurrent anterior uveitis. In an open trial[109], 14 pediatric patients with uveitis who had failed other therapies were treated with adalimumab: 80.8% improved and 3.8% worsened. In another retrospective study of 20 pediatric patients with chronic uveitis[110] of whom 19 were previously treated with infliximab or etanercept, seven showed improvement, one worsening, while the remaining 12 did not show any change in the activity of uveitis. These studies suggest that adalimumab is a potential treatment option in JIA-associated uveitis. So far only open uncontrolled trials have indicated clinical usefulness but randomized controlled trials are ongoing.

Infliximab is a chimeric human/mouse anti-TNF monoclonal antibody, which binds to TNF-alpha, preventing its interaction with cell-surface receptors. Currently, infliximab is not approved for JIA treatment. A randomized, placebo-controlled double-blind study did not achieve primary endpoint efficacy at 3 months of infliximab therapy in the dose of 3 mg/kg or 6 mg/kg intravenously compared to placebo[111]. At 1 year infliximab showed sustained efficacy and that was also shown in some observational studies and anecdotal reports. RCT safety data indicated that the 6 mg/kg dose may provide a more favorable risk/benefit profile (less infusion reactions than in the 3 mg/kg arm). A recent multicentre randomised open-label clinical trial targeting to achieve minimally active or inactive disease in early pJIA showed that infliximab plus MTX was superior to synthetic DMARD in combination and strikingly superior to MTX alone[75]. In clinical practice infliximab has been used in pediatric patients that are refractory to etanercept or adalimumab therapies. The best indication seems to be its use in the treatment of refractory JIA associated uveitis[112].

Golimumab is a transgenic monoclonal anti-TNF antibody for subcutaneous application, binding both soluble and membrane bound forms of TNF. Currently it is not licensed for JIA treatment but a multicenter RCT, *GoKids*, is underway (ClinicalTrials.gov Identifier NCT01230827).

There are currently no data on ***certolizumab*** pegol for JIA treatment. A study in patients with juvenile Crohn's disease aged 6-17 years was stopped during interim analysis.

Interleukin-1 inhibitors – Currently there are three IL-1 inhibitor biologic drugs: *anakinra*, an IL-1 receptor antagonist; *rilonacept*, an IL-1 receptor fusion protein and *canakinumab*, a human anti IL-1 antibody. None of them are approved for JIA treatment although all of them were already tested or used in clinical practice to treat JIA patients[113].

More evidence exists upon ***anakinra***. Due to their similar chemical structure, anakinra binds competitively to the physiological IL-1 receptor, however without inducing a stimulatory signal. Anakinra has been used in refractory patients and as a first-line treatment in pJIA and sJIA. In a placebo-controlled trial in patients with pJIA, no benefit of treatment with anakinra over placebo was demonstrated[114], but when subtypes were analyzed, the effectiveness of anakinra in sJIA patients was superior to those with other categories of JIA.

A French retrospective study[115] in 35 adults and children (20 with sJIA and 15 with adult-onset Still's disease) using anakinra at a dosage of 1–2 mg/kg (maximum 100 mg) daily subcutaneous, demonstrated improvement in 15 (75%) of sJIA patients. At treatment onset, fever was present in 45% of the juvenile patients and 87% of adults. All patients had refractory active arthritis and were previously treated with corticosteroids, MTX, TNF inhibitors and/or thalidomide. Systemic symptoms (fever and rash) remitted in 14 of 15 cases. The corticosteroid dose was reduced in 50% of the patients. From out of the 35 patients, two discontinued therapy because of severe skin reactions and another two due to infection.

In 2011, a multicentre, randomized, double-blind, placebo-controlled trial with anakinra in 12 patients

with sJIA (ANAJIS trial) was published[116]. The primary objective was to compare the efficacy of 1-month treatment with anakinra (2 mg/kg subcutaneous daily, maximum 100 mg) with placebo between two groups, each one with 12 patients with sJIA. Response was defined by a 30% improvement of the ACR Pedi criteria for JIA, resolution of systemic symptoms and a decrease of at least 50% of both CRP and ESR compared with baseline. After one month, patients taking placebo were switched to anakinra. Secondary objectives included tolerance and efficacy assessment for 12 months, and analyses of treatment effect on blood gene expression profiling. The study showed an immediate and beneficial effect on systemic manifestations of the disease (fever and rash), as well as on joint inflammation. After 1 month on anakinra, eight out of 12 patients but only one out of 12 patients under placebo showed a response according to ACR Pedi criteria (p=0.003). Then, 10 patients under placebo were switched to anakinra. A total of nine of these 10 patients showed a response according to ACR Pedi criteria. Between month 1 and 12, six patients stopped treatment owing to an adverse event (n=2), lack of efficacy (n=2) or a disease flare (n=2). No differences in adverse effects were observed between groups. The authors concluded that anakinra treatment is effective in sJIA, at least in the short term.

