The evolving landscape of rheumatic drugs and their indications in paediatric and adolescent care

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Abstract:

Paediatric rheumatic diseases (RMDs) are characterised by dysregulation of the immune system functions due to a combination of genetic, epigenetic and environmental factors. In many cases, children and young people (CYP) with RMDs require long-term pharmacological interventions to control their symptoms, minimise the risk of disease relapse and organ damage, and ultimately preserve their quality of life. The last decades have seen significant progress in the expansion of therapeutic options licensed or available off-license for CYP with RMDs, and an unprecedented number of paediatric interventional clinical trials testing new therapies.

This review aims to appraise the paediatric rheumatology community on available pharmacological therapies for use in childhood-onset RMDs, including conventional, biologic and targeted synthetic disease modifying anti-rheumatic drugs, immunoglobulins, and cell-based therapies, highlighting their known indications, as well as current guidelines and consensus recommendations supporting their use off-license. We review the paediatric dosing regimens available for the treatment of RMDs and other autoimmune conditions, the toxicity profile of available therapeutic agents and provide a comprehensive evaluation of emerging therapies for childhood RMDs, currently tested in clinical trials.

Key words: paediatric rheumatic drugs, targeted biologic treatments, small molecules, cell therapies, licensed therapies, toxicity.

Key messages:

- Recent research advances led to revised guidelines and recommendations for treatment of paediatric RMDs
- A large number of biologic and targeted synthetic DMARDs are currently tested in clinical trials
- Established and novel cell-based therapies hold the promise for long-term remission off-treatment in severe/refractory cases
- Investment in equitable access to established/emerging therapies is needed to ensure better outcomes for children

Introduction

Notable progress has been achieved in the last decades in the treatment of rheumatic diseases (RMDs) due to significant industry and academic research investment in developing and testing new therapies. The main purpose of pharmacological intervention in paediatric rheumatology is to control the inflammatory processes underlying different clinical presentations, aiming for alleviation of symptoms, minimisation of long-term damage or complications (including glucocorticoid toxicity), as well as preserve function and ensure the maintenance of adequate quality of life, irrespective of the molecular mechanisms underpinning different pathology.

Paediatric rheumatic conditions include monogenic autoinflammatory diseases (AID) characterised by key mutations affecting innate immune functions, multifactorial AID underpinned by interactions between genetic and environmental factors (1), and autoimmune rheumatic diseases (ARDs), typically involving the adaptive immune responses with a degree of overlap with innate immunity dysregulation (2).

RMDs that start early in life are broadly considered to have increased genetic burden. Recent research advances have facilitated better understanding of mechanisms of disease heritability and that of other complex molecular mechanisms contributing to disease pathogenesis, as well as facilitating novel biomarker discoveries enabling patient stratification within the same disease phenotype for improved management strategies (3).

We advocated that, based on genetic, molecular and clinical similarities, some RMDs should be classified in a similar way in children and adults, while conditions underpinned by significant differences require distinct childhood classification criteria (4) to enable timely recognition and diagnosis and support high quality research and inclusion of homogeneous cohorts of children and adolescents in clinical trials.

Both the European Medicines Agency (EMA) and the Food and Drug Administration (FDA) recommend, where possible, testing of new adult therapeutic agents in children if they manifest with a similar clinical phenotype. These recommendations have facilitated many clinical trials in paediatric rheumatology leading to the licensing of new therapies for children with AID and ARDs. However, there is still a disconnect between paediatric and adult therapeutic indications, primarily related to the different disease labels across the life span, which sees many of the young people having their

diagnostic changed when they transition into adulthood to fit adult-licensed treatment pathways, which limits the chance for high quality research into long-term outcomes of RMDs with childhood onset.

In the UK, access to medications for children and young people (CYP) with rheumatic conditions is primarily mandated by the National Institute for Health and Care Excellence (NICE), the national health technology assessment body evaluating the cost-effectiveness of medicines granted marketing authorisations ("product licences") by the Medicines and Healthcare Products Regulatory Agency (MHRA) for medicines in the UK, and making them available on the National Health System (NHS) through reimbursement. Additionally, access to drugs which are not NICE approved for use for paediatric rheumatology indications has been historically facilitated by the NHS England Medicines for Children Commissioning pathway, which enabled access to treatments for CYP aged less than 18 years old, where specific commissioning conditions within a NICE Technology Appraisal or NHS England clinical policy are met (5). It is uncertain what process(es) will replace that when NHS England is fully decommissioned in October 2026, although it is likely to be similar, albeit sitting within the Department of Health and Social Care.

This review aims to update the rheumatology community on the current knowledge regarding the mechanism of action, doses and indications of the main therapies used in paediatric rheumatology, as well as review new emerging therapies currently tested in clinical trials for rheumatological indications; and explore both established and emerging treatments that can potentially be used off-license in CYP with RMDs based on their licensing for other indication.

Drugs used in paediatric rheumatology

Specialised therapeutic approaches for paediatric RMDs include the use of non-steroidal anti-inflammatories (NSAIDs), intra-articular Glucocorticoid (GC) injections (IAGC), systemic GC treatment, and disease modifying anti-rheumatic drugs (DMARDs) including conventional DMARDs (cDMARDs), biologic DMARDs [bDMARDs, comprising fusion proteins, monoclonal antibodies (mAb) or bi-specific mAb such as T-cell engagers], targeted synthetic DMARDs (tsDMARDs, also called 'small molecules'), immunoglobulins, and cell-based therapies. The last category includes hematopoietic stem cells (HSC) and mesenchymal stem cells [MSC - renamed Medicinal Signalling cells (6)], autologous or allogeneic haematopoietic stem cell transplant therapies (7), and more recently chimeric antigen receptor T-cell (CAR-T) therapies currently available only in clinical trials (8).

Although the terms immunosuppressant and immunomodulatory are used interchangeably, there are some important distinctions to consider. Immunosuppressants have a broader and non-selective impact on the immune functions and act by suppressing and dampening them to control inflammation associated with RMDs (e.g. most cDMARDs are immunosuppressant), while immunomodulatory therapies, target more specific functions of the immune system, being designed to block certain molecules, cells or immune pathways, and regulate and modulate their function, aiming to restore the immune homeostasis (bDMARDs, tsDMARDs or specific cell-therapies are immunomodulatory).

NSAIDs and GC

NSAIDs are frequently used as first line therapy in juvenile idiopathic arthritis (JIA) and management of acute musculoskeletal or glandular pain, which are frequent symptoms of childhood onset RMDs (9). They are recommended at the lowest effective dose for the shortest possible duration, although, in order to achieve their therapeutic benefit, NSAIDs need to be taken on a continuous scheduled basis for a duration of 4-8 weeks. Long-term use requires regular monitoring. The most commonly used NSAIDs are: *ibuprofen* (max. 30 mg/kg in 3-4 doses), *naproxen* (5–7.5 mg/kg twice daily, max. 500 mg, licensed from age 5), *indometacin* (0.5–1 mg/kg twice daily), *diclofenac* (1.5–2.5 mg/kg twice daily, max. 75 mg per dose), *piroxicam* (5-20 mg daily, as per body weight, licensed from age 6) and *etoricoxib* (60 mg once daily, increased if necessary to 90 mg once daily, licensed from age 16), while *paracetamol* is used from 30–60 mg every 8 hours in very young children (maximum 60 mg/kg daily) to 0.5–1 g, every 4–6 hours; maximum 4 doses per day in older adolescents.

The most common side-effects of NSAIDs include gastro-intestinal (GI) upset, rarely complicated with more severe manifestations such as GI bleeding. It is routine to use proton pump inhibitors alongside NDAIDs in children to minimise these side effects. Other side-effects include haematuria, skin rashes, allergic reactions, accentuation of asthma symptoms, and tinnitus. A recent study comparing *ibuprofen* with *naproxen* in children with JIA found similar efficacy, but increased side-effects with *naproxen* (10), although this observation does not quite reflect the experience in practice where the less-frequent administration of *naproxen* coupled with its acceptable toxicity profile, support its wide use.

