# The development and assessment of biological treatments for children

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**Abstract (250 words max)**

The development of biological agents with specific immunological targets has revolutionised the treatment of a wide variety of paediatric diseases where traditional immunosuppressive agents have been partially ineffective or intolerable. The increasing requirement for pharmaceutical companies to undertake paediatric studies has provided impetus for studies of biologics in children. The assessment of biologic agents in children to date has largely relied upon randomised control trials using a withdrawal design, rather than a parallel study design. This approach has been largely used due to ethical concerns including use of placebo treatments in children with active chronic disease, and justified on the basis that treatments have usually already undergone robust assessment in related adult conditions. However, this study design limits the reliability of the data and can confuse the interpretation of safety results. Careful on-going monitoring of safety and efficacy in real-world practice through national and international biologics registries and robust reporting systems is crucial. The most commonly used biologic agents in children target TNF-α, IL-1, IL-6 and CTLA-4. These are most frequently used in paediatric rheumatic diseases. This review will discuss the development and assessment of biologics within paediatric rheumatology with reference to the lessons learned from use in other sub-specialties.

**Introduction:**
Biological treatments are defined as 'a pharmacological group of specific proteins with high molecular weight, specifically targeting pro-inflammatory cytokines or cell surface antigens' [1]. Their mechanism of action contrasts to traditional immunosuppressives and disease modifying anti-rheumatic drugs (DMARDs) like methotrexate, which inhibit the overall inflammatory process. The identification of the role of the pro-inflammatory cytokines tumor necrosis factor (TNF) alpha, interleukin-1β (IL-1β) and interleukin-6 (IL-6) in experimental arthropathy models and human disease has been critical to the development of specific biological treatments [2, 3]. Evolving knowledge of the nature of such cytokines through preclinical studies of the immunobiology of synovial fluid harvested from patients with active disease and the development of recombinant genetic techniques has facilitated production of humanised monoclonal antibodies and soluble cytokine receptors. These are able to almost completely eliminate or block target pro-inflammatory cytokines. Biologics may also block particular cell-to-cell interactions and consequently inhibit cellular activation or deplete specific cell types from the circulation [4, 5].

Important changes in patients, families and healthcare professionals expectations have contributed towards a significant and continued motivation for developing and improving clinical outcomes using biologics in children.

Key drivers for biologic development include: recognition of the need for true disease suppression for the prevention of joint damage in rheumatoid arthritis (RA), and identification of the critical role of TNF-alpha in juvenile idiopathic arthritis (JIA) [6, 7]; growing expectations of higher standards of sustained clinical improvement; the goal of striving for complete disease remission, both on medication and more importantly, after cessation of treatment with an ultimate goal of disease cure.

**Assessment tools used in clinical trials in JIA:**

Table 1 summarises how clinical response is assessed and defined in JIA clinical trials. The magnitude of treatment response is generally defined in terms of attainment of the American College of Rheumatology Paediatric 30, 50, 70, 90  (PedACR30, 50, 70, 90) response, which assesses the percentage improvement in 3 of the 6 JIA core set measures. 'Flare' is defined in terms of worsening of these core set measures [8]. The proportion of patients achieving 'inactive disease' or 'clinical remission' is also reported [8, 9].

**Design of clinical trials in paediatric rheumatology:**

To date, many biologics trials within paediatric rheumatology have used the 'withdrawal design' (see Figure 1). All trial participants are initially exposed to the drug. Those who reach a predefined response are randomised to treatment with active drug or placebo, with the trial primary outcome being a predefined disease flare [10] (see Table 1). Efficacy is defined by the difference in the number of patients flaring, and the time taken to flare. The rationale for this trial design is that all patients receive the active drug, that a smaller sample size can be used and that the time on placebo is minimised, making it more acceptable to parents and many clinicians. Such biologic treatments have generally already been shown to be efficacious in robust parallel design randomised control trials (RCTs) in related adult conditions (e.g. RA), providing *a-priori* proof of efficacy in children. However in some diseases there is arguably inadequate overlap between the pathogenesis of adult-onset diseases for these data to be extrapolated directly to paediatric diseases.

The safety profile of the study drug can be difficult to assess when a withdrawal study design is used due to potential for a 'carry over' effect during the placebo phase. The relatively short time on placebo treatment also limits the power to compare the active drugs safety profile with placebo [11]. Therefore although such RCTs have shown important efficacy of biologics in paediatric disease, there is critical need for long-term, open label studies and registries to determine the long-term safety profile and efficacy of biologic drugs. The withdrawal study design may preselect responders who continue to retain their response throughout all phases of the study, due to the placebo effect [11, 12]. Inclusion of physicians' and parents' global assessments of

disease activity as part of the core set measures detailed in Table 1, is also susceptible to the inadvertent placebo response, whereby the child and parent may report improvement as they are keen to believe that their has been a positive response [13, 14].