The efficacy of anakinra as a first-line agent was also reported in 2011[37]. Patients with sJIA receiving anakinra as part of initial DMARD therapy were identified from 11 centers in 4 countries. Medical records were abstracted using a standardized instrument, and resulting data were analyzed to characterize concomitant therapies, clinical course, adverse events, and predictors of outcome. This work resulted in a report of data from 46 patients from an international multicenter series. In this study anakinra was used as a first-line disease-modifying therapy in sJIA and in 10 cases it was used as monotherapy. Fever and rash resolved very rapidly in >95% of patients and CRP 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 8 of 10 patients on anakinra monotherapy. Anakinra was discontinued in one patient due to inefficacy. Although anakinra seems to be effective in sJIA, there are patients who are refractory to this therapy. Several case-series described a sustained response in around 50% of the cases. Gattorno et al[117] advocated a differential anakinra treatment effect in subgroups with sJIA. In an open-label study with 22 patients with sJIA with anakinra in a starting dose of 1 mg/kg, they observed a dramatic therapeutic success in 10 patients, mostly in the first week. All of them were able to completely end the comedication and be treated solely with anakinra. The other half of patients did not respond. Increased dosages of up to 4 mg/kg were also ineffective. The systemic symptoms were mostly well controlled with treatment, while joint inflammation and CRP/ESR increases occurred during relapse. They studied the baseline characteristics of either groups and depicted that patients who presented a good response had at baseline fewer active joints (p = 0.02) and higher neutrophil counts (p = 0.02). Besides local reactions, no major side effects were observed.

Several authors suggested that anakinra is significantly better in controlling systemic features than in improving arthritis[118]. In fact, the latest recommendations for JIA treatment from ACR divided systemic onset (soJIA) patients in active systemic and active arthritis and recommended anakinra in cases of systemic manifestations without arthritis, while synthetic DMARDs and other biologic drugs, such as etanercept and abatacept, are preferred in cases of active arthritis without systemic manifestations. Currently, anakinra is mostly used in sJIA patients with active systemic symptoms and less in systemic or pJIA with active arthritis but without systemic manifestations. Aditionally, treatment with anakinra as a first steroid sparing treatment has recently been proposed in the US guidelines[18]. Gattorno's study[117] also supports the fact that for some patients blocking of IL-1 signaling could have 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 sJIA, in agreement with the efficacy demonstrated by other drugs with different mechanism of action.

Anakinra has very good results in the short term, but these may not be sustained in the long term. Another caveat is the need for daily injection, often associated with pain and injection site reactions. Furthermore, the risk of infections seems increased. According to data from adult RA patients, for whom the drug is approved, anakinra and TNF antagonists should not be combined[119]. Some cases of MAS were described in patients taking anakinra, but the occurrence is rare.

Conversely, there are MAS case reports described in the literature, successfully treated with anakinra [120,121]. Anakinra, as a proof of concept, encouraged further study of IL-1 inhibitors in sJIA[113].

Rilonacept (IL-1R/IL1RacP/Fc-fusion protein) has a longer plasma half-life when compared with anakinra. It blocks soluble IL-1 , thereby preventing binding of IL-1 to its cell receptor. Like anakinra, rilonacept is not approved for JIA treatment and, moreover, it was not referred as a therapeutic option in the US guidelines mentioned above[18]. However, a randomized controlled double-blind study in nine patients with soJIA showed a good effect[122]. After 2 weeks, 55% of patients and after 4 weeks, 78% of patients treated with a dose of 2.2 mg/kg showed an ACR Pedi 50 criteria response. Fever remission, reduction of the number of affected joints (by 43% after 2 and 57% after 4 weeks), improvement of childhood health assessment questionnaire (CHAQ) score (decrease of 48% after 2 and of 78% after 4 weeks) and of laboratory parameters (CRP declined 48% after 2 weeks and 78% after 4 weeks) were reported. No major adverse events were found. An open-label extension[83] with long-term rilonacept treatment of 23 patients showed improvement of the mean values of all six ACR Pedi core set criteria. After 6 months, 87%/78%/61% of patients and after 24 months 70%/70%/57% achieved the ACR Pedi 30/50/70. Systemic symptoms and signs like fever, skin rash, leukocytosis, thrombocytosis, anemia, CRP and fibrinogen improved significantly. 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 seems to be promising for soJIA treatment, but before being approved, larger and and long-term randomized clinical trials are needed.