Aspirin at a dose at a dose of 30-50 mg/kg/day is still recommended combined with intravenous immunoglobulin (IVIG) for Kawasaki Disease (KD) during the acute inflammatory phase, reducing to

antiplatelet doses of 3-5mg/kg/day when fever subsides (11). Some studies suggested recently that the use of aspirin at 3-5 mg/kg/day from the outset is equally efficacious with potentially fewer side effects, but high-level evidence for this approach is lacking (12).

GC have been widely used for severe systemic manifestations of paediatric RMDs for decades, and despite attempts to minimise GC exposure they still are used widely for the treatment of children with RMDs. Pulse therapy with intravenous (IV) *methyl-prednisolone* at a dose of 30 mg/kg (max 1g/daily) for 3 days and/or oral *prednisolone* at a dose of 1–2 mg/kg once daily (max. 60 mg per dose), is recommended as induction regimen for severe childhood-onset systemic lupus erythematosus (cSLE), including lupus nephritis (LN)(13); severe inflammation or weakness associated with juvenile dermatomyositis (JDM)(14); Takayasu Arteritis (TA)(15); polyarteritis nodosa (PAN); and for high-risk KD presentation or in KD cases with unsatisfactory response to IVIG(12); childhood primary central nervous system vasculitis; or severe small vessel vasculitis, including granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), and eosinophilic granulomatosis with polyangiitis (EGPA) with significant organ involvement (15, 16). A similar regimen has been historically used as first line therapy in systemic-onset JIA (soJIA), recently renamed Still's disease (comprising both soJIA and the adult-onset Still's disease), although this should not delay early initiation of biologic therapy with interleukin (IL)-1 or IL-6 blockade as first line therapy, which results in better outcomes (17). High GC doses (IV pulsed methylprednisolone dose as above; or dexamethasone 10 mg/m2/daily IV) followed by oral prednisolone (1-2mg/kg/day), in combination with IVIG or IL-1 inhibition, depending on aetiology and severity, are also recommended as first-line therapy in hemophagocytic lymphohistiocytosis (HLH)/ macrophage activation syndrome (MAS) with persistent and severe inflammation and organ dysfunction (18, 19).

Following IV GC administration for induction regimens for paediatric RMDs with systemic manifestations and severe organ involvement, for the maintenance of disease control, GC dose should be tapered gradually in combination with other immunosuppressive therapies, to minimise the risk of GC toxicity. A paediatric glucocorticoid toxicity index (pGTI) has been developed and validated to assess the impact of morbidity related to GC exposure, which can be used in research and clinical practice (20, 21).

A consensus regimen for GC tapering has been proposed by the Childhood Arthritis and Rheumatology Research Alliance (CARRA), in collaboration with the Paediatric Rheumatology European Society (PReS) Lupus Working Party, and the Paediatric Nephrology Research Consortium

for the induction and maintenance therapy of proliferative LN, advocating for achieving a dose of 15 mg prednisolone daily or equivalent by week 12 (22). Similarly, the European Alliance of Associations for Rheumatology (EULAR)/PReS recommendations for management of Still's disease advocate for gradual tapering of oral GC at a dose of less than 0.2 mg/kg/day of prednisolone or equivalent and complete cessation of GC therapy after 6 months (17). Short courses of oral GC are also recommended in the early inflammatory phase of juvenile localised scleroderma (23). GC 'bursts' defined as maximum 2 mg/kg equivalent of prednisolone dose (maximum daily dose of 60 mg), with or without tapering over 6 weeks, were recommended by CARRA clinicians for chronic non-bacterial osteomyelitis (CNO), including recurrent multifocal osteomyelitis (CRMO) refractory to NSAIDs (24), and can also be used in the Periodic Fever, Aphthous Stomatitis, Pharyngitis, and Adenitis (PFAPA) syndrome or in IgA-related vasculitis (25).

Side-effects of GC include mood swings, difficulty sleeping, weight gain, headaches, stomach pain and acne, hypertension, dyslipidaemia and increased glucose levels leading to increased cardiovascular risk, effects on growth and bone strength, delayed puberty, period abnormalities, impact on vaccine responses, increased risk of infections, while other side-effects such as glaucoma, cataract or steroid-induced myopathy are less common in children. The efficacy as well as side-effects of GC are treatment duration/dose-dependent, and are explained by strong genomic effects (mediated by the activation of the cytosolic glucocorticoid receptor – cGCR) (26). GC also have non-genomic effects through influencing the function of cell membrane proteins or mediated by proteins released from the cGCR–multiprotein complex following the binding of GC to the cGCR, which are considered responsible for some of the rapid effects of GC (26).

Intra-articular administration of GC

IAGC injections are commonly used as first line therapy in the management of JIA, aiming to bring joint inflammation under rapid control, provide symptomatic relief while allowing other therapies, such as methotrexate (MTX), to become effective. Out of all GC depot preparations available, triamcinolone hexacetonide (TH) is the option of choice, due to its unique characteristics, such as prolonged benefit, decreased systemic absorption, and similar toxicity profile compared to more soluble GC preparations. When not available, triamcinolone acetonide (TA) can be used as an alternative, although its level of systemic absorption is higher than that of TH, in addition to having an increased rate of joint inflammation relapse (27). The doses of TH that are usually used in

paediatric population are 1mg/kg per joint for large joints such as knees, shoulders, or hips (max. 40mg/joint); 0.5mg/kg per joint for medium joints, such as ankles, subtalar joints, elbows and wrists (max. 30mg/joint); and 0.04–1mg in total dose per each small joint injected, such as fingers and toes (28).

IAGC injections for management of temporomandibular joint (TMJ) inflammation associated with JIA typically used a dose of 0.25mg/kg per joint. Despite their recognised benefit (29), more recently there are concerns that they may have deleterious effects on TMJ growth during childhood (30), and current guidelines are that intraarticular glucocorticoid injection is not recommended as first-line management of TMJ arthritis in skeletally immature young people, but may be considered in cases refractory to optimised systemic treatment; or once skeletal maturity has been reached (31).

The side-effects of IAGC injections depend on the dose. CYP who undergo multiple IAGC injections may experience short-lived side-effects similar to those associated with of systemic GC treatment. Additionally, IAGC injections are usually administered under local or general anaesthetic as age-appropriate, can in rare cases can cause joint infection, subcutaneous fat atrophy or incidental intra-articular calcification (28). It is widely recommended that a specific joint should not be injected more than **3** to 4 times per year (32).

Conventional Disease Modifying Anti-rheumatic Drugs (cDMARDS)

Conventional Disease Modifying Anti-rheumatic Drugs (cDMARDS) are widely used in RMDs in children despite the relatively poor-quality evidence for their efficacy in paediatric populations, as many disease-specific recommendations are based on data derived from clinical trials in adults with similar disease phenotypes. Many cDMARDs are used outside the licensed age where there are no good-quality studies in children (off-license), and also as unlicensed drugs, in refractory cases of paediatric RMDs, where no suitable licensed therapeutic alternatives are available for either adults or children (see **Table 1**).

Methotrexate

The best quality of evidence for dosing and efficacy of MTX in children is derived from studies in JIA. MTX is the most used cDMARD in paediatric rheumatology, being conditionally recommended over other cDMARDs for the treatment of oligoarticular JIA (oligoJIA) and TMJ arthritis (33), and for polyarticular JIA (pJIA) (34) by the American College of Rheumatology (ACR), with the subcutaneous

formulation being preferred. The British Society of Rheumatology (BSR) guideline for management of psoriatic arthritis (PsA) across the life course also recommends MTX as the preferred cDMARD for management of juvenile PsA (JPsA) (35) despite low quality evidence for efficacy (36). The SHARE initiative also advocates for its use in JIA-associated uveitis associated with poor prognostic factors, as the first choice for systemic immunosuppression (37). Only two randomised controlled trials (RCTs) evaluated the efficacy of MTX vs. placebo in JIA overall (38), and specifically in extended-oligo articular and soJIA (39). MTX is not effective and therefore not recommended in Still's Disease in children (soJIA) (33) or across the life course (17), although is still used for polyarticular disease course, usually in combination with bDMARDs (40).

