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The development and assessment of biological treatments for children

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The development of biological agents with specific immunological targets has revolutionized the treatment of a wide variety of paediatric diseases where traditional immunosuppressive agents have been partly 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 biological agents in children to date has largely relied upon randomized controlled 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 ongoing 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 biological agents in children target tumour necrosis factor-α, interleukin-1, interleukin-6 and cytotoxic lymphocyte-associated antigen-4. These agents are most frequently used in paediatric rheumatic diseases. This review discusses the development and assessment of biologics within paediatric rheumatology with reference to the lessons learned from use in other subspecialties.

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 tumour necrosis factor-α (TNF-α), 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 have facilitated production of humanized 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 the expectations of patients, families and healthcare professionals have contributed towards a significant and continued motivation for developing and improving clinical outcomes using biologics in children. Key drivers for development of biologics include the following: 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-α in juvenile idiopathic arthritis (JIA) [6, 7]; growing expectations of higher standards of sustained clinical improvement; and the goal of striving for complete disease remission, both on medication and, more importantly,

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after cessation of treatment, with an ultimate goal of disease cure.

Assessment tools used in clinical trials in juvenile idiopathic arthritis

Table 1 summarizes how clinical response is assessed and defined in JIA clinical trials. The magnitude of the treatment response is generally defined in terms of attainment of the American College of Rheumatology (ACR) Paediatric 30, 50, 70, 90 (PedACR30, 50, 70, 90) response, which assesses the percentage improvement in three of the six 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 trials of biologics 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 randomized 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 minimized, making it more acceptable to parents and many clinicians. Such biologic treatments have generally already been shown to be efficacious in robust parallel-design randomized 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, owing to potential for a 'carry-over' effect during the placebo phase.

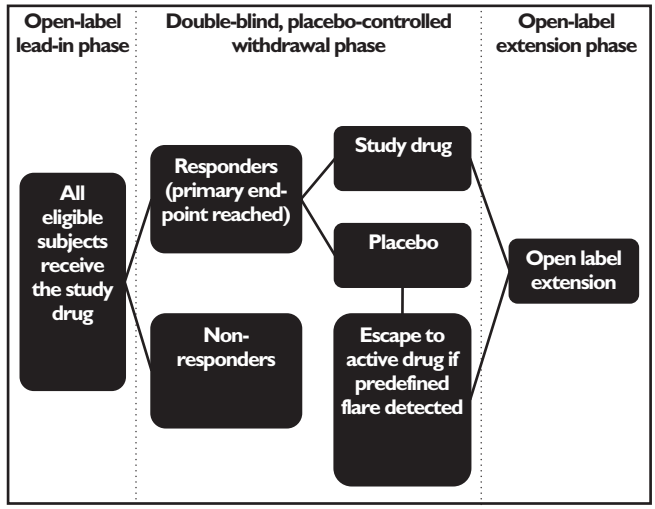

Figure 1

Diagram outlining the withdrawal study design frequently used in clinical trials of biologics in children

Table 1

Description of the end-points used in paediatric rheumatology clinical trials [8, 9]

Criteria	Components	Definitions of end-points used
PedACR criteria for determining the magnitude of the treatment response in juvenile idiopathic arthritis	Core set measures: (i) Physician's global assessment of disease activity (10 cm visual analog scale) (ii) Patient and/or parent global assessment of overall wellbeing (iii) Number of active joints (iv) Number of joints with limited range of movement (v) Disability index [childhood health assessment questionnaire (CHAQ) score] (vi) Erythrocyte sedimentation rate	• PedACR30 response is frequently used to assess treatment response in paediatric rheumatology clinical trials. A significant clinical response to treatment is defined as improvement of ≥30% in at least three of the six criteria, without worsening of ≥30% in no more than one criterion • PedACR50, 70, 90 response is defined as improvement of ≥50, ≥70, ≥90% in at least three of the six criteria, Without worsening by ≥50, ≥70, ≥90% in no more than one criterion • Disease flare can be defined using the PedACR criteria and is defined as three of the six core set variables worsening by ≥30%, with no more than one of the six improving by ≥30%
Inactive disease	• No joints with active arthritis • No fever, rash, serositis, splenomegaly or generalized lymphadenopathy attributable to juvenile idiopathic arthritis • No active uveitis • Normal erythrocyte sedimentation rate or C-reactive protein • No disease activity according to the doctor's evaluation	
Clinical remission	• On medication – criteria for inactive disease met for 6 months on treatment • Off medication – criteria for inactive disease met for 12 months off treatment	

Abbreviation is as follows: PedACR, paediatric American College of Rheumatology criteria.