Canakinumab (human anti IL-1 antibody) has also a longer plasma half-life compared to anakinra. It binds selectively to IL-1 without interfering with IL-1RA. It is administered as a subcutaneous injection once monthly. Its efficacy in the treatment of IL-1-dependent auto-inflammatory syndromes makes canakinumab an interesting option for use in systemic arthritis[123]. Data from a phase II dosage escalation open-label trial[124] in 23 children receiving a single injection of canakinumab subcutaneously at a dosage from 0.5 to 9 mg/kg showed an immediate response, achieving at least an ACR Pedi 50 on day 15. Remission was observed in four patients (18%). 17 out of 23 patients were previously treated with anakinra. Six of 11 non-responders to anakinra achieved at least an ACR Pedi 50 on day 15 after a single dose of canakinumab. A new dose was administered at the time of the disease flare. The best baseline predictor of improvement was the number of active joints. The median number of active joints in non-responders was 33.5 but only 9 in responders. The injections were well tolerated. Adverse events were mild to moderate in severity and consisted mainly in infections and gastrointestinal symptoms. Three serious adverse events occurred. Like the former, canakinumab thus appears to be effective in the treatment of sJIA. Currently a placebo-controlled double-blind study with monthly subcutaneous injections of canakinumab is ongoing.

Co-stimulatory blockade – ***Abatacept*** is a soluble, fully human fusion protein constituted by the extra-cellular domain of CTLA4 (cytotoxic T-lymphocyte-associated antigen) linked to a modified Fc portion of human immunoglobulin G1, which does not activate complement. The molecule of abatacept binds to CD80 and CD86, thereby blocking interaction with CD28, inhibiting T cell activation and affecting the production of many downstream cytokines involved in the pathogenesis of auto-immune disease. Abatacept is administered as an intravenous 10 mg/Kg infusion every 4 weeks, but a subcutaneous weekly formulation was recently approved by the FDA for the treatment of RA. It has been shown that abatacept improves disease activity and health-related quality of life[125-128] and inhibits structural damage progression[127] in RA patients resistant to other DMARDs, including anti-TNF therapy. The same type of efficacy has been shown in pJIA in a randomized, double-blind, placebo-controlled withdrawal trial[129] in which patients were excluded if they had active uveitis, active systemic features, major concurrent medical conditions or were pregnant or lactating. To be included in this study, patients needed to be resistant to at least one DMARD, including biological agents such as etanercept, infliximab or adalimumab[107]. MTX was the only DMARD allowed during the study. The ACR Pedi 30 response was obtained in 65% of the 190 patients; results were better in anti-TNF naïve patients (76% of 133 patients) than in patients who were resistant to previous TNF inhibitors (ACR Pedi 30 in 39% of 57 patients). Response levels of ACR Pedi 70 (28%) and ACR Pedi 90 (13%) were also observed. A state of inactive disease was reached by a total of 13% of the patients (being this figure of 18% in anti-TNF naïve patients and 0% in pa-

tients previously treated with anti-TNF drugs)[129]. In the withdrawal phase of the study, flares were significantly more frequent in placebo (53%) than in abatacept (20%) treated patients. Abatacept (10mg/Kg up to a maximum dose of 1000g) was approved by the European Medicines Agency (EMA) as a second line biological agent for the treatment of anti-TNF resistant pJIA. However, strong evidence also supports its efficacy and safety in biological naïve JIA[129].

A long-term extension (LTE) follow-up of this study was performed[130] and it is specially worth to mention that in patients who were resistant to abatacept (failed to reach an ACR Pedi 30 response at the end of the 4-month open-label lead-in phase), and proceeded directly to the LTE, 73%, 64%, 46%, 18% and 5% achieved ACR Pedi 30, ACR Pedi 50, ACR Pedi 70, ACR Pedi 90 and ACR Pedi 100 responses, respectively. This shows that the therapeutic response may be somehow delayed in some patients, particularly when comparing to the fast response observed with TNF inhibitors. Health–related quality of life, pain and sleep quality are also improved in abatacept treated JIA patients[131]. There is some evidence showing that tolerance induced by abatacept might led to long-term remission of disease in some JIA patients[132]. Some recent data also suggest that abatacept might have a role in the treatment of refractory cases of JIA-associated uveitis[133,134].