## Overview of biologic treatments and their uses

## Anti-TNF-alpha treatments

## Etanercept

**Identification and efficacy:**
Etanercept is a fully human, soluble fusion protein that binds to TNF-α and -β with high affinity, preventing binding to cell surface TNF receptors [15]. Etanercept was the first biologic treatment to be used in JIA following a multi-centre, randomised, placebo-controlled trial in 69 methotrexate-resistant JIA patients with a polyarticular disease course [16]. At the end of the initial open-label study, 74% responded to etanercept treatment, achieving a PedACR30 response. In the double-blind phase, 81% of patients on placebo flared, as compared with 28% of etanercept treated patients (p=0.003). The median time to disease flare was 28 days compared with 116 days with etanercept respectively (p<0.001) [16].  Those flaring on placebo were re-started on etanercept. The response to etanercept improved over 2 years during the open-label extension phase, with 63% of patients achieving clinical remission [17].

Etanercept efficacy noticeably varied according to JIA subtype. Children with systemic-onset JIA (SoJIA) generally responded less favorably than other JIA sub-types [17-19]. The on-going multicentre 'CLinical Study In Paediatric Patients of Etanercept for Treatment of enthesitis related arthritis (ERA), psoriatic arthritis (PsA), and extended oligoarthritis' study (CLIPPER) demonstrated etanercept to be effective and well tolerated in patients with these specific subtypes of JIA, with an overall PedACR 50, 70, 90 response and inactive disease being achieved in 81%, 62%, 30% and 12% respectively [20].

Longer-term outcomes on etanercept are generally favorable. The German biologics registry has shown that males with a shorter disease duration, a lower active joint count, lower childhood health assessment questionnaire (CHAQ) disability score at baseline, are more likely to achieve inactive disease and remission on etanercept over a mean of 4.6 years [21]. Similarly, the Dutch biologics register has shown a lower CHAQ score at baseline, less DMARD failures prior to starting etanercept and a younger age at onset to also be predictive of achieving an excellent response to etanercept, 15

months after initiation of treatment [22]. Co-administration of methotrexate raises the chance of remission, especially in patients with rheumatoid factor negative polyarthritis (odds ratio 2.0, p = 0.03) [21].

Etanercept is currently licensed by the European Medicines Agency (EMA) for the treatment of polyarticular JIA in children >4 years old who have had an inadequate response to methotrexate or who are intolerant [23]. In the UK, the National Institute for Clinical Excellence (NICE) guidelines from 2002 recommend use of etanercept in children with an active polyarticular-course of JIA, widening it's use to patients with extended oligoarthritis, psoriatic arthritis, enthesitis related and systemic onset arthritis. These guidelines are due for review in 2015 [24].

**Long-term efficacy and safety:**
Long-term open labeled follow up of the original etanercept trial over 8 years, showed a good safety profile and a durable response with sustained reductions in disease activity [17, 25, 26]. To date, some 2896 cumulative patient years of safety data have been published from 1273 patients who have individually received a maximum of 6.8 years of etanercept (see Table 2) [18, 19, 26-29]. Both the Dutch and German national biologics registries have reported a decrease in the rate of adverse events (AEs) over time [19, 27], from 0.20 AEs/patient during the first year of treatment, reducing to 0.12 AEs/patient/year thereafter [27]. The Italian JIA cohort reported a higher rate of AEs over a mean of 24.1 months of follow-up (0.51 AEs/patient/year) [29]. The main AEs associated with etanercept use are shown in Table 3.

Cases of new onset / worsening uveitis (see table 3) [18, 28-30] have led to avoidance of etanercept if uveitis is present (see adalimumab section below). Notably, no significant adverse events (SAEs) were reported from a French cohort where etanercept was administered weekly (dose 0.8mg/kg/week) [18], and further studies have demonstrated comparable safety / efficacy of weekly and twice weekly etanercept administration [30-32]. Cases of pulmonary and extra-pulmonary mycobacterium tuberculosis infection have been reported in children with JIA on anti-TNF treatment, and vigilance for the condition must continue to be maintained during treatment, despite negative pre-treatment screening [33, 34].