The relatively short time on placebo treatment also limits the power to compare the safety profile of the active drug 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 because they are keen to believe that there has been a positive response [13, 14].

Overview of biologic treatments and their uses

Anti-tumour necrosis factor-α treatments

Etanercept

Identification and efficacy – Etanercept is a fully human, soluble fusion protein that binds to TNF-α with high affinity, preventing binding to cell surface TNF receptors [15]. Etanercept was the first biologic treatment to be used in JIA, following a multicentre, randomized, 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, compared with 28% of etanercept-treated patients ($P = 0.003$). The median time to disease flare was 28 days on placebo compared with 116 days with etanercept ($P < 0.001$) [16]. Those flaring on placebo were restarted 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 favourably than other JIA subtypes [17–19]. The ongoing 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 favourable. The German biologics registry has shown that males with a shorter duration of disease, a lower active joint count and 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]. Likewise, 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 also to 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 its 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-label 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 the German national biologics registries have reported a decrease in the rate of adverse events (AEs) over time [19, 27], from 0.20 AEs per patient during the first year of treatment, reducing to 0.12 AEs per patient per 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 per patient per 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 0.8 mg kg^{-1} $week^{-1}$) [18], and further studies have demonstrated comparable safety/efficacy of weekly and twice-weekly etanercept administration [30–32]. Cases of pulmonary and extrapulmonary *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 pretreatment screening [33, 34].

Conflicting results exist regarding the relative safety of treating with etanacept and methotrexate in combination. Data from the USA, 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

Table 2

Adverse events related to different anti-tumour necrosis factor agents used in juvenile idiopathic arthritis (data mainly from long-term studies and biologics registries)

	Etanercept						Adalimumab	Infliximab	
References	**[18]**	**[26]**	**[29]**	**[19]**	**[28]**	**[27]**	**[44]***	**[29]**	**[72]**
No. of patients	61	58	95	146	397	604	171	68	78
Median/mean exposure (years)	1.1	NA	2.0	2.5	NA	NA	NA	1.8	2.2
Maximal exposure (years)	2.5	8	5.9	7.3	3	NA	2	6.1	3.9
Cumulative patient-years of exposure	NA	318	258	312	859	1149	319.3	140	NA
No. of adverse events	68	NA	133	65	179	190	2549	71	71
No. of serious adverse events	NA	39	NA	9	NA†	52	17	NA	17
Anaphylactoid/serious drug reactions (%)	0	0	NA	0	0	0	0	1.5	3.6
Serious infections (%)	NA	15.5	3.2	2.7	2.8	4.3	4.1	1.5	2.6
Opportunistic infections (%)	NA	0	0	0	NA	0.2	0	0	0
New auto-antibody development (%)	20.6	NA	2.1	NA	3.8	NA	NA	10.3	32.5
New/worsening uveitis (%)	2.9	0	4.2	0	0.3	1.5	0	4.2	5.0
Demyelinating events (%)	1.5	0	0	0	0	0.3	0	0	0
Malignancies (%)	0	0	1‡	0	0	0.5§	0	0	0
Deaths	0	0	0	0¶	0	0	0	0	2.6**

Abbreviation: NA, not applicable. *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 serious adverse events per 100 patient-years to be 4.6, 7.1 and 6.0, respectively, but the study did not provide the absolute number of serious adverse events. ‡One case of malignancy (thyroid cancer). §Three cases of malignancy (thyroid carcinoma, yolk-sac carcinoma, non-Hodgkin's lymphoma). ¶Three nonresponders to etanercept subsequently died of tuberculosis, suspected macrophage activation syndrome and sepsis whilst on other immunosuppressives, at least 8 months after 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 systemic-onset juvenile idiopathic arthritis, experienced a severe flare of their disease and died of a cardiac arrest 3 months after discontinuation of infliximab (in the 3 mg kg^{-1} infliximab group), whilst in the open-label extension phase of the study.