MTX is also used off-license in various other RMDs, including cSLE, JDM, anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV), localised scleroderma, sarcoidosis, as well as in childhood psoriasis or inflammatory bowel disease (**Table 1**). The main side-effects CYP treated with MTX encounter are the GI upset and liver dysfunction. Overall, there is better MTX tolerability in younger children compared to adolescents (41). To minimise the side-effects to MTX, different strategies can be employed, such as optimization of the timing of the dose (e.g. administration at bedtime, evening, weekend) and route of administration (subcutaneous administration or liquid/syrup formulations); dietary adjustments (administration with food, adequate hydration); increase in the folic acid supplementation (up to 5 mg daily, 6 days a week, with the exception of the day of MTX administration), and use of antiemetic medications. Additionally, educational and behavioural approaches to tackle anticipatory nausea, combined with the change in route of MTX administration can help improve treatment tolerability (42).

Other cDMARDs for use in JIA

There is scarce evidence for efficacy of other cDMARDs in paediatric populations, and many are used off-label across the world for various indications, especially in refractory disease with no other suitable therapeutic alternatives available (**Table 1**). The ACR guidelines for management of pJIA include leflunomide (LEF), sulfasalazine (SSZ) and hydroxychloroquine (HCQ) as potential alternative to MTX (in this order)(34), acknowledging the more recent evidence derived from RCTs which tested the efficacy of LEF (43, 44) and SSZ (45) in JIA, as well as the superiority of combination cDMARD therapy over MTX monotherapy for early JIA treatment (46). Other DMARDs historically used in

inflammatory arthritis, such as penicillamine or gold therapy are not considered suitable treatment alternatives for JIA (47).

A recent study from the USA assessing commercially insured children identified a declining trend in the new use of cDMARDs in JIA, paralleled by an increasing trend in use of the bDMARDs (48), which reflects advances in therapeutic strategies in JIA.

cDMARDs used in paediatric systemic RMDs

Various cDMARDs have been used in paediatric RMDs, including cSLE, JDM, systemic sclerosis, vasculitis, or childhood-onset Sjögren's Disease (cSjD) associated with refractory manifestations or organ involvement, such as mycophenolate mofetil (MMF), MTX, azathioprine (AZA), ciclosporin, tacrolimus (TAC), and cyclophosphamide (CYC). Based on the evidence derived primarily from adult studies and smaller, low-quality studies in paediatric populations, some cDMARDs are preferentially used for certain indications (see **Table 1**).

Historically IV CYC therapy has been used with success in children with severe disease manifestations, and it is still recommended over oral CYC regimens due to reduced toxicity profile, for rapidly progressive RMDs, with significant organ involvement or poor prognostic factors, such as CNS lupus, LN (13), systemic vasculitides (15) or JDM (14). MMF is superior to other cDMARDs as induction and maintenance regimen for class III and IV +/- V LN (49, 50), and based on the merging evidence from recent clinical trials in adult LN, it is recommended for use in association with a calcineurin inhibitor (CNI), such as ciclosporin or TAC, which can be used off-license in children with poor prognostic factors and when the renal function is not severely impaired (49, 50).

AZA, MTX or MMF are recommended as first-line maintenance cDMARD therapy for paediatric systemic vasculitides (15). The rates of remission induction in childhood PAN were similar with MMF and CYC in an open-label, randomized, Bayesian noninferiority trial, although MMF was associated with better health-related quality of life than CYC (51).

AZA, TAC, MTX, and MMF can be used in JDM as first, second or third-line treatment options, with no preferential recommendation, because of lack of comparative evaluation of their efficacy. cDMARDs are not recommended for routine use in cSjD, unless there is evidence of specific-organ involvement(52). MTX is the first-line cDMARD therapy for juvenile localised scleroderma, although

other cDMARDs can also be used (23). Etoposide and ciclosporin are also therapeutic alternatives for treatment of refractory HLH/MAS (18) (see **Table 1**).

MTX or SSZ are also used in CNO/CRMO refractory to NSAIDs or GC 'bursts' as per consensus recommendations (24); MTX, SSZ, AZA, MMF or even CYC in childhood-onset sarcoid refractory to short courses of GC, mirroring adult practice (53).

cDMARDs should be prescribed and monitored according to existing age appropriate national and international guidelines, taking into account safety aspects during conception, pregnancy and breast-feeding (54), which are potentially relevant to older adolescents who need to be counselled appropriately regarding pregnancy risk.

Table 1 includes details of licensed doses as well as the doses used off-license in children for various rheumatological indications, as well as their most commonly encountered side-effects. Of note, only MTX and SSZ are licensed for use in JIA, while the majority of other cDMARDs are used off-license in paediatric RMDs.

Biologic therapies in paediatric rheumatology

Undoubtedly, the greatest advance of the therapeutic armamentarium leading to improved outcomes in paediatric rheumatology has been achieved through the clinical implementation of biologic immunosuppressive therapies, which only became widely available in the last decades, with the first biologic receiving FDA approval for use in JIA in 1999.

Biologic agents are genetically engineered proteins that selectively block individual components of the immune system and inflammatory pathways responsible for chronic inflammation, developed using recombinant DNA technology. The research underpinning their discovery has also revolutionised the understanding of the pathogenesis of many paediatric RMDs.

Overall, bDMARDs are currently recommended for the treatment of JIA, including Still's Disease (soJIA), JIA-associated uveitis, AIDs and connective tissue diseases such as cSLE and JDM, with some of them having the advantage of being better characterised in terms of both safety and efficacy than many cDMARDs used in CYP with RMDs, following successful completion of RCTs in JIA (55), cSLE (56) or AAV (57).

However, there are still unknown aspects related to their life-long efficacy and safety, hampered by the lack of long-term follow-up of cohorts from paediatric to adult rheumatology services. Additionally, despite the availability of many bDMARDs, CYP with JIA experienced high rates of relapse following treatment discontinuation after achieving remission, both in clinical trials (58) and in real-life (59), suggesting that future research is still required to identify biomarkers with adequate flare predictive value in clinical practice (60) and support the development of effective therapeutic strategies to ensure that profound remission in JIA (61) for ultimate patient benefit.

There is also little consensus on the best approaches to tackle immunogenicity leading to secondary bDMARD treatment failure in CYP who develop anti-drug neutralising antibodies (62), as pro-active drug monitoring strategies are not widely implemented in paediatric rheumatology clinical practice, as the impact is questionable (63).

Despite these limitations, bDMARDs have changed the paradigm of treatment of many paediatric RMDs, being currently recommended as first line DMARD therapy in severe presentations associated with Still's disease (17), AAV (15, 64), Takayasu arteritis (15) , HLH-MAS (18), or in combination with cDMARDs as first line therapy for LN associated with poor prognostic factors (50) across the life span.

Biologics for JIA

Anti-tumour necrosis factor (TNF)-α inhibitors (TNFi) are the most used therapeutic agents for non-systemic JIA refractory to cDMARD therapy, due to their proven efficacy across various JIA-subtypes (65). The TNFi currently licensed in JIA are *adalimumab* (66) and *golimumab* (67) (both human monoclonal antibodies) and *etanercept* (68), a soluble TNF receptor fusion protein. *Infliximab* (a chimeric monoclonal antibody) has also been successfully used off-label in JIA (69). The mechanism of action of TNFi, licensed indications or off-label recommendations, and corresponding dosage regimens are detailed in **Table 2**.