Conflicting results exist regarding the relative safety of treating with etanacept and methotrexate in combination. Data from the US, Canada and Germany have mainly reported a similar rate of AEs in children with JIA receiving etanercept alone or in combination [27, 28], although a trend was seen towards a higher number of SAEs in those on combination treatment in the German registry (p=0.06) [27]. Preliminary data from the UK biologics registry

have shown nearly twice as many AEs in patients on combination etanercept / methotrexate treatment [35].

**Further uses of Etanercept:**
Etanercept use has been reported in children with: Behcet's disease [36], Familial Mediterranean fever (FMF) [37], Tumour necrosis factor receptor-associated periodic syndrome (TRAPS) [38], Kawasaki disease [39], cutaneous granulomas, common variable immunodeficiency and idiopathic pneumonia syndrome following allogeneic hematopoietic stem cell transplantation [40]. In Crohn's disease (CD), it is avoided due to reports of triggering of inflammatory bowel disease (IBD) [41]. Clinical trial data support its use in severe paediatric plaque psoriasis [42]; case reports indicate that etanercept may help in other types of psoriasis [43].

**Adalimumab**

**Identification and efficacy:**
Adalimumab is a humanised monoclonal anti-TNF antibody, administered to JIA patients by subcutaneous injection fortnightly. In RA, concomitant use of methotrexate prolongs its half-life. The clinical trial of adalimumab in JIA compared efficacy of monotherapy or combination therapy using a withdrawal trial design. In the open label lead in phase (first 16 weeks), 171 JIA patients aged between 4-17 years with a polyarticular disease course were treated with 24 mg/m$^2$ of adalimumab on alternate weeks; 84/171 continued with previous methotrexate treatment. PedACR 30, 50, 70 and 90% response was achieved in 74%, 64%, 46% and 26% of children receiving adalimumab monotherapy compared to 94%, 91%, 71% and 28% receiving combination therapy respectively. During the double blind phase of the study, flares were significantly more frequent in those treated with methotrexate / placebo or placebo alone [44]. A preliminary open label study including children <4 years of age or <15kg has shown a similar improvement in PedACR criteria, and a comparable safety profile as compared to older children [45]. In Europe, adalimumab is licensed for use in active polyarticular JIA (in combination with methotrexate or alone if methotrexate is inappropriate) and in children with enthesitis related arthritis who have failed to respond to one or more DMARD [23]. NICE guidelines relating to adalimumab use in children are not yet available [24].

**Long-term efficacy and safety:**
Fewer data are available regarding the long-term safety and efficacy of adalimumab (see Tables 2 and 3). During the 2-year RCT open-label extension phase, dosing of adalimumab changed with patients weighing <30kg receiving 20mg and patients weighing ≥30kg receiving 40mg. Adalimumab showed on-going efficacy with sustained PedACR responses

with no change in tolerability. 40% of patients were in remission by the end of the open label extension [44].

Cumulative safety data on 398 patient years of adalimumab exposure have been published from 171 patients with 103 receiving adalimumab for >3 years [44]. The safety profile of adalimumab in children appears similar to adults. In 2009, the Food and Drugs Administration (FDA) collated adalimumab safety data from the US Healthcare AE Reporting System, including 108 SAEs occurring following in utero exposure or in paediatric patients with JIA, CD, ulcerative colitis (UC), uveitis, psoriasis, PsA and vasculitis. Four deaths occurred, 3 involving *in utero* exposure; the fourth was of a 16 year old who developed macrophage activation syndrome (MAS), pneumonia and respiratory failure. There were 24 reports of serious infections and two cases of malignancy. Both patients had an approximately 10-year history of using multiple immunosuppressants, making it difficult to establish direct causality [46].

**Further uses of Adalimumab:**
A recent qualitative study indicated uveitis is the most important factor impacting on the clinician's choice between adalimumab and etanercept, in light of evidence that etanercept can contribute to worsening or new development of uveitis (see etanercept section above) [19, 30, 47]. Two retrospective observational open label studies have explored adalimumab use in JIA-associated uveitis.  One demonstrated adalimumab to be effective in 16/18 patients [48]. The other showed 7/20 (35%) children to have a reduction in uveitis activity, 1/20 (5%) had worsening activity, and 12/20 (60%) had no change [49]. Adalimumab and infliximab have been compared in an open label, prospective, multi-centre study including 16 children with JIA-associated uveitis, 3 with idiopathic uveitis and one with Behcet's disease. No significant difference was noted between the treatments, although a higher probability of uveitis remission was seen with adalimumab [50]. A UK-based multicentre RCT of the clinical effectiveness, safety and cost effectiveness of adalimumab in combination with methotrexate versus methotrexate alone for the treatment of JIA associated uveitis (SYCAMORE) is underway [51].