IL-6 signaling inhibition – ***Tocilizumab*** is a recombinant humanized anti-IL-6R monoclonal antibody that acts as an IL-6 antagonist[135]. It was approved by EMA in January 2009 for the treatment of moderate and severe RA and in August 2011 for the treatment of sJIA (once every two weeks IV infusion at a dose of 8 mg/kg in children weighing 30 kg or more, or 12 mg/kg in children weighing less than 30 kg). Two phase II studies of tocilizumab for soJIA suggested that it can be a very effective treatment[136,137]. In these studies patients received 2, 4 or 8mg/kg and, although 2 or 4 mg/Kg could suppress disease activity, it seems that 8mg/kg is required to control disease activity more effectively. The phase III trial conducted in Japanese children with sJIA who were resistant to conventional treatment was an open-label study with 3 phases: an open-label phase of 6 weeks; a double-blind, randomized, placebo-controlled phase of 12 weeks; and an open-label extension phase of 48 weeks[138]. Tocilizumab was administered intravenously at 8mg/kg, every two weeks. At the end of the open-label phase, ACR Pedi 30, 50 and 70 were achieved by 91, 86 and 68% of the patients, respectively. In the double-blind phase, ACR Pedi 30, 50 and 70 response in the tocilizumab group was achieved in 80, 80 and 75% of children, compared with 17, 17 and 13% in the placebo group. The TENDER study is an ongoing global multicentre 5 year, phase III trial consisting of three parts: a randomized double-blind phase[139], an extension of 96 weeks, followed by a 3 year continuation phase, in children with soJIA[140]. In this study the dose of tocilizumab was 8mg/kg if the body weight was ≥30 or 12 mg/kg if the body weight was 30kg. The 52 week data showed ACR Pedi 30, 70 and 90 responses of 77, 78 and 57%. In these two trials acute phase reactants rapidly normalized (2 weeks after the first infusion) as well as fever. There is one published study of the use of tocilizumab in patients with polyarticular course of JIA with polyarticular or oligoarticular onset[141] and another trial is still recruiting patients[142]. In the first trial (an open-label initial study of 12 weeks duration, followed by an extension study of 48 weeks) all patients received 8mg/kg of tocilizumab every 4 weeks. ACR Pedi 30, 50, 70 and 90 responses at week 12 were achieved by 94.7, 94.7, 57 and 10.5% of the patients and these responses increased over time. At week 48 the response rates were 100, 94.1, 88.2 and 64.7%.

Based on anecdotal reports, tocilizumab might also be useful in the treatment of secondary amyloidosis[143]. Regarding safety, in phase III trials[138-141] the most common adverse events were nasopharyngitis, upper respiratory tract infections and gastroenteritis, but they were mild, as all the laboratory abnormalities. Serious adverse events were more frequent in tocilizumab group than in placebo group, but none led to discontinuation.

CRITERIA FOR MAINTENANCE OF BIOLOGICAL THERAPY

MAINTENANCE OF BIOLOGICAL THERAPY

RECOMMENDATION 5 – Biologic treatment should only be maintained in patients who achieve at least an ACR Pedi 30 after 3 months on treatment, in the case of pJIA, or who are free of systemic manifestations in the case of sJIA.

PROCEDURE IN CASE OF INADEQUATE RESPONSE

RECOMMENDATION 6 – In case of inadequate response consider switching to another biologic agent or to other alternative therapeutic strategy.

REMISSION

RECOMMENDATION 7 – Reducing or stopping biologic therapy might be attempted if sustained remission is achieved and maintained for more than 24 months.

The monitoring of JIA patients according to a previous protocol published by our group, the PMAIJ[144], which is included in Reuma.pt[6], allows the standardization of procedures in different pediatric rheumatology clinics. In addition to the assessment of articular and extra-articular disease activity, this protocol includes the evaluation of function and quality of life at regular time points. Since the development of the preliminary definitions of improvement in 1997[145], the American College of Rheumatology pediatric (ACR Pedi) response criteria have become the primary outcome measures in therapeutic trials in pJIA. This is a useful instrument for evaluating improvement following a given treatment, but the "core set" has not been validated as an instrument for performing comparison between patients, and thus it does not provide a complete disease activity score. The ACR Pedi includes the following core set components: PhGA as measured in a 10 cm visual analogue scale (VAS), PtGA as measured in a 10 cm VAS, number of active joints, number of joints with limitation of motion, CHAQ and measurement of an acute phase reactant (CRP or ESR).

Definitions of flare, minimal clinical disease activity, remission and inactive disease have subsequently been added. Flare (tested only in pJIA patients) is defined as worsening in any 2/6 core response variables (CRV) by ≥40% without concomitant improvement of more than one of the remaining CRV by ≥30%[146].

A state of minimal clinical disease activity (MDA) can be defined as the presence of a PhGA ≤ 2.5 cm and a swollen joint count of 0 in patients with oligoarthritis; and as the presence of a PhGA ≤ 3.4 cm, a PtGA ≤2.1 cm, and a swollen joint count ≤1 in patients with polyarthritis[147].

Wallace et al defined inactive disease on the following criteria: no joints with active arthritis, no fever, rash, serositis, splenomegaly, or generalised lymphadenopathy attributable to JIA; no active uveitis as defined by the SUN Working Group; ESR or CRP level within normal limits or, if elevated, not attributable to JIA; PhGA indicating no active disease (i.e. best score attainable on the scale used) and duration of morning stiffness of < 15 minutes[148].

Six continuous months of inactive disease on medication defines clinical remission on medication, while 12 months of inactive disease off all anti-arthritis (and anti-uveitis) medications defines clinical remission off medication[149]. The finalized criteria for remission off medication ideally should predict that a patient has less than 20% probability of disease recurrence within the next 5 years.

Currently, the paramount goal of modern treatment in JIA is to achieve inactive disease and remission with or without medication. At 3 months at least an ACR Pedi 30 must be achieved in pJIA to maintain biological therapy, although a higher response level should be aimed. Treatment response in sJIA is defined as a patient free of systemic manifestations.