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 and methotrexate treatment [35].

Further uses of etanercept – Etanercept use has been reported in children with the following conditions: 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 haematopoietic 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 humanized 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 the 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 and 17 years with a polyarticular disease course were treated with 24 mg m^{-2} of adalimumab on alternate weeks; 84 of 171 continued with previous methotrexate treatment. The PedACR 30, 50, 70 and 90% response was achieved in 74, 64, 46 and 26% of children receiving adalimumab monotherapy compared with 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 and placebo or placebo alone [44]. A preliminary open-label study including children <4 years of age or <15 kg has shown a similar improvement in PedACR criteria, and a comparable safety profile to that for 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 study, dosing of adalimumab changed, with patients weighing <30 kg receiving 20 mg and patients weighing ≥30 kg receiving 40 mg. Adalimumab showed ongoing efficacy, with sustained PedACR responses and no change in tolerability. Forty per

Table 3

Main adverse events reported in association with anti-tumour necrosis factor use in children with rheumatic diseases [17–19, 26, 28–30, 46, 70, 123–127]

AE category	Generic anti-TNF AEs	Etanercept	Adalimumab	Infliximab
Musculoskeletal	Arthritis flare, arthralgia	MAS, sarcoidosis, aseptic necrosis (femoral head), vasculitic rash, osteoporosis	Elevated CPK, myositis, back pain, muscle spasms	MAS
Haematological	–	Pancytopenia, lymphadenopathy, epistaxis	Neutropenia, leucopenia	–
Gastrointestinal and/or renal	Vomiting	CD, UC, aspecific bowel inflammation, biliary calculosis, nausea, abdominal pain, weight loss or gain, anorexia, oral apthosis, proctorrhagia	Increased ALT and AST, appendicitis, abdominal pain, gastroduodenitis, gastrointestinal bleeding	Persistent macroscopic haematuria
Cardiorespiratory	Hypertension	Cough, chest pain, asthma, tachycardia, extrasystolia	Chest pain	Cough
Infectious	Upper respiratory tract infections, pneumonia, CMV, gastrointestinal infection, soft tissue infections	Urosepsis, pyelonephritis, meningoencephalitis, appendicular abscess, prosthetic hip infection, EBV, recurrent urinary tract infections, dental infections, otitis	Tuberculosis, herpes zoster, herpes simplex, streptococcal infection, urinary tract infection, pharyngitis, *Clostridum difficile*	Tuberculosis, candidiasis (vaginal and oral), herpes zoster, varicella zoster, viral thyroiditis, histoplasmosis, pharyngitis, bronchiolitis
Autoimmune and/or immunological	Injection-site or infusion reactions	New onset of JSLE, Takayasu's arteritis, dermatomyositis, DM, alopecia, new auto-antibodies, autoimmune hepatitis	Lupus-like syndrome, injection-site reaction, new antibodies to ADA, DM	Infusion reactions*, newly induced auto-antibodies, development of antibodies to infliximab
Ophthalmological	–	Uveitis, blurred vision	Keratitis	Uveitis
Neurological	Headache	Demyelinating retrobulbar neuritis, neuropathy, epileptic insult, hearing loss, vertigo, dysaesthesia, insomnia	'Sporadic seizure', dizziness, syncope	Irritability, paraesthesia
Psychiatric	–	Depression, personality disorder, emotional lability, panic attacks, anxiety, agitation, concentration disorder, hallucinations, aggression	–	Psychoses, depression, panic attacks, anxiety, hyperactivity
Oncological	–	Lymphomas, thyroid carcinoma, yolk-sac tumour	Lymphomas	–
Gynaecological	–	Ovarian cyst, endometriosis, irregular/painful menses	Menorrhagia	–
Dermatological	New-onset psoriasis	Skin ulcer, hair loss, pruritic/urticarial rash, pityriasis, onychodystrophy, coccygeal cyst, eczema	Granuloma annulare, excoriation, purpura	Urticaria
Deaths	–	–	Four deaths†	Two deaths‡