In adult CD, adalimumab is effective in the induction and maintenance of remission, reducing hospital admissions and related surgery [52-55]. Paediatric studies are limited to open-label prospective studies, retrospective analyses and case series [56-60]. The IMAgINE 1 phase III RCT investigated safety and dosing of adalimumab treatment in 191 children with moderate-severe CD [61]. Following 4 weeks of induction treatment, patients were randomised to receive low or high dose adalimumab. 36% were in remission by 22 weeks, with no difference between dosages (p=0.075). The safety profile was comparable to adult CD studies [61].

Adalimumab is also used in paediatric psoriasis after failure of other systemic and biologic agents [62-64], and an on-going RCT is testing its efficacy and safety paediatric chronic plaque psoriasis [65]. Adalimumab is both effective and well tolerated in juvenile-onset AS [66]. Patients with primary systemic vasculitis [67] and Behcet's have also received adalimumab [68, 69].

**Infliximab**

**Identification and efficacy:**
Infliximab is a chimeric murine-human monoclonal antibody with high affinity for TNF-α, administered by intravenous (IV) infusion at 0, 2 and 4 weeks, with subsequent doses being administered at 4-8 week intervals. A double blind RCT including 122 children with polyarticular JIA failed to demonstrate superiority of infliximab over placebo. In this study 3mg/kg of infliximab or placebo was given for 14 weeks in combination with methotrexate. A higher proportion of patients receiving infliximab reached a PedACR30 response, however the difference between the treatment groups was not statistically significant (p=0.12). Patients on placebo then went on to receive high dose infliximab (6mg/kg). By week 52, a PedACR50 and 70 response was achieved in 70% and 52% of patients overall, with no difference depending on the infliximab dosage [70]. Despite these results, infliximab is frequently used in refractory polyarticular JIA (unlicensed indication), with good clinical results reported.

**Long term efficacy and safety:**
In the RCT discussed above, the 3mg/kg/dose infliximab group had double the number of SAEs, a higher rate of infusion reactions and anaphylactic reactions than the 6mg/kg/dose group, correlating with an increased incidence of anti-infliximab antibodies. New anti-nuclear (ANA) and double stranded DNA antibodies (dsDNA) were also seen more frequently in those on low dose infliximab. The optimal dosage warrants further investigation, as some have reported doses as high as 10-20mg/kg/dose as being rapidly effective and well tolerated [71].

During the open label extension phase of the study discussed above (weeks 52-204), 42/78 patients discontinued infliximab due to consent withdrawal, lack of efficacy or patient / physician / sponsor requirements. By week 204 the proportion of patients with PedACR30, 50, 70, 90 responses or inactive disease was 44%, 40%, 33%, 24% and 13% respectively. Infusion reactions occurred in 32% of patients with a higher incidence in patients positive for infliximab antibodies [72]. Other studies have also looked at infliximab treatment in paediatric rheumatology practice (see Tables 2 and 3).

**Further uses of Infliximab:**

Infliximab is effective as induction [73-75] and maintenance treatment in children with CD [61, 75, 76], when used regularly [77]. FDA approval for use in paediatric CD was obtained following the randomised, multicentre, open-label REACH study in children with moderate – severe CD [75]. 58% of the 112 patient treated achieved clinical remission following a 5mg/kg induction dose. Longitudinal follow-up of patients on maintenance infliximab showed 56% and 33% to still be in remission at 54 weeks and 3 years respectively [75, 76]. This secondary loss of response associated with anti-infliximab antibodies may be reduced by giving infliximab regularly, and with a concomitant immunosuppressive [78]. Infliximab treatment in CD is also associated with reduced rates of hospitalisation and surgery for complications of active disease [79, 80] and improvements in growth [81]. In 2010, NICE recommended that infliximab is used for the treatment of severe active CD not responding to conventional treatment, or where conventional treatment cannot be used due to intolerance or contraindications [24].