If patient fails the first biologic agent there is some evidence that a second biologic can be used with success[150]. After withdrawal of a biologic a washout period is required before starting a second biologic agent. Although no exact rules exist, there is some suggestion that the minimal waiting period after stopping etanercept is 3 weeks, after stopping tocilizumab is 4 weeks and after stopping abatacept, adalimumab, or infliximab is 8 weeks[151].

SAFETY CONSIDERATIONS

MYCOBATERIAL INFECTION

Screening for tuberculosis

RECOMMENDATION 8 – All patients must be screened for tuberculosis infection prior to biological therapy

The risk of developing tuberculosis (TB) is high among individuals treated with biological agents. With regard to TNF antagonists the relative risk for TB is increased from 1.6 up to more than 25 times, depending on the clinical setting and the TNF antagonist used[152-159], being higher for monoclonal antibodies. Nevertheless, the existing data support a difference in the risk of developing TB between adults and children who receive TNF antagonist therapies in industrialized countries, probably as a consequence of the lower prevalence of latent infection with *Mycobacterium tuberculosis* (MT) in children as compared to adults [79,90,111,160-167].

Screening for latent tuberculosis infection (LTBI) or active TB includes:

1) Full clinical history and physical examination comprising ethnicity, place of birth, history of recent exposure to TB, previous TB and its treatment, any additional risk factors.
2) Tuberculin Skin Test (TST) performed before ini-

tiating any immunosuppressive treatment and repeated at screening prior to biological therapy. TST is considered positive in BCG-vaccinated children if > 10 mm and in non-vaccinated children > 5 mm induration, taking epidemiological risk factors into account.

3) Interferon- release assay (IGRA)[168]
4) Chest radiograph (findings suggestive of previous or active TB)

If any of these screening procedures is positive, or in case of uncertainty, the child should be referred to a Pediatric Infectious Disease specialist or Pulmonologist. When TST and IGRA tests gave discordant results, the result of IGRA should prevail over TST in BCG--vaccinated children. On the other hand, in non-vaccinated children a positive test result (either TST or IGRA) should qualify for the individual to undergo preventive therapy. Preventive chemotherapy against TB is indicated in all patients with evidence of LTBI. In this case, biological therapy should be postponed for 4 weeks after MT therapy is started. In patients with active tuberculosis biological therapy should be preferentially initiated after a full course of TB treatment has been completed. If JIA activity is very high an earlier initiation of biological treatment can be considered but never before the end of the first 2 months of TB treatment.

Patients should be carefully monitored for TB symptoms throughout the period they receive treatment with biological agents and for six months after discontinuation. Repeated testing for latent MT infection (every year) may be considered, especially in patients treated with anti-TNF monoclonal antibodies. However, repeated TST should be avoided as results might be distorted by boosting.

IMMUNIZATIONS

RECOMMENDATION 9 – The national vaccination plan should be updated before starting biologics. The decision to administer additional vaccines is taken on an individual basis.

RECOMMENDATION 10- Life-attenuated vaccines should not be administered while under biologics.

Whenever possible at the time of the diagnosis of rheumatic disease and before initiating any immunosuppressive therapy (see Annex I for detailed information available online at www.spreumatologia.pt/content/artrite-idiopatica-juvenil):

1) Update the National Vaccination Programme (NVP) (HBV, IPV, TDaP, Hib, NeisVac-C, TD, HPV, MMR)*
2) Include the following additional vaccines: VZV (in absence of previous varicella infection or vaccination consistent history, up to 1 month before), pneumococcus and influenza virus
3) Consider the HAV vaccine

When indicated, all non-live vaccines recommended by the National Vaccination Program (HBV, IPV, DTaP, Hib, NeisVac-C, TD, HPV) can and should be administered to these patients, even under systemic treatment with corticosteroids, MTX or other synthetic DMARD or biological agents[169-171]. Until more data is available, it is recommended to withhold the administration of all live-attenuated vaccines in patients on high-dose corticosteroids, DMARDs or biological agents. However, the vaccination may be considered on a case-to-case basis weighing the risk of infections vs. the hypothetical risk of inducing infections by vaccination. Booster vaccination of live-attenuated vaccines included in the National Vaccination Program (eg. MMR), as well as the vaccine against the VZV, can also be considered on a case-to-case basis in patients on low-dose corticosteroids (eg. prednisolone dose <0.5 mg/kg/day or 20mg/day) or DMARD (MTX<15mg/m2/week)[171]. To ensure an adequate immune response, the determination of pathogen-specific antibody concentrations (serology) after any vaccination is advised in all patients on high-dose steroids (≥ 2 mg/kg/day or ≥ 20mg/day for ≥ 2 weeks) and the same can be considered in patients on anti-TNF treatment[171].

SURGERY

RECOMMENDATION 11 – Biological therapy should be discontinued prior to elective surgery and re-introduced only in the absence of infection and after satisfactory healing of surgical wound.