There are several agents blocking IL-1 licensed for use in children (*anakinra, canakinumab and rilonacept*). *Anakinra and canakinumab* have revolutionised the outcomes of Still's disease in children (soJIA), being currently recommended as first line DMARD therapy (similarly to IL-6 blockade with *tocilizumab*) as early as possible after the diagnosis is made, even in CYP with risk factors for developing Still's lung disease as per data currently available (17). IL-1 blockade is also indicated for treatment of AIDs, such as Cryopyrin-Associated Periodic Syndromes (CAPS), Familial Mediterranean

Fever (FMF) (70), TNF Receptor Associated Periodic Syndrome (TRAPS), and Mevalonate Kinase Deficiency (70-72), and in HLH/MAS (18, 19). *Rilonacept* is also licensed for CAPS but rarely used in Europe.

Pro-inflammatory cytokine therapeutic blockade targeting IL-6 (*tocilizumab*) (73), IL-17A (*secukinumab*) (74) and IL12/23 (*ustekinumab*) (75), in addition to T-cell costimulatory blockade (*abatacept*) (76), have subsequently received license for treatment of specific JIA phenotypes (see **Table 2**). *Ixekizumab* (IL17A blockade) has shown benefit in JPsA as per preliminary data from the COSPIRIT-JIA trial (not published as yet).

B cell targeted therapies such as CD20 blockade with *rituximab* has also been used off license in seropositive pJIA (77).

Multiple biosimilars, defined as biologic molecules which are similar in quality, safety and efficacy with their originator, have been developed and tested over time in JIA, and they have been proven equivalent with their originators in real-life clinical practice (78), successfully contributing to improved treatment accessibility (see **Table 2**).

Biologics for paediatric RMDs

B cell depletion with *rituximab* (anti CD20) is currently recommended as first line DMARD therapy in severe/refractory GPA and MPA with childhood onset (15, 64) based on the data derived from a successful phase IIa clinical trial (57), which is one of the major advances in management of paediatric RMDs. *Rituximab* administered every 4-6 months is also superior to azathioprine for maintenance of remission in AAV, and is thus recommended (16, 79).

Belimumab (anti BAFF) is the first biologic to be licensed for use in cSLE after meeting the primary endpoint in the PLUTO trial (56), and is currently recommended to be used in combination with cDMARDs as first line therapy for class III/IV LN with poor prognosis(49), and for refractory cSLE with various manifestation as thrombocytopaenia, cutaneous, musculoskeletal and systemic vasculitis as per recommendations available for adults (80), as the SHARE recommendation for management of cSLE require updating (13).

Biologic therapies have also been used off-license and are currently recommended by paediatric guidelines for use in other RMDs with severe and refractory presentations, based on data available form adult studies and lower quality evidence from paediatric cases (see **Table 2**). *Abatacept* and

rituximab are recommended for use in severe/refractory JDM (14); *tocilizumab* and *TNFi* as second or third line therapeutic agents for induction and/or maintenance of severe paediatric vasculitides (15); *belimumab* and *rituximab* for glandular manifestations in cSjD, and *tocilizumab* and *rituximab* for severe skin fibrosis or interstitial lung disease (ILD) in juvenile systemic sclerosis, both based on adult recommendations (52, 81); *rituximab* for refractory HLH/MAS (18); *TNFi* for refractory CNO/CRMO (24) and juvenile systemic granulomatosis with genetic causes, including early-onset sarcoidosis and Blau syndrome, as well as refractory sarcoidosis, irrespective of age an onset (53).

IVIG treatment is recommended as first line therapy for KD (11), for refractory JDM (14) and as first line therapy of HLH/MAS associated with infection, in combination with GC and *anakinra* (18). *Emapalumab*, a human mAb against interferon (IFN)γ is indicated (but not yet widely available in the UK or Europe) in primary HLH and MAS, supported by successful clinical trial data in children (82) or in HLH associated with Ebstein-Barr virus infection (18), and *anifrolumab*, a type I IFN receptor antagonist although not licensed in children, is emerging as potentially efficacious (off-licence) in the management of autoinflammatory type I Interferonopathies (83, 84).

Iloprost is a synthetic prostacyclin analogue, used off license in CYP with digital ulcers secondary to vasculopathy and pulmonary hypertension based on indications available in adults (81). *Therapeutic plasma exchange* is not routinely recommended, but can be used off-license on a case by case basis in AAV (16, 79).

Side-effects of biologic DMARDs

The most common side-effects to targeted biologic therapies are related to the blockade of the immune system to reduce inflammation, which can increase the susceptibility to infective complications, including viral, fungal and bacterial infections (85). Screening to exclude chronic viral hepatitis, human immunodeficiency virus (HIV) infection or tuberculosis, vaccination in younger children before starting treatment or evidence for immunity to varicella and measles in older children, are all recommended before starting therapy, while life vaccines are contraindicated while on biologics (86). Other common side-effects include injection-site reactions for drugs with subcutaneous administration and infusion reactions for the one administered intravenously, in addition to laboratory abnormalities, including elevated liver enzymes and low blood cell counts (with neutropenia being the most frequent), various GI manifestations, and headache (87). With the expansion of the biologic treatment options and their broader use, it became apparent that the selective blocking of the immune system could recapitulate some of the phenotypes of inborn errors of autoimmunity clinicians need to be aware of (88, 89).

Synthetic targeted DMARDs (small molecules) used in paediatric rheumatology

Based on the recent successful clinical trials, *tofacitinib, baricitinib* and *upadacitinib* have received approval to be used as monotherapy or in combination with MTX for the treatment of active polyarticular course JIA, including rheumatoid factor (RF) positive and RF negative JIA, extended oligo JIA and juvenile PsA in CYP in which one or more cDMARD or bDMARD has/have been proven inadequate or not well tolerated (90-92). *Baricitinib* is also licensed for use in refractory JIA-associated uveitis (93) and enthesitis related arthritis (ERA) (91) refractory to DMARDs therapy.

JAKi are also recommended for treatment of interferonopathies as per EULAR/ACR 'points to consider' guideline (83), and evidence of clinical efficacy (94, 95). JAKi can offer a suitable therapeutic alternative for refractory JDM(96), particularly if associated with calcinosis (97), with a RCT comparing the efficacy of *baricitinib* vs. MTX in JDM (the BARJDM trial) currently in set-up (98).

Apremilast, a phosphodiesterase type-4 inhibitor licensed for use in adult PsA, is also recommended for use off-license in juvenile PsA by the BSR guideline (35), while trials in children are ongoing in Behçet's Disease (see **Table 3**).

Tapering of DMARDs

A few paediatric studies explored biologic DMARD tapering strategies in JIA and provided evidence that the duration of JIA remission of minimum 1.5 to 2 years was usually associated with better outcomes (99), although overall, a high proportion of JIA cases flared post treatment withdrawal (59), highlighting the need for cautious and individually-tailored approaches. Although some clinicians preferred gradual vs. abrupt withdrawal of biologic treatments, others were concerned by the risk of immunogenicity to adalimumab and infliximab when tapering the dose or increasing the interval between administration. A study of etanercept in JIA found no difference between the two tapering approaches in terms of the flare risk (100).

Additionally, there is no general consensus regarding the decision of which medication to stop first, MTX or the biologic treatment, with some clinicians preferring to stop biologics for reasons related to cost and convenience, while others prioritizing the withdrawal of the medication with the most side effects or associated with a poor safety profile as per a recent CARRA survey (101).

Several biomarkers, such as serum S100 proteins (e.g. myeloid-related protein MRP8/14 or calprotectin) and interleukin-18 (IL-18) (102, 103), along with imaging biomarkers, such as Power Doppler musculoskeletal ultrasound (104) and magnetic resonance imaging (MRI) (105), including whole body MRI (106, 107) have been proposed as promising candidates to help guide the DMARD tapering in JIA, while shorter duration from JIA onset and treatment initiation or before starting biologics for people who required biologics, longer sustained remission, absence of uveitis, and certain JIA subtypes (99) were all associated with better chance of successful DMARD treatment cessation.