**Certolizumab pegol and Golimumab**

Certolizumab is a PEGylated Fab fragment of a humanised anti-TNF- α antibody, and golimumab is a humanised monoclonal anti -TNF- α antibody. These newer TNF antagonists have been shown to be effective in the treatment of RA, PsA, AS, UC and CD in adults [82-87]. Certolizumab does not possess an Fc-region and therefore should not lead to cell mediated cytotoxicity, decreasing the infection risk, however, this does not seem to have translated into a clear reduction in infection risk in clinical practice. It may also be of use in pregnancy, as the lack of an Fc-region will prevent transplacental transfer [87]. Golimumab is similar to adalimumb in respect to its molecular weight and it's affinity for soluble and transmembrane TNF, however golimumab has a longer half-life and can be administered monthly [4]. Currently there are ongoing multicentre trials looking at the efficacy and safety on golimumab and certolizumab in JIA [88, 89]. Certolizumab pegol and golimumab are not currently licensed for use in children [23].

**Agents targeting interleukin-1**

**Anakinra**

**Identification and efficacy:**

Anakinra is an interleukin-1 (IL-1) receptor antagonist administered by daily subcutaneous injection at a dose of 1-2mg/kg/day. It has not demonstrated a significant benefit over placebo in polyarticular JIA [90], but in a multicentre, RCT of anakinra in SoJIA, 8/12 patients on anakinra and 1/12 on placebo

achieved a PedACR30 response. 9/10 of the placebo treated patients who were switched to anakinra, subsequently responded. The tolerability of anakinra was comparable to placebo [91].

Use of anakinra as part of the initial therapeutic strategy in SoJIA has been assessed in a multicentre case series including 46 patients. Anakinra was used as monotherapy in 28%, with 67% and 33% also receiving corticosteroids and additional DMARDs respectively. Fever and rash resolved within 1 month in >95%, and CRP / ferritin also normalised in >80% over this time period. Persistence of arthritis was seen in 39%, 27% and 11% after 1, 3 and >6 months of treatment, respectively. Inactive disease was achieved in 8/10 patients receiving anakinra monotherapy [92]. In another study including patients who had previously received long-term corticosteroids ± DMARDs, the clinical response to anakinra was more heterogeneous. The majority experienced an initial amelioration of systemic features and acute phase reactants, however, subsequently one group displayed on-going disease remission and the other showed a tendency towards recurrence [93].

**Long term efficacy and safety:**
Studies looking at the efficacy and safety of anakinra beyond 1 year are warranted. The main AEs reported in associated with IL-1 blocker use are shown in Table 4. Injection site reactions were the most common AE, decreasing over time [90, 94, 95].

**Further uses of Anakinra:**
Anakinra is licensed for use in cryopyrin-associated periodic syndrome (CAPS) with dramatic amelioration of clinical characteristics. It has also been shown to be of benefit in deficiency of the interleukin-1-receptor antagonist (DIRA), nod-like receptor protein-12 (NLRP-12) associated periodic fever syndrome, FMF and TRAPS. A variable treatment response has been found in Blau's syndrome, pyogenic sterile arthritis, pyoderma gangrenosum and acne syndrome (PAPA) [96].

**Rilonacept**

Rilonacept is a fusion protein, which acts as a long acting soluble IL-1 receptor with a longer half-life than anakinra. In an RCT, 24 SoJIA patients were treated with weekly rilonacept (2.2-4.4mg/kg, maximum dose 360mg) or placebo for 4 weeks. 23/24 patients subsequently entered an open-label trial lasting up to 24 months. There was no significant difference in efficacy between rilonacept and placebo during the initial double blind phase. Within 3 months, fever and rash resolved in all patients and a PedACR30, 50, 70 response of 78.3%, 60.9% and 34.8% respectively was seen and subsequently maintained. All patients developed an AE (see Table 4), with

13% developing an SAE and discontinuing treatment [97]. Rilonacept has also been used in CAPS and FMF [96]. Rilonacept is not currently licensed for use in children [23].

**Canakinumab**

Canakinumab is a fully human monoclonal anti-IL-1β antibody with a long half-life, given monthly by subcutaneous injection. In a double blind study, a PedACR30 response of 84% was seen at 15 days post treatment in SoJIA patients who received a single dose of canakinumab and 10% who received placebo (p<0.001) [98]. Patients who achieved greater than a PedACR30 response were enrolled into a phase III trial with a two-part withdrawal design. All patients initially received canakinumab and corticosteroid tapering was attempted on open label treatment. 45% were able to reduce their corticosteroid dosage by at least 50%, and 33% discontinued steroids all together. In the placebo controlled phase, 75% on placebo flared, as compared to 26% in the canakinumab group (relative risk reduction of 64%, hazard ratio 0.36; 95% CI: 0.17 to 0.75) [99]. Canakinumab was initially licensed for treatment of CAPS, but it's license has been extended by the FDA and EMA to include the treatment of SoJIA patients > ≥2 years old [23, 100]. NICE guidance is not yet available.