A temporary suspension of the biological agent before elective surgery is recommended in order to reduce the risk of postoperative infection. It is assumed that the complete elimination of the drug occurs after 4-5 half-lives and this should be taken into account for pre-surgical interruption. Likewise, the type of surgery and risk of infection based on the surgical procedure, as well as the general health of the patient and other risk factors for infection should be considered in determining the time required to restart the treat-

*HBV – hepatitis B virus; IPV – inactivated poliovirus; TDaP – tetanus--diphtheria-acellular pertussis vaccines; Hib – Haemophilus influenzae type B; NeisVac-C – meningococcal serogroup C conjugate vaccine; TD – tetanus-diphtheria vaccine; HPV – human papillomavirus; VZV – varicella zoster virus; HAV – hepatitis A virus.

TABLE IV. DISCONTINUATION OF BIOLOGICAL THERAPY BEFORE AN ELECTIVE SURGERY

Biologic	Half-live	Suspension before surgery
Infliximab/Remicade®	8-10 days	4 weeks
Etanercept/Enbrel ®	3-4 days	2 weeks
Adalimumab/Humira®	10-14 days	4 weeks
Anakinra/Kineret®	4-6 hours	24-48 hours
Abatacept/Orencia®	13 (8-25) days	8 weeks
Tocilizumab/Roactemra®	8-14 days	4 weeks

TABLE V. CONTRAINDICATIONS FOR BIOLOGICAL THERAPY

Absolute contraindications	Relative/temporary contraindications
Active infection, including tuberculosis and HBV	Sexually active female without an effective contraception
Serious and/or recurrent infections	Ongoing or planned pregnancy
Recent history (<5 years) of malignancy	Breastfeeding
Demyelinating disease or optic neuritis	HCV infection
Primary or secondary immunodeficiency (HIV infection)	Live attenuated vaccines in the last month
Cardiac insufficiency class III/IV	Acute infection
Known hypersensitivity to the active substance or excipients	Scheduled major surgery
	Specific contraindication for each biological agent
Concomitant use of two or more biologics	Active liver disease/hepatic impairment with AST or ALT>5x upper normal range

HBV – hepatitis B virus; HCV – hepatitis C virus; HIV – human immunodeficiency virus; AST – aspartate transaminase; ALT – alanine transaminase

ment after surgery[172].

Thus, although not consensual[173-175] it is recommended the suspension of the biological agent as indicated in Table IV. In case of an urgent surgery, treatment should be temporarily discontinued and the use of prophylactic antibiotics considered. Biologics may be restarted after satisfactory healing of the surgical wound and excluded signs of infection.

Infections

RECOMMENDATION 12 – Biological therapy should not be initiated in presence of active infection and must be interrupted until a serious infection is controlled.

Precaution is recommended in the use of biological agents in patients with history of chronic or recurrent infections or with situations that can predispose them to infection. The patients who develop a new infection during treatment with these agents must be carefully evaluated and monitored (accompanying systemic symptoms; complete blood count, CRP, bacteriological tests, imaging studies). Its administration must be interrupted in situations of serious infection: presence of fever and other symptoms suggestive of systemic commitment and/or rise of acute phase reagents: leukocytosis with high neutrophilia and CRP (eg: bacteraemia/sepsis, abscess/cutaneous ulcer, pneumonia, cellulitis, impetigo, bacterial endocarditis, acute pyelonephritis, acute gastroenteritis, osteomyelitis, septic arthritis, peritonitis, sinusitis); consider also biological agent interruption in case of a potentially serious or complicated viral infection (eg: EBV, CMV, parvovirus).

RECOMMENDATION 13 – Consider passive immunization if a significant contact with infected individuals occurs

Regardless of the immunization status, in situations of significant contact with an individual infected with HBV, HAV, measles and VZV, or in the case of wounds provoked by contaminated materials (tetanus) the patient under treatment with biological agents should be

considered to receive polyclonal human immunoglobulin in the case of hepatitis and measles and specific immunoglobulin for each one of the other cited situations to prevent or to modify the course of the illness.

Contraindications

Absolute and relative contraindications, as well as reasons for temporary suspension of biologics are depicted in Table V.

CONCLUSIONS

Biological therapy represents an advance in the treatment of JIA. The benefits and risks of these agents are known mainly from RCT and many questions still remain unanswered. National registries will certainly add relevant information to the existing knowledge. Precautions related to adverse events associated with the use of biologicals, namely infections, injection site reactions and potential risks associated to live vaccines should be taken into account when these drugs are prescribed.

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ANNEX I - VACCINES

Whenever possible, vaccines should be administered before starting treatment with immunosuppressive agents:

1) Varicella zoster vaccine (Varivax ® and Varilrix ®)

Patients with autoimmune diseases have an increased risk for serious varicella active disease, besides the additional risks related with the chronic use of immunosuppressant drugs and the possible induction of macrophage activation syndrome. However, there is no evidence available in the literature concerning its safety and immunogenicity in patients with rheumatic diseases.