Other treatments

Pilocarpine, a M1-M3 muscarinic receptor agonist, is recommended for use in cSjD associated with severe dryness by the BSR guideline across the life course (52) based on data available in adults, and *dapaglifozin, a* sodium-glucose cotransporter-2 inhibitor, can be used in children with LN and diabetes, based on KDIGO (Kidney Disease: Improving Global Outcomes) and EULAR recommendations for management of LN in adults (49, 50).

Sildenafil is a phosphodiesterase type 5 (PDE-5) inhibitor used off license in CYP with severe Raynaud's associated and pulmonary hypertension as per adult recommendation for use in systemic sclerosis (81).

Bosentan is a dual endothelin agonist licensed for use in children with idiopathic pulmonary arterial hypertension (PAH), used off license I juvenile scleroderma associated with PAH, as well as severe Raynaud's associated with digital ulcers (108).

Pamidronate and zolendronate, synthetic analogues of pyrophosphate, have been used off-license in CNO/CRMO with spinal lesions(24), as well as in the treatment of osteogenesis imperfecta (109) and juvenile osteoporosis (110, 111). *Zoledronate* has been effective in decreasing the risk of fractures in children with GC-induced osteoporosis in a recent RCT (112).

Avacopan, a targeted synthetic complement 5a receptor (C5aR) antagonist, is recommended by the recently published BSR guideline for use in active AAV across the whole life-course to minimise the GC toxicity (16), although the paediatric dose is not established (trials ongoing).

The toxicity profile of DMARDs and the recommendations regarding their use during conception, pregnancy and breastfeeding period, which may be relevant to older adolescents, have been reviewed recently (113).

Transplant therapy in refractory paediatric RMDs

Allogeneic HSCT (allo-HSCT) is mainly reserved for the treatment of severe monogenic autoinflammatory diseases refractory to conventional treatments, with or without associated immune deficiency. Examples with good outcomes include deficiency of adenosine deaminase 2 associated with immunodeficiency (114) and mevalonate kinase deficiency (115), amongst others. Overall there may be 10-20% mortality from the procedure, and outcomes are more favourable with good donor HLA match, limiting availability for some patients.

In JIA, allo-HSCT is mainly used for refractory sJIA (116), usually relapsing MAS (with or without refractory arthritis), or lung disease (117). Results are encouraging, albeit with the aforementioned burden of morbidity associated with the procedure.

Autologous HSCT may still be considered for refractory non-systemic JIA (118), but is used less frequently in view of the emergence of newer drugs.

Emerging treatments in paediatric rheumatology

There are currently many ongoing clinical trials in paediatric rheumatology, testing many of the therapies that have been developed or already proven successful in adult trials for corresponding rheumatological indications. We summarised in **Table 4**, all the treatments that are currently evaluated in paediatric clinical trials as available on the https://clinicaltrials.gov website as of 16th June 2025, including the indications for which they are tested, and the trial design and dose regimens explored. There is a plethora of bDMARDs and tsDMARDs currently explored in paediatric trials, in addition to new cell therapies, with the outcome of chimeric antigen receptor T cell-based (CAR-T) therapies being probably the most eagerly awaited as they hold the promise of resetting the immune system and leading to disease cure. The majority of the clinical trials for bDMARDs and tsDMARDs are phase III clinical trials, with a minority of head to head paediatric clinical trials comparing TNFi with IL-17 and IL-23 blockade for treatment of ERA/JPsA.

Ianalumab is the only monoclonal antibodies with a dual mechanism of action, targeting both BAFF and causing B cell depletion through anti body-dependent cellular cytotoxicity is currently tested in children with active cSLE, while T cell engagers (CD19/CD3) are currently used in children with B-cell lineage malignancies in children (119) and are currently tested in adults with SLE.

The eagerly awaited clinical trials investigating the efficacy of *CD19- CAR-T cell based therapies* can offer children the opportunity to achieve long-term remission in various RMDs (8), although characterisation of larger cohorts of individuals undergoing this type of treatment will provide the ultimate answer regarding their long-term efficacy and safety (120). Compared to haematological malignancies, CD19 CAR-T seems to be better tolerated as no severe incidence of cytokine release syndrome (CRS) or immune-effector-cell-associated neurotoxicity syndrome (ICANS) have been reported (121). Recently, a new type of self-limiting adverse reaction has been described, affecting 77% individuals treated with CD19 CAR-T therapy, which will require further evaluation in larger cohorts (122).

The relatively high rate of relapse 12-24 month post CD19 CAR-T therapy in haematological malignancies (123), as well as the variable proportion of children achieving long-term remission off treatment with autologous or allogeneic transplant, associated with a more profound resetting of the immune system (124, 125) may suggest that achieving a permanent cure with CD19 CAR-T therapy in RMDs has relatively limited biological plausibility, although the preliminary reports of

outcomes of young people with SLE are very encouraging (126). Efforts to develop allogeneic CD19 CAR-T therapy may increase accessibility and decrease the costs in the future (127).

Several new therapies are currently tested in adult RMDs, and may be investigated in paediatric disease in the future: *atacicept and talitacicept*, TACI (transmembrane activator and calcium modulator and cyclophilin ligand interactor) recombinant fusion proteins that block both BAFF and APRIL (a proliferation-inducing ligand) are currently trialled in SLE, LN and IgA-related nephropathy in adults; *ofatumumab* (human mAb anti CD20) has been found efficacious in phase III trials in adult LN, and has been used off-label with success in cSLE (128); *brepocitinib* (TYK2 and JAK1 inhibitor) was used off-label with success in refractory DM; *ibrutinib, elsubrutinib, remibrutinib* (Bruton tyrosine kinase-BTK inhibitors) and *iscalimab/dazodalibep* (anti-CD40mAb and anti-CD40L fusion protein) were associated with signals of efficacy in trials of adult SLE and SjD; *nipocalimab/efgartigimod* (anti-neonatal Fc receptor (FcRn) mAb that reduces circulating IgG) was associated with efficacy in preliminary studies in adult SLE/SjD.

The research advances in understanding the pathogenesis of monogenic lupus have open the possibility of new treatments, such as analogues of DNase1L3 (e.g. *NTR-441*, the first in class DNASE1L3 enzyme analogue), *myeloid differentiation factor 88 (MyD88) inhibitors* (129), as well as *phosphoinositol 3 kinase (PI3K) and mTOR inhibitors* (130), associated with therapeutic success in paediatric cases of LN (131). Defects of endosomal nucleic acid sensing, associated with gain of function TRL7/9 mutations leading to cSLE-type phenotypes in children usually younger than 5 years, broadly defined as TLRopathies can be manipulated therapeutically by *TLR7/8 inhibition* (132). Genetic abnormalities of the intracytoplasmic innate sensors, such retinoic acid-inducible gene-I (RIG-I) and melanoma differentiation-associated protein 5 (MDA5) (RNA sensors), or cyclic GMP-AMP synthase (cGAS) that binds STING leading to the SAVI (Sting Associated Vasculopathy with Onset in Infancy) phenotype associated with cSLE features (DNA sensor) can potentially be treated with JAKi (133), or *STING/cGAS inhibitors* (134).

Although not currently tested in trials in children, the IL-18 inhibition (e.g. with *Tadekinig alfa*, which is a recombinant IL-18 binding protein) has been investigated in severe autoinflammatory conditions characterized by IL-18 dysregulation. *Tadekinig alfa* is currently tested in Adult Still's Disease (135) and has been used in compassionate settings for children with certain genetic mutations involving IL-18 signalling pathway, and if proven efficacious in clinical trials, could be added in the future to the therapeutic armamentarium for Still's Disease in children.