**Safety:**
In the placebo-controlled phase of the study detailed above, one patient developed MAS and a serious infection in each treatment group. Seven patients developed serious infections during the open label treatment phase (two associated with MAS). There were two deaths associated with cannakinumab treatment but no reports of cancer, tuberculosis or opportunistic infection (see Table 4) [99, 101].

**Further uses of Canakinumab:**
Canakinumab has been shown to be effective in CAPS. There is an on-going clinical trial assessing use in TRAPS and anecdotal reports of use in FMF [96].

**<u>Tocilizumab</u>**

**Identification and efficacy:**
Tocilizumab is a humanised monoclonal antibody that targets the IL-6 receptor, preventing IL-6 from exerting pro-inflammatory effects. Serum and synovial IL-6 levels are elevated in SoJIA and correlate with disease activity, decreasing with effective treatment [102, 103]. The first phase III RCT of tocilizumab in SoJIA used a withdrawal study design. 56 Japanese SoJIA patients were initially treated with 8mg/kg of tocilizumab, 2 weekly over 6

weeks, with responders subsequently being randomised to tocilizumab or placebo for 12 weeks. A PedACR30, 50, 70 response was achieved in 91%, 86%, 68% respectively. Flares were more common in the placebo group (83% vs. 20%, p<0.0001). By 48 weeks, in the open-label extension, PedACR30, 50, 70 responses were achieved in 98%, 94%, 90% respectively [104].

In a multinational, phase III, 5-year, double blind RCT (TENDER trial), significantly more patients on tocilizumab than controls achieved a PedACR30, 50, 70 by week 12 of treatment (85%, 71%, 37% versus 24%, 8%, 5% respectively; p<0.0001). A progressive improvement in treatment response was observed during the 52 week open label extension, with 59% reaching an ACR90 response and 28% attaining clinically inactive disease [105]. Tocilizumabs was approved by the FDA and NICE in 2011, for the treatment of children >2 years old with SoJIA who have not responded adequately to non-steroidal anti-inflammatory drugs, corticosteroids and methotrexate [24, 100].

**Safety:**
The range of AEs associated with tocilizumab are summarized in Table 5. In the Japanese tocilizumab phase III trial mentioned above 8.9% developed anti-tocilizumab antibodies and mild-moderate infusion reactions, leading to discontinuation of tocilizumab in most patients [106]. Within the TENDER trial, infusion reactions occurred in 16% on tocilizumab and 5% on placebo [105].

**Further uses of Tocilizumab:**
Preliminary results from the global, phase III, placebo-controlled CHERISH trial of tocilizumab in polyarticular JIA (American College of Rheumatology conference, 2012, abstract number 1957) have revealed a significantly higher PedACR30, 50, 70 response with tocilizumab than placebo, with 65% attaining an ACR70 response by week 40. 48% on placebo and 26% on tocilizumab flared within this time period (p=0.0024) [107]. An open label study is on-going.

**Abatacept**

**Identification and efficacy:**
Cytotoxic lymphocyte-associated antigen-4 (CTLA-4) is a potent inhibitor of the co-stimulatory pathway that is necessary to activate T cells. Abatacept is a fully human soluble fusion protein that is composed of a modified Fc portion of IgG1, linked to CTLA-4. It binds to CD80/CD86 on antigen presenting cells, inhibiting it's interaction with CD28 on T-cells, thereby inhibiting T-cell co-stimulation and activation. In a phase III, multinational, double blind, RCT in polyarticular JIA patients using a withdrawal design, 70% of patients

responded to abatacept during the open label lead in phase. Subsequently, flares occurred in 53% of patients receiving placebo, and 20% of abatacept patients (p=0.0003), with the median time to flare being shorter in those on placebo. PedACR30, 50, 70 and 90 responses in the abatacept and placebo group were 82%, 77%, 53%, 40% and 69%, 52%, 39% and 16%, respectively [108].

The majority (153/190) of patients subsequently entered an open label extension study, for a median of 35 months (range 5.5-47.8). By day 589, a PedACR30, 50, 70, 90 and 100% response was achieved in 90%, 88%, 75% 57% and 39% of patients who had been treated with abatacept during both the double blind and extension phases of the study. The response to abatacept was maintained or progressively improved over the studies duration, with 73% of children who had not reached a PedACR30 response at the end of the lead-in phase subsequently achieving this during the open label extension [109]. The FDA approved abatacept for use in children >6 years old with moderate to severe JIA of a polyarticular course in 2009, with the EMA also approving it in 2010.