Indications: Adolescents from 13 years-old who have never been vaccinated and did not have varicella in their past history; immunosuppressed patients above 1 year-old.

a) Assess the child's immunization status to varicella zoster virus (VZV) (if the child already had chickenpox before and/or prior vaccination history; if not or in case of doubts, perform serology for VZV);
b) Administer vaccine, ideally before initiation of biologic treatment or 3 months after its suspension, if the child (over 12 months) is not immunized

Administration: 2 doses at least 4 weeks apart (3 months interval if £12 years-old or 2 months interval if older than 13 years-old)

Consider administration of varicella zoster vaccine to seronegative family members to provide indirect protection for immunosuppressed patients

2) Pneumococcal vaccine

There is no evidence in the literature concerning Pneumococcal vaccine effectiveness in children with rheumatic diseases, but studies in children transplanted showed effectiveness in more than 70% with both conjugate and polysaccharide vaccines. It is generally well tolerated by patients with rheumatic diseases

Children should be immunized before starting biological therapy. If this is not possible, pneumococcal vaccine can be administered during treatment unless a definitive discontinuation is expected within 6 months, according to age:

<2 years-old

- ***13-valent conjugate pneumococcal vaccine – Prevenar 13®***
  - If 6 weeks – 6 months: give 3+1 doses (0,5ml) (eg: 2,4 and 6 months or 3, 5 and 7 months + booster dose at 12-15 months-old)
  - If >7 months: 2+1 (2 doses with ≥ 4 weeks' interval + booster dose at 12-15 months-old)
  - If 12 – 23 months: 2 doses, with ≥ 8 weeks' interval

≥ 2 years-old

- ***Non-live 23-valent capsular polysaccharide vaccine – Pneumo 23®***

1 single dose plus1 booster dose:

- If 2-10 years-old: administer booster 3 to 5 years after the first dose;
- If >10 years-old: administer booster 5 years after the first dose
- If ≥2 and <5 years-old: if they received previously less than 3 doses of Prevenar 13®, should receive 2 additional doses at least 8 weeks apart, followed by 1 dose of Pneumo 23® 8 weeks after the last dose of the conjugate vaccine
- ≥ 5 years-old: although there are limited data on safety and efficacy of 13-valent conjugate pneumococcal vaccine in children over 5 years-old without prior immunization, some studies in children with HIV infection and sickle cell disease suggest that Prevenar 13® is safe and immunogenic and its administration is considered acceptable by the AAP and the National Advisory Committee on Immunization (Canada). The main objective is to optimize the protection conferred for all serotypes included in both vaccines. In these cases it is recommended 1 dose of Prevenar 13® followed by Pneumo 23®, with a minimum interval of 8 weeks.

To ensure an adequate immune response, monitoring of antibody responses (serology) is recommended immediately after vaccination with Pneumo 23®, in case of being under treatment with MTX (the immune response to the majority of vaccines has been good in patients treated with MTX at doses ≥ 15 mg/m2/week, except for the Pneumo 23®, and possibly also for other polysaccharide vaccines); this is not recommended for anti-TNF treatments (Evidence level C). If the immune response is inadequate, Prevenar 13® can be considered, because conjugate vaccines appear to be more immunogenic in immunosuppressed patients.

3) Influenza vaccine (Influvac® and Istivac®)

Is safe and effective. A prospective study showed protective levels of antibodies in 95% of 34 children with JIA and the adverse events were comparable to the control group (Evidence level B)

Administer Influenza vaccine annually in Autumn, from age of 6 months

Age	Dose	From 6 months to 8 years-old
6 to 35 months-old	0,25 ml/dose	• 1st vaccination: 2 doses, 4 weeks apart • subsequent vaccinations: 1 single dose
≥ 36 months	0,5 ml/dose	**Over 8 years-old** • 1 single dose

4) Hepatitis A vaccine (Havrix® 720 or 1440)

Non-live vaccine. There is no available data concerning safety and efficacy of this vaccine in rheumatic diseases. There is no contraindication and immunization is recommended for rheumatic patients before travelling to endemic regions.

Administration: over 12 months-old (2 doses, at least 4 weeks apart)

TABLE I. VACCINATION IN JIA PATIENTS. EVIDENCE LEVEL FOR VACCINE EFFICACY AND SAFETY

Vaccine	Type	Efficacy evidence	Safety evidence
BCG (Tuberculosis)	Live (attenuated)	D	D
Haemophylus influenzae type B	Conjugate	D	D
Hepatitis A	Inactivated	D	D
Hepatitis B	DNA recombinant	D	D
Rotavirus	Live (atenuated)	0	0
Influenza A and B	Non-live combined	B	B
Combined Measles, Mumps and Rubella	Live (attenuated)	B	B
Meningococcus (group C)	Non-live, polysaccharide	B	B
Pneumococcus	Non-live, polysaccharide or conjugate	D	D
Poliomyelitis	Live (attenuated), oral	D	D
	Non-live, IM	D	D
Varicella zoster	Live (attenuated)	B	B
Pertussis	Non-live	D	D
Tetanus	Toxoid	D	D
Diphtheria	Toxoid	D	D
Yellow fever	Live (attenuated)	0	0
Human Papiloma Virus	Non-live	0	0