Abbreviations are as follows: ADA, adalimumab; AE, adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; CD, Crohn's disease; CMV, cytomegalovirus; CPK, creatinine phosphokinase; DM, diabetes mellitus; EBV, Epstein–Barr virus; JSLE, juvenile-onset systemic lupus erythematosus; MAS, macrophage activation syndrome; TNF, tumour necrosis factor; UC, ulcerative colitis. *Reported infusion reactions to infliximab include anaphylaxis, vomiting, fever, headache, hypotension, abdominal pain, coughing, face oedema, rash, urticaria, chills, fatigue, sleepiness and insomnia. †Described by the FDA US Healthcare AE Reporting System. ‡Deaths described in Table 2.

cent 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 that for adults. In 2009, the US 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, three 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 a ~10 year history of using multiple immunosuppressants, making it difficult to establish direct causality [46].

Further uses of adalimumab – A recent qualitative study indicated that 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 of 18 patients [48]. The other showed seven of 20 (35%), of children to

have a reduction in uveitis activity, one of 20 (5%) had worsening activity, and 12 of 20 (60%) had no change [49]. Adalimumab and infliximab have been compared in an open-label, prospective, multicentre study including 16 children with JIA-associated uveitis, three 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 *vs*. 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-to-severe CD [61]. Following 4 weeks of induction treatment, patients were randomized to receive low- or high-dose adalimumab. Thirty-six per cent 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 biological agents [62–64], and an ongoing RCT is testing its efficacy and safety in paediatric chronic plaque psoriasis [65]. Adalimumab is both effective and well tolerated in juvenile-onset ankylosing spondylitis [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 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 that study, 3 mg kg^{-1} of infliximab or placebo was given for 14 weeks in combination with methotrexate. A higher proportion of patients receiving infliximab reached a PedACR30 response, but the difference between the treatment groups was not statistically significant ($P = 0.12$). Patients on placebo then went on to receive high-dose infliximab (6 mg kg^{-1}). 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 3 mg kg^{-1} per dose infliximab group had double the number of SAEs and a higher rate of infusion reactions and anaphylactic reactions than the 6 mg kg^{-1} per dose group, correlating with an increased incidence of anti-infliximab antibodies. New antinuclear and double-stranded DNA antibodies were also seen more frequently in those on low-dose infliximab. The optimal dosage warrants further investigation, because some have reported doses as high as 10–20 mg kg^{-1} per dose as being rapidly effective and well tolerated [71].

During the open-label extension phase of the study discussed above (weeks 52–204), 42 of 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]. US FDA approval for use in paediatric CD was obtained following the randomized, multicentre, open-label REACH study in children with moderate-to-severe CD [75]. Of the 112 patients treated, 58% achieved clinical remission following a 5 mg kg^{-1} induction dose. Longitudinal follow-up of patients on maintenance infliximab showed 56 and 33% still to 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 hospitalization 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 humanized anti-TNF-α antibody, and golimumab is a humanized 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, because the lack of an Fc region will prevent transplacental transfer [87]. Golimumab is similar to adalimumb with respect to its molecular weight and its 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 1–2 mg kg^{-1} day^{-1}. It has not demonstrated a significant benefit over placebo in polyarticular JIA [90], but in a multicentre RCT of anakinra in SoJIA, eight of 12 patients on anakinra and one of 12 on placebo achieved a PedACR30 response. Nine of 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 in 80%, c-reactive protein and ferritin also normalized 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 eight of 10 patients receiving anakinra monotherapy [92]. In another study, including patients who had previously received long-term corticosteroids with or without DMARDs, the clinical response to anakinra was more heterogeneous. The majority of patients experienced an initial amelioration of systemic features and acute-phase reactants, but subsequently, one group displayed ongoing 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 association 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 and 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