**Safety:**
In the RCT discussed above, the number of AEs was similar across all treatment groups. The AEs reported in association with abatacept are shown in Table 5. No patients randomised to receive abatacept experienced an SAE, whereas two of the patients receiving the placebo developed SAEs (although placebo patient's received four months of abatacept prior to randomisation). Five patients experienced infusion reactions. Anti-abatacept and anti-CTLA-4 antibodies were present in 11% of the 149 patients with samples available, but did not correlate with occurrence of infusion reactions or loss of treatment efficacy [109].

**Further uses of Abatacept:**
Abatacept has been assessed in a small retrospective case series of patients with severe anti-TNF- α refractory JIA associated uveitis. All patients responded within 6 months of treatment with the frequency of uveitis flares decreasing from a mean of 3.7 episodes to 0.7 episodes / 6 month period [110]. Clinical studies in adults are investigating use of abatacept in RA, UC, CD, diabetes mellitus, SLE, graft versus host disease, uveitis, Takayasu's arteritis, Wegener's granulomatosis, polymyositis, dermatomyositis and sarcoidosis.

**Rituximab**

Rituximab is a chimeric anti-CD20 monoclonal antibody that binds and causes apoptosis of CD20 positive B cells, leading to their prolonged depletion. It is

licensed for use in RA and has shown promising results in children for a variety of off label indications including JSLE, JIA, primary systemic vasculitis, relapsed non-Hodgkins lymphoma and leukemia, chronic immune thrombocytopenic purpura, autoimmune hemolytic anemia, nephrotic syndrome, acute and chronic solid organ transplant rejection and post transplantation lymphoproliferative disease [111]. There are however no RCTs of rituximab use in children.

In paediatric rheumatology practice, rituximab is most frequently used in JSLE despite robust evidence for its efficacy being limited. A retrospective case series of rituximab treatment in 19 JSLE patients with severe general symptoms or acute life / organ threatening manifestations, un-responsive to standard treatment, demonstrated a rapid reduction in disease activity after two infusions in the majority of patients, with improvements in renal, immunological and haematological parameters and no serious side effects [112]. In a French cohort, 11 children with severe JSLE received 2-12 infusions of rituximab in addition to standard immunosuppressive agents in 6/11 patients. Remission was achieved in 8/11 patients and maintained over a mean of 13.2 months, but SAEs occurred in 45% [113].

The largest rituximab study in JIA included 55 children with refractory disease (polyarticular and SoJIA patients) who received 4 weekly infusions as necessary. Within 6-8 weeks there was a decrease in systemic, articular and laboratory disease manifestations, and by 24 weeks, 98%, 50% and 40% achieved an ACR 30, 50, 70 response [114]. Due to the uncontrolled nature of the study and the range of concomitant medications, the results should be interpreted with caution. In contrast to adults treated with rituximab, children may develop long standing B cell depletion and hypogammaglobuminaemia requiring IVIG [115].

**Belimumab**

Belimumab is a fully human monoclonal antibody which blocks soluable BLyS, a B-cell survival factor and prevents it from binding to B-cell receptors. The FDA and EMA approved belimumab use in adults with serologically positive SLE in 2011 following the outcome of the BLISS trials, which showed that belimumab was associated with a reduction in disease activity, prevented worsening of internal organ involvement and reduced the rate of severe flares over 52 weeks in 1684 patients [116, 117]. Belimumab is currently being evaluated alongside standard JSLE therapy.

**Specific considerations**

**Biologics and risk of malignancy:**

In 2009, the FDA reported an increased risk of lymphoma and other cancers associated with anti-TNF treatment in children and adolescents in light of post-marketing surveillance data. Interpretation of these data is complex due to the potential confounding effects of concomitant immunosuppressives (used in 88% reported upon), and uncertainty regarding the incidence of malignancy in uncontrolled inflammatory diseases [118]. A Swedish study looking at cancer risk in biologic naïve JIA patients using linkage through national databases and matched general population comparators found an elevated risk of malignancy in biologic naïve JIA patients in whom the diagnosis was made during the past 20 years [119]. In the FDA report, ten cases of hepatosplenic T cell lymphoma (HSTCL) were reported in IBD patients, however, the concomitant medications used (6-mercaptopurine and azathioprine) are also independently associated with HSTCL [120]. Similarly, there are case reports of non-Hodgkin's lymphoma in JIA patients treated with methotrexate [121].