Legend: A) Experimental and observational studies with better consistency; B) Observational and experimental studies with less consistency; C) Case reports (uncontrolled studies); D) Opinion without critical assessment, based on consensus, physiological studies or animal models; 0) Absence of studies

TABLE II. RECOMMENDED VACCINES FOR IMMUNOSUPPRESSED PATIENTS AND FAMILY MEMBERS

Vaccines	Patients		Contacts	
	Before treatment	While on treatment	Ambulatory	Hospital
BCG (Tuberculosis)	No	No	Yes	Yes
Diphtheria/ Tetanus/ Pertussis	Yes	Yes	Yes	Yes
Poliomyelitis (oral)	No	No	No	No
Poliomyelitis (IM)	Yes	Yes	Yes	Yes
Hepatitis B	Yes	Yes	Yes	Yes
Combined Measles, Mumps and Rubella	Yes	No	Yes	Yes
Varicella zoster	Yes	No	Yes	Yes
Haemophylus influenzae type B	Yes, if <19 years	Yes, if <19 years	Yes	Yes
Influenza	Yes	Yes	Yes	Yes
Hepatitis A	Yes	Yes	No	No
Meningococcus (group C)	Yes	Yes	No	No
Pneumococcus (conjugate, polysaccharide)	Yes	Yes	No	No

TABLE III. PASSIVE IMMUNIZATION

Disease/Indications	Composition	Administration
MEASLES Exposure to infected patients	Human Ig (polivalent)	Until 6 days after exposure
VARICELLA		
Contact with a patient with varicella or herpes zoster in the contagious stage	Human Ig (specific, hyperimmune (VZIG))	Until 96 hours after exposure
HEPATITIS B Accidental exposure to percutaneous or mucosal blood, sexual contact with individuals with acute hepatitis B; sexually abused, even if vaccinated	Human Ig (specific, hiperimmune B (IGHAHB)) + Vaccination	The earliest after exposure (maximum up to 14 days)
HEPATITIS A Contact	Human Ig (polivalent)	Before virus exposure and until 14 days after
TETANUS Susceptible individuals who suffered serious injuries (extensive, multiple or deep) with contaminated material	Heterologous hyperimmune serum Specific Human Ig with high titres of antibodies against Tetanus + Vaccination	As soon as possible (maximum up to 2 weeks after exposure)

ANNEX II

RECOMMENDATIONS FOR THE USE OF BIOLOGICAL THERAPIES IN CHILDREN AND ADOLESCENTS WITH JIA

1) Biological therapy should only be initiated and managed by physicians with experience in the diagnosis and treatment of JIA. A definitive diagnosis of JIA is required.
2) Active arthritis is eligible for treatment with biologics when 5 or more active joints are present on two separate occasions at least 3 months apart, despite standard treatment. The decision to initiate a biologic earlier or in patients with fewer active joints, enthesitis or systemic manifestations should be made on an individual basis and taking into account prognostic features, functional status and drug side effects.
3) Biological therapy can be started in active polyarthritis despite the use of NSAIDs, intra-articular corticosteroid injections (if indicated) and synthetic DMARDs, including MTX in a standard effective dose for at least 3 months, unless contraindicated or not tolerated. Sustained severe systemic features regardless of concurrent therapy (systemic corticosteroids with or without DMARDs) also constitute an indication for treatment with biologics. Patients with active uveitis despite corticosteroids and immunossupressants or requiring long term corticosteroids or presenting severe side effects related to these medications are also eligible for biological therapy.
4) The choice of the biologic agent must take into consideration the JIA subtype, children's age, individual risk evaluation and drug label.
5) Biologic treatment should only be maintained in patients who achieve at least an ACR Pedi 30 after 3 months on treatment, in the case of pJIA, or who are free of systemic manifestations in the case of sJIA.
6) In case of inadequate response consider switching to another biologic agent or to other alternative therapeutic strategy.
7) Reducing or stopping biological therapy might be attempted if sustained remission is achieved and maintained for more than 24 months.
8) All patients must be screened for tuberculosis infection prior to biological therapy
9) The national vaccination plan should be updated before starting biologics. The decision to administer additional vaccines is taken on an individual basis.
10) Life-attenuated vaccines should not be administered while under biologics.
11) Biological therapy should be discontinued prior to elective surgery and re-introduced only in the absence of infection and after satisfactory healing of surgical wound.
12) Biological therapy should not be initiated in presence of active infection and must be interrupted until a serious infection is controlled.
13) Consider passive immunization if a significant contact with infected individuals occurs.