Table 4

Adverse events reported in association with interleukin-1 receptor blockers

Adverse event categories	Examples of adverse events reported during use of interleukin-1 receptor blockers		
	Anakinra [90, 94, 95]	Rilonacept [97]	Cannakinumab [97, 99, 101]
Musculoskeletal	Arthritis flare, arthralgia, limb pain, osteonecrosis of the femoral head, vertebral collapse, MAS	Arthritis flare, MAS	Arthritis flare, MAS, leg fracture
Haematological	Transient neutropenia, anaemia	Pancytopenia, anaemia	Leucopenia, thrombocytopenia, prolonged activated partial thromboplastin time
Gastrointestinal	Diarrhoea, nausea, abdominal pain, vomiting, elevated alanine aminotransferase, new-onset CD	–	Abdominal pain, vomiting, pneumonia, aminotransferase elevations
Cardiorespiratory	Cough, sore throat	Pulmonary fibrosis	Cough
Infectious	Hepatitis due to CMV, URTI, visceral *Leishmania* infection, varicella, rhinopharayngitis, labial herpes, uncomplicated hepatitis A	URTI, gastroenteritis, nasopharyngitis, skin infection, ear infection, influenza	Nasopharyngitis, URTI, varicella, otitis media, urosepsis, measles, pneumonia, Epstein–Barr virus
Immunological and/or autoimmune	Local injection-site reactions (ecchymosis, erythema, inflammation, pain, pruritis), anti-IL-1 receptor antibody development	Local injection-site reactions (erythema, bruising), development of anti-rilonacept antibodies	Non-neutralizing anti-canakinumab antibody development
Ophthalmological	–	–	Uveitis
Neurological	Headache	–	Headache, syncope
Renal and/or urological	Dysuria, nephrosis	–	–
Malignancy	None reported	None reported	None reported
Psychiatric	–	Depression	–
Dermatological	Rash	–	Rash
Other	Fever, whole-body pain	Fever	Fever, arm pain, lymphadenopathy, splenic cyst, haematoma, two deaths*

Abbreviations are as follows: CD, Crohn's disease; CMV, cytomegalovirus; IL-1, interleukin-1; MAS, macrophage activation syndrome; URTI, upper respiratory tract infection. *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.

than anakinra. In an RCT, 24 SoJIA patients were treated with weekly rilonacept (2.2–4.4 mg kg^{-1}, maximal dose 360 mg) or placebo for 4 weeks. Twenty-three of 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. Forty-five per cent 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, in comparison to 26% in the canakinumab group (relative risk reduction of 64%, hazard ratio 0.36; 95% confidence interval 0.17–0.75) [99]. Canakinumab was initially licensed for treatment of CAPS, but its license has been extended by the US 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 ongoing clinical trial assessing use in TRAPS and anecdotal reports of use in FMF [96].

Tocilizumab

Identification and efficacy – Tocilizumab is a humanized 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. Fifty-six Japanese SoJIA patients were initially treated with 8 mg kg^{-1} of tocilizumab, 2 weekly over 6 weeks, with responders subsequently being randomized to tocilizumab or placebo for 12 weeks. A PedACR30, 50, 70 response was achieved in 91, 86 and 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 and 90%, respectively [104].

In a multinational, phase III, 5 year, double-blind RCT (TENDER trial), significantly more patients on tocilizumab than control subjects achieved a PedACR30, 50, 70 by week 12 of treatment (85, 71 and 37% *vs*. 24, 8 and 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]. Tocilizumab was approved by the US FDA and NICE in 2011, for the treatment of children >2 years old with SoJIA who have not responded adequately to nonsteroidal anti-inflammatory drugs, corticosteroids and methotrexate [24, 100].

Safety – The range of AEs associated with tocilizumab is summarized in Table 5. In the Japanese tocilizumab phase III trial mentioned above, 8.9% of patients developed anti-tocilizumab antibodies and mild-to-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 [107] have revealed a significantly higher PedACR30, 50, 70 response with tocilizumab than placebo, with 65% attaining an ACR70 response by week 40. Forty-eight per cent of patients on placebo and 26% on tocilizumab flared within this time period ($P = 0.0024$) [108]. An open-label study is ongoing.