**Biologics registries:**
In order to understand the long-term safety profile of biological therapies it is important to collect data through Registries and to continue data collection into adult years. Clearly there are significant challenges involved especially as some SAEs (such as malignancy are likely to be rare. A summary of the current biologics Registries for children is given in Table 6 and it is hoped that pooling of data will help address long-term safety issues. There are challenges with the governance and structure of data pooling, but to this end, the international pharmacovigilance databank (Pharmachild) has recently started [122]. Whilst uncertainties exist, it is important that experienced specialist teams use biological agents, that patients and parents are aware of the rationale, and that discussions regarding risk versus benefit are carefully discussed and documented.

**Conclusions**

The development of biologics for use in children has significantly changed the treatment pathways of a wide range of autoimmune diseases, enabling clinicians to aim for complete disease remission in complex conditions that were previously associated with long-term damage and disability. Reliance upon the withdrawal study design during the assessment of biologics in children has complicated the interpretation of efficacy and safety data, leading to a need for national and international collaboration for delivery of biologics registries and long-term, open label studies. Development of new biologics and personalised treatment strategies based on biology, genetics and pharmacogenetics will be crucial for further improvements in treatment options and patient outcomes.

**Table 1: Description of the end-points used in paediatric rheumatology clinical trials [8, 9].**

PedACR = paediatric American College of Rheumatology criteria, ESR = erythrocyte sedimentation rate, CRP = c-reactive protein.

**Figure 1: Diagram outlining the withdrawal study design frequently used in biologic clinical trials in children.**

**Table 2: Adverse events related to different anti-TNF agents used in JIA – data mainly from long-term studies and biologics registries**


ADA = adalimumab, serious adverse events = SAEs. ˜Safety data available from the original clinical trial to date. ∞This study compared patients on methotrexate, etanercept, and etanercept plus methotrexate, and found the exposure-adjusted rates of SAEs per 100 patient-years to be 4.6, 7.1, and 6.0 respectively, but the study did not provide the absolute number of SAEs. ¥1 case of malignancy (thyroid cancer). ¶ 3 cases of malignancy (thyroid carcinoma, yolk sac carcinoma, non-hodgkins lymphoma). * 3 non-responder to etanercept subsequently died of tuberculosis, suspected macrophage activation syndrome and sepsis whilst on other immunosuppressives, at least 8 months post etanercept discontinuation. ·The first died at week 2 of the trial, 10 days after a placebo infusion from septic shock and an associated deterioration in cardiac function. The second patient had SoJIA, experienced a severe flare of their disease and died of a cardiac arrest 3 months after discontinuation of infliximab (in the 3mg/kg infliximab group), whilst in the open label extension phase of the study.

**Table 3: Main adverse events reported in association with anti-TNF use in children with rheumatic diseases [17, 18, 27-30, 44, 46, 70, 123-127]**

AE = adverse event, TNF = tumor necrosis factor, ADA = adalimumab, MAS = macrophage activation syndrome, CPK = creatinine phosphokinase, CD = crohns disease, UC = ulcerative colitis, ALT = alanine aminotransferases, AST = aspartate aminotransferases, CMV = cytomegalovirus, EBV = Epstein Barr virus, JSLE = juvenile onset systemic lupus erythematosus, DM = diabetes mellitus. §Reported infusion reactions to infliximab include anaphylaxis, vomiting, fever, headache, hypotension, abdominal pain, coughing, face oedema, rash, urticaria, chills, fatigue, sleepiness, insomnia. *Described by the FDA US Healthcare AE Reporting System. ¶Deaths described in table 2.

**Table 4: Adverse events reported in association with interleukin-1 receptor blockers**

IL-1 = interleukin-1, macrophage activation syndrome = MAS, CD = crohns disease, CMV = cytomegalovirus, upper respiratory tract infection = URTI, *One patient had urosepsis and MAS whilst on placebo (following eight doses of canakinumab). The second patient died of MAS and severe pulmonary hypertension whilst on Canakinumab.

**Table 5: Adverse events reported in association with tocilizumab and abatacept use [4, 104-106, 108, 109]**

AE = adverse event, URTI = upper respiratory tract infections. [#]Developed after 19 months of abatacept treatment. [§]Diagnosed at day 89 of the open-label lead in phase and thought to have been initially misdiagnosed as JIA. [o]dizziness, nausea, vomiting, headache, hypersensitivity, rhinitis. *Four benign neoplasms were reported but no malignancies.

**Table 6: Registries for monitoring biologic treatments in Juvenile Idiopathic Arthritis**

PRINTO = Paediatric Rheumatology International Trials Organisation, PRES = Pediatric Rheumatology European Society

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