Holistic and personalised care in paediatric rheumatology

Although this review has been focused on pharmacological interventions in paediatric rheumatology, we acknowledge the importance of non-pharmacological strategies, including physical and occupational therapy and exercise-based interventions, as well as psychological, behavioural, life-style and self-care strategies, underpinned by multidisciplinary, developmentally-appropriate and holistic approaches to address the complex physical, psychological, educational, vocational and social aspects of RMDs, and support children and young people live normal lives despite their conditions.

We recognise the emerging field of theragnostic, which aims to combine personalised diagnostic with the selection of the most appropriate therapies. The theragnostic armamentarium with potential clinical utility in paediatric rheumatology comprises many genetic tests, serum biomarkers (with S100 proteins and cytokine profiling being the most used), imaging biomarkers, and validated outcomes measures describing well-defined disease states, in addition to therapeutic drug monitoring, pharmacogenomics, and pharmacokinetic/pharmacodynamic modelling, which can all help facilitate the 'molecular' diagnosis of various paediatric RMD phenotypes, predict individuals more likely to respond to a certain therapy, monitor disease activity and treatment response, and if appropriate, help guide tapering strategies, as reviewed elsewhere (136).

Conclusion

Clinicians and researchers in the field of paediatric rheumatology have witnessed the enormous progress that has been achieved in the last decades in expanding the pharmacological armamentarium used in the management of CYP with childhood-onset RMDs, which enabled unprecedented improvement in outcomes with broad societal benefit. Despite this, access to medications for children is still restricted in many parts of the world, which perpetuates health inequalities. Advances in genomics and precision medicine have facilitated early diagnosis and new therapeutic discoveries. However, the scarcity of approved therapeutic options, with evidence-based dosing regimens and established efficacy and safety in paediatric populations, highlights an ongoing unmet need. We advocate for accelerated approval of emerging paediatric therapies, facilitated by increased commitment to research, innovation and collaboration to match the progress seen in adult rheumatology. Pharmacological interventions should be integrated in a comprehensive care

approach, promoting children's overall health and wellbeing, ultimately aiming to preserve their quality of life and ensure their adequate access to high-quality healthcare they deserve.

Funding: CC is supported by the National Institute of Heath Research (NIHR) University College London Hospital (UCLH) Biomedical Research Centre (grant BRC4/III/CC).

Conflict of interest statement: CC has received institutional grants from GSK and consultancy fees from Novartis. PB has received institutional grants and/or consultancy fees from SOBI, Novartis, and Roche. MS has received speaker fees from SOBI, Abbvie, and Novartis. DE has declared no conflicts of interest.

Data availability statement: No new data were generated or analysed in support of this article.

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cDMARD/ Mechanism of action/ Type of molecule	Clinical indications the treatment is licensed for in children	Off-license use in children	Dosage recommendation	Side-effects
Methotrexate Folic acid antagonist	pJIA, ≥2 years of age *Metoject* (subcutaneous formulation) is licensed from age 3.	Childhood psoriasis, Crohn's disease, other forms of JIA, JDM, localized scleroderma, AAV, sarcoidosis, cSLE.	10-15 mg/m²/week, orally or subcutaneous or intramuscularly. In refractory cases, the weekly dosage may be increased to 20 mg/m²/week. Recommended to be prescribed with folic/folinic acid supplementation.	Nausea, vomiting, diarrhoea, stomach pain, mouth sores or ulcers, hair loss or thinning, headaches, dizziness, tiredness or fatigue, loss of appetite, increased sensitivity to sunlight. Serious side-effects: Liver damage (including cirrhosis), lung problems (such as inflammation or fibrosis), kidney damage (potentially leading to kidney failure), bone marrow suppression, severe skin reactions (like Stevens-Johnson syndrome), severe allergic reactions (anaphylaxis), increased risk of certain cancers, such as lymphoma.Contraindicated during conception, pregnancy, and breastfeeding
Leflunomide Pyrimidine synthesis inhibitor	Not licensed	Used off-license as alternative to methotrexate.	**pJIA**: loading dose to 100 mg daily for 3 days, followed by 10 mg/1.73 m²/day, which can be increased to 20 mg/1.73 m²/day, up to a max dose of 20 mg daily. It can be used either as monotherapy or in combination with methotrexate.	Diarrhoea; nausea, abdominal pain; hair loss; decrease in appetite/weight loss; rash, hypertension, asthenia; mouth ulcers; headache; hypersensitivity;;, abnormal liver function tests; lung involvement: bone marrow suppression; neuropathy; Contraindicated during conception, pregnancy, and breastfeeding. Washout recommended in the context of severe side-effects.
Sulfasalazine Anti-inflammatory and immunomodulatory effects, by inhibiting TNF-α expression, leukocyte accumulation and B cell function	pJIA (≥ 6 years of age) UC (≥ 2 years of age)	Crohn's disease.	**JIA**: Initial 10mg/kg/day, increase weekly by 10mg/kg/day, usual doses: 30-50 mg/kg/day in 2 divided doses, maximum dose: 2g/day. **UC**: 30 mg/kg/day divided into 4 doses.	Headache; loss of appetite; rash; itching; fever; increased sensitivity to sunlight; orange-yellow discoloration of urine, sweat, or tears (which can also stain soft contact lenses), dizziness; low sperm count in men (this is usually reversible upon stopping the medication); liver abnormalities; blood disorders. Rare: agranulocytosis.
Hydroxychloroquine Antimalarial	Treatment and prophylaxis of malaria	JIA (in combination with other therapies),	≥ 31 kg: 5 mg/kg based on ideal body weight up to 400 mg, once a day.	Nausea; vomiting; diarrhoea; stomach pain; headache; dizziness; hair loss; rash; itching; skin discoloration (blue-black or gray); tinnitus; loss of appetite; ocular toxicity; vomiting;

immunomodulatory and anti-inflammatory agent		discoid lupus, cSLE, APS, cSjD.		acute hepatic failure; agranulocytosis; QT interval prolongation.
Mycophenolate mofetil Antimetabolite immunosuppressant	Prophylaxis of organ rejection in paediatric recipients (≥ 3 months of age) and older of allogeneic kidney, heart or liver transplants.	AAV, severe and/or MTX-refractory juvenile localized scleroderma, cSLE, LN, systemic sclerosis, , for primary systemic vasculitides.	**SLE/PAN**: 600 mg/m²/day (max. 1 g/day) for the first week, followed by 1,200 mg/m²/day (maximum 2 g/day) in 2 divided doses. **Kidney transplant**: 600 mg/m2 orally twice daily, up to max. of 2 g daily **Liver transplant:** 600 mg/m2 orally twice daily up to max. of 900 mg/m BD (3 g or 15 mL of oral suspension).	Diarrhoea; nausea; vomiting; stomach pain; headache; dizziness; fatigue; weakness; loss of appetite; rash; hair loss; high blood pressure; increased risk of severe infections; bone marrow suppression; liver damage; gastrointestinal bleeding or ulcers; an increased risk of certain cancers (such as lymphoma and skin cancer); progressive multifocal leukoencephalopathy (PML).Contraindicated during conception, pregnancy, and breastfeeding.
Azathioprine Purine antimetabolite	Prevention and treatment of rejection in solid organ transplantation.	cSLE, JIA, JIA-associated uveitis, autoimmune hepatitis, inflammatory bowel disease, myasthenia gravis, LN, immune thrombocytopenia, AIHA, , for primary systemic vasculitides.	1-2.5 mg/kg/day, single dose or a twice-daily schedule, maximum 200 mg/day.	Nausea; vomiting; diarrhoea; stomach pain; bone marrow suppression (leading to low white blood cell counts, anaemia, and low platelets); increased risk of severe infections; hepatotoxicity; pancreatitis; flu-like symptoms; rash; hair loss; and an increased risk of skin cancer and lymphoma.
Tacrolimus Calcineurin-inhibitor	Systemic Prophylaxis of organ rejection patients receiving allogeneic liver, kidney, heart, or lung transplant, with other immunosuppressants. Topical use - severe atopic dermatitis (0.03% ointment in ages ≥ 2	Systemic: LN, refractory nephrotic syndrome, IgA vasculitis nephritis, Crohn disease, Graft-versus-host disease, myasthenia gravis. Topical: active plaque morphoea, cutaneous cSLE.	0.15- 0.3 mg/kg/day, divided in two doses, every 12 hours. Target blood trough concentration: 5-20 ng/mL, 12 hours after dose.	Nephrotoxicity; hepatotoxicity; neurotoxicity (tremor, headache, paraesthesia, seizures); hyperglycaemia; hypertension; hyperkalaemia; gastrointestinal symptoms (diarrhoea, nausea, vomiting, abdominal pain); alopecia; rash; insomnia; an increased risk of severe infections; and an increased risk of malignancy, particularly post-transplant lymphoproliferative disorder (PTLD).