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 its 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

Table 5

Adverse events reported in association with tocilizumab and abatacept use [4, 104, 106, 109, 110]

Adverse event categories	Tocilizumab	Abatacept
Musculoskeletal	Arthritis flare, fracture, septic arthritis, hip dislocation MAS	Arthritis flare, arthralgia, foot deformity
Haematological	Neutropenia, leucopenia	–
Gastrointestinal	Gastrointestinal bleeding, increase in transaminases, diarrhoea	Vomiting
Cardiorespiratory	Pneumothorax, cardiac failure, pulmonary veno-occlusive disease	–
Infectious	Infectious mononucleosis, nasopharyngitis, URTI, gastroenteritis, varicella/herpes zoster infections, pneumonia	Nasopharyngitis, URTI, dengue fever, erysipelas, gastroenteritis, herpes zoster, bacterial meningitis, pyelonephritis, varicella infection
Opthalmological	–	Uveitis
Immunological and/or autoimmune	Anaphylactic reaction, mild-to-moderate infusion reactions, anti-tocilizumab antibodies, angioedema, urticaria	Anti-abatacept antibodies, multiple sclerosis*, acute infusion reactions†
Neurological	Headaches	–
Dermatological	Chronic panniculitis	–
Oncological	–	Acute lymphoblastic leukaemia‡, benign neoplasms§
Other	Elevated total cholesterol, testicular torsion	Pyrexia, ovarian cyst

Abbreviation is as follows: MAS, macrophage activation syndrome, URTI, upper respiratory tract infection. *Developed after 19 months of abatacept treatment. †Dizziness, nausea, vomiting, headache, hypersensitivity, rhinitis. ‡Diagnosed at day 89 of the open-label lead-in phase and thought to have been initially misdiagnosed as juvenile idiopathic arthritis. §Four benign neoplasms were reported but no malignancies.

receiving placebo and in 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 and 40% and 69, 52, 39 and 16%, respectively [109].

The majority of patients (153 of 190) subsequently entered an open-label extension study, for a median of 35 months (range 5.5–47.8 months). By day 589, a PedACR30, 50, 70, 90 and 100% response was achieved in 90, 88, 75 and 57% and 39% of patients who had been treated with abatacept during both the double-blind and the extension phases of the study. The response to abatacept was maintained or progressively improved over the duration of the study, 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 [110]. The US 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 randomized to receive abatacept experienced an SAE, whereas two of the patients receiving the placebo developed SAEs (although placebo patients received 4 months of abatacept prior to randomization). 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 [110].

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 per 6 month period [107]. Clinical studies in adults are investigating use of abatacept in RA, UC, CD, diabetes mellitus, systemic lupus erythematosus (SLE), graft *vs*. 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 juvenile-onset systemic lupus erythematosus (JSLE), JIA, primary systemic vasculitis, relapsed non-Hodgkin's lymphoma and leukaemia, chronic immune thrombocytopenic purpura, autoimmune haemolytic anaemia, 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, unresponsive 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 two to 12 infusions of rituximab in addition to standard immunosuppressive

agents in six of 11 patients. Remission was achieved in eight of 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 respectively [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 intravenous immunoglobulin [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 US FDA and the 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 US FDA reported an increased risk of lymphoma and other cancers associated with anti-TNF treatment in children and adolescents in light of postmarketing 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 matching 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 US FDA report, 10 cases of hepatosplenic T cell lymphoma were reported in IBD patients; however, the concomitant medications used (6-mercaptopurine and azathioprine) are also independently associated with hepatosplenic T cell lymphoma [120]. Likewise, 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 to 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 *vs*. 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

Table 6

Registries for monitoring biological treatments in juvenile idiopathic arthritis

Registry name	Country	Web link
Pharmachild	Participating centres of >50 countries belonging to PRINTO or PRES	http://www.pharmachild.org/
Childhood Arthritis and Rheumatology Research Alliance (CARRA)	North America	https://www.carranetwork.org
Biologics for children with rheumatic disease (BCRD) – the extended biologics study	UK	http://www.bcrdstudy.org
British Society of Paediatric and Adolescent rheumatology (BSPAR) etanercept cohort	UK	https://www.aruk.manchester.ac.uk/bspar
Dutch national arthritis and biological in children (ABC) register	The Netherlands	https://www.abc-register.nl/
Biologika in der Kinderrheumatologie (BIKER) register (paediatric)	Germany	http://biker-register.de
Juvenile arthritis methotrexate/biologics long-term observation (JuMBO study including adults)	Germany	http://dgrh.de/jumbo-forschung.html

Abbreviations are as follows: PRES, Paediatric Rheumatology European Society; PRINTO, Paediatric Rheumatology International Trials Organization.

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 personalized treatment strategies based on biology, genetics and pharmacogenetics will be crucial for further improvements in treatment options and patient outcomes.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

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