	years; 0.1% ointment in ages ≥ 16 years);			
Ciclosporin Calcineurin-inhibitor	Solid organ transplantation; bone marrow transplantation, endogenous uveitis, nephrotic syndrome, severe psoriasis, severe atopic dermatitis	LN, JIA, JIA-associated uveitis, MAS, relapsed/refractory AIHA and refractory Kawasaki disease.	2-4 mg/kg/day in 2 divided doses, gradually increased to a maximum dose 6 mg/kg/day. **Nephrotic syndrome**: 6 mg/kg/day in 2 divided oral doses.	Nephrotoxicity; hypertension; hyperkalaemia; hyperuricemia; hepatotoxicity; gingival hyperplasia; hirsutism; neurotoxicity (e.g., headache, tremor, seizures, encephalopathy); increased susceptibility to infections; an increased risk of malignancy (particularly lymphoma and skin cancer); dyslipidaemia; gastrointestinal disturbances (e.g., nausea, vomiting, diarrhoea, abdominal pain); hypomagnesemia; and myalgia.
Etoposide Topoisomerase II inhibitor	Not licensed	HLH/MAS	50-150 mg/m2/dose 1-2 doses per week	Myelosuppression (leading to neutropenia, leukopenia, thrombocytopenia, and anaemia); gastrointestinal toxicity (including nausea, vomiting, stomatitis, mucositis, and anorexia); alopecia; hepatotoxicity; asthenia; hypersensitivity reactions (anaphylaxis); peripheral neuropathy; hypotension or hypertension; and an increased risk of secondary malignancies (acute myeloid leukaemia).
Cyclophosphamide Alkylating agents	Minimal change nephrotic syndrome in paediatric populations, malignant lymphomas.	Proliferative LN, neuropsychiatric lupus, primary systemic vasculitides, primary central nervous system vasculitis, JDM with severe extra-muscular or refractory disease or major organ involvement, juvenile SSc - related ILD, early diffuse cutaneous SSc with poor prognosis.	**Nephrotic syndrome:** 2 mg/kg/day oral dose for 8 to 12 weeks (maximum cumulative dose 168 mg per kg). **LN** (Low-dose - Euro-Lupus regimen): 300-500 mg/m^2, IV maximum dose 500 mg, every 2 weeks for 6 doses. **Organ- or life-threatening disease** (High-dose - NIH protocol): 0.75- 1 g/m^2 /month IV (maximum 1g) for 6 months.	Nausea and vomiting; myelosuppression (leukopenia, anaemia, thrombocytopenia); alopecia; haemorrhagic cystitis; mucositis; stomatitis; amenorrhea; azoospermia; anorexia; asthenia; diarrhoea; abdominal pain; Cardiotoxicity (myocarditis, pericarditis, congestive heart failure); pulmonary toxicity (interstitial pneumonitis, pulmonary fibrosis); secondary malignancies (e.g., leukaemia, bladder cancer); infertility (permanent or temporary); veno-occlusive liver disease; anaphylaxis; severe skin reactions (e.g., Stevens-Johnson syndrome).Contraindicated during conception, pregnancy, and breastfeeding.

			AAV (CYCLOPS regime): 15 mg/kg IV every 2 weeks for 3 pulses, then every 3 weeks for 7 pulses. **JDM**: 500-1000mg/m^2 monthly IV for 6 months. **Juvenile SSc with ILD**: 500mg/m^2 IV followed by monthly 750mg/m^2 for 6 months then every 2 months. **PAN**: 500 mg/m^2 for first dose, IV then increase to 750 mg/m^2/day (maximum dose 1.2 g) at weeks 0, 2, and 4 and then every 3 weeks until remission, (maximum 10 IV doses and minimum 6 doses).	

Table 1. Conventional DMARDs used in paediatric RMDs

Legend: AAV – ANCA-associated vasculitis; AIHA- autoimmune haemolytic anaemia; ANCA – anti-neutrophil cytoplasmic antibodies; APS- antiphospholipid syndrome; BSA - body surface area; cSLE - childhood-onset Systemic Lupus Erythematosus; HLH - hemophagocytic lymphohistiocytosis; JDM – juvenile dermatomyositis; ILD - interstitial lung disease; LN- lupus nephritis; MAS - macrophage activation syndrome; MTX – methotrexate; NIH – National Institute of Health; PAN - polyarteritis nodosa; pJIA – polyarticular juvenile idiopathic arthritis; SSc - systemic sclerosis; UC – ulcerative colitis.

bDMARDs	Mechanism of action	Clinical indications the treatment is licensed for in children	Off-license use in children	Dosage recommendation
TNF-α blockade				
Adalimumab	Human monoclonal antibody against TNF-α	pJIA (≥ 2 years) ERA (≥ 6 years) Uveitis (≥ 2 years) Crohn's disease (≥ 6 years)	Severe/refractory JDM, sarcoid, CRMO	**JIA**: 10 mg EOW (10 to <15 kg) 20 mg EOW (15 to <30 kg) 40 mg EOW (≥30 kg) **Crohn's disease**: Initial Doses: 80 mg on Day 1, then 40 mg 2 weeks later (17 to <40 kg) 160mg on Day 1, then 80 mg 2 weeks later (≥40 kg) Maintenance Dose: 20 mg EOW (17 to <40 kg); 40 mg EOW (≥40 kg)
Etanercept	Soluble TNFα receptor fusion protein	pJIA (≥ 2 years) JPsA (≥ 2 years) ERA (≥ 12 years) Plaque psoriasis (≥ 4 years)	N/A	0,4 mg/kg x2/ Week 0.8 mg/kg EW 50 mg EW
Infliximab	Chimeric monoclonal antibody against TNF-α	Crohn's Disease (≥ 6 years) Ulcerative Colitis (≥ 6 years)	pJIA, sarcoid, uveitis, JDM	5-10 mg/kg IV as an induction regimen at 0, 2 and 6 weeks, followed by a maintenance regimen of 5-10 mg/kg Q8W
Golimumab	Human monoclonal antibody against TNF-α	pJIA (≥ 2 years) JPsA ((≥ 2 years)	N/A	50 mg Q4W
Co-stimulatory blockade				
Abatacept	Human CTLA4 fusion protein co-stimulatory blockade	Licensed for pJIA (≥ 2 years)	Severe/refractory JDM	< 75 kg: 10 mg/kg IV at 0-2-4 weeks and Q4W thereafter > 75 kg, adult doses are recommended: 60 kg - 100 kg - 750 mg More than 100 kg - 1,000 mg
IL-1 blockade				
Anakinra	Human recombinant IL-1 receptor antagonist	CAPS, FMF, Still's disease from 8 months of age and weighing at least 10 kg	N/A	< 50 kg: 1-2mg/kg/day SC >50 kg: similar to adult doses, 100 mg daily Severe CAPS: 3-4 mg/kg/day, which can be adjusted to a maximum of 8 mg/kg/day

	IL-1β and IL-1α blockade			
Canakinumab	Human monoclonal antibody anti IL-1β	Still's Disease (≥ 2 years) CAPS (≥4 years) TRAPS - adult and paediatric patients MKD - adult and paediatric patients FMF- adult and paediatric patients	N/A	**Still's Disease (SoJIA)**: ≥ 7.5 kg: 4 mg/kg (maximum dose of 300 mg) SC Q4W **CAPS**: > 40 kg: 150 mg subcutaneously, every 8 weeks. ≥ 15 kg and ≤ 40 kg: 2 mg/kg SC Q8W. 15 kg to 40 kg with an inadequate response, the dosage can be increased to 3 mg/kg SC Q8W. **TRAPS, HIDS/MKD, and FMF**: > 40 kg: 150-300 mg subcutaneously, Q4W. ≤ 40 kg: 2-4 mg/kg SC Q4W
Rinolacept	Dimeric fusion protein of human IL-1 receptor (IL-1R1) and IL-1 receptor accessory protein (IL-1RAcP) IL-1β and IL-1α blockade	Licensed for CAPS (≥12 years)	N/A	Loading dose of 4.4 mg/kg, up to a max. 320 mg SC Then 2.2 mg/kg, up to a maximum of 160 mg SC EW
IL-6 blockade				
Tocilizumab	Human monoclonal antibody anti IL-6 receptor	Licensed for: Still's Disease (≥ 2 years pJIA (≥ 2 years)	Severe juvenile systemic sclerosis, JDM.	**pJIA**: <30 kg: 10 mg/kg IV Q4W 162 mg SC Q3W ≥ 30kg: 8 mg/kg IV Q4W 162 mg SC Q2W **Still's**: <30 kg: 12 mg/kg IV Q2W 162 mg SC Q2W ≥30kg: 8 mg/kg IV Q2W 162 mg SC EW
IL-17 blockade				
Secukinumab	Human monoclonal antibody anti IL-17A	ERA (≥ 4 years) JPsA (≥ 2 years) Plaque psoriasis (≥ 6 years)	N/A	**ERA, JPsA, Plaque psoriasis**: ≥15 kg and < 50 kg: 75 mg SC ≥ 50 kg: 150 mg SC Weeks 0,1, 2, 3, and 4 and then Q4W

Ixekizumab	Human monoclonal antibody anti IL-17A	Plaque psoriasis (≥ 6 years)	JPsA	> 50 kg: 160 mg SC (two 80 mg injections) at Week 0, then 80 mg Q4W 25-50 kg: 80 mg SC at Week 0, then 40 mg Q4W <25 kg: 40 mg SC at Week 0, then 20 mg Q4W
IL12/23 blockade				
Ustekinumab	Human monoclonal antibody anti IL-12 and IL-23 (p40)	JPsA (≥ 6 years) Plaque psoriasis (≥ 6 years)	N/A	<60 kg: 0.75 mg/kg SC at Weeks 0, 4 and then Q12W 60-100 kg: 45 mg SC at Weeks 0, 4 and then Q12W >100 kg: 90mg SC at Weeks 0, 4 and then Q12W
INF blockade				
Emapalumab	Human monoclonal antibody anti IFNγ	Licensed for: - Newborn and older children with primary HLH with refractory, recurrent or progressive disease or intolerance with conventional HLH therapy (FDA approval) - MAS in Still's disease with an inadequate response or intolerance to glucocorticoids, or with recurrent MAS (FDA approval)	N/A	**HLH**: Starting dosage: 1 mg/kg as an IV infusion over 1 hour twice per week (every three to four days) **Still's Disease and MAS**: 6 mg/kg load; then 3 mg/kg every 72h Can increase to 10 mg/kg every 72h if required.
CD20 blockade				
Rituximab	Chimeric monoclonal antibody anti CD20	GPA (≥ 2 years) MPA (≥ 2 years) Mature B-cell NHL (≥ 6 months) Mature B-cell acute leukaemia (≥ 6 months)	pJIA, refractory/severe cSLE, JDM, systemic sclerosis, cSjD, monogenic lupus, refractory HLH/MAS	**GPA and MPA**: The induction dose, in combination with glucocorticoids: 375 mg/m^2 IV weekly for 4 weeks The follow up dose, in combination with glucocorticoids: two 250 mg/m^2 IV infusions separated by two weeks, followed by a 250 mg/m^2 IV infusion every 6 months thereafter based on clinical evaluation **pJIA** 375 mg/m^2 IV infusion x2, 2 week apart per course
BAFF blockade				
Belimumab	Human monoclonal antibody anti-BAFF	cSLE (≥ 5 years) Lupus nephritis (≥ 5 years) Limitations of Use: The efficacy of Belimumab has not been evaluated in patients with severe active CNS lupus	cSjD with glandular manifestations, monogenic lupus	IV: 10 mg/kg at 2-week intervals for the first 3 doses and then Q4W SC: ≥ 40kg, 200 mg EW SC: 15- 40kg, 200mg E2W

Biosimilars				
Etanercept-SZZS **Etanercept-YKRO** **Benepali** **Nepexto**	Soluble TNFα receptor fusion protein	JIA (pJIA, extended oligoarthritis, JPsA, ERA) - (≥ 2 years) Plaque psoriasis(≥ 6 years)	N/A	0.8 mg/kg EW, maximum dose 50 mg per week
Adalimumab-ADAZ **Adalimumab- ATTO** **Adalimumab- AACF** **Adalimumab- FKJP** **Adalimumab-AATY** **Adalimumab- AFZB**	Human monoclonal antibody against TNF-α	pJIA (≥ 2 years) ERA (≥ 6 years) Uveitis (≥ 2 years) Crohn's disease (≥ 6 years)		**JIA**: 10 mg EOW (10 to <15 kg) 20 mg EOW (15 to <30 kg) 40 mg EOW (≥30 kg) **Crohn's disease**: Initial Doses: 80 mg Day 1, then 40 mg 2 weeks later (17 to <40 kg) 160mg on Day 1, then 80 mg 2 weeks later (≥40 kg) Maintenance Dose: 20 mg EOW (17 to <40 kg); 40 mg EOW (≥40 kg)
Infliximab-AXXO **Infliximab-DYYB** **Infliximab-QBTX** **Infliximab-ABDA**	Chimeric monoclonal antibody against TNF-α	Crohn's Disease (≥ 6 years) Ulcerative Colitis (≥ 6 years)	pJIA, sarcoid, uveitis, JDM	5 mg/kg IV as an induction regimen at 0, 2 and 6 weeks, followed by a maintenance regimen of 5 mg/kg Q8W.
Rituximab-ABBS **Rituximab-PVVR** **Rituximab-ARRX**	Chimeric monoclonal antibody anti CD20	GPA (≥ 2 years) MPA (≥ 2 years) Mature B-cell NHL (≥ 6 months) Mature B-cell acute leukaemia (≥ 6 months)	pJIA, refractory/severe cSLE, JDM, systemic sclerosis, cSjD, monogenic lupus, refractory HLH/MAS	**GPA and MPA**: The induction dose, in combination with glucocorticoids: 375 mg/m^2 IV weekly for 4 weeks The follow up dose, in combination with glucocorticoids: two 250 mg/m^2 IV infusions separated by two weeks, followed by a 250 mg/m^2 IV infusion every 6 months thereafter based on clinical evaluation. **pJIA** 375 mg/m^2 IV infusion x2, 2 week apart per course.
Tocilizumab-ANOH **Tocilizumab-BAVI** **Tocilizumab- AAZG**	Human monoclonal antibody against IL-6 receptor	Licensed for: Still's Disease (≥ 2 years) pJIA (≥ 2 years)	Severe/refractory JDM	**pJIA**: <30 kg: 10 mg/kg IV Q4W 162 mg SC Q3W ≥ 30kg: 8 mg/kg IV Q4W

				162 mg SC Q2W **Still's Disease**: <30 kg: 12 mg/kg IV Q2W 162 mg SC Q2W ≥30kg: 8 mg/kg IV Q2W 162 mg SC EW
Other therapies				
Intravenous immunoglobulins (IVIG), 10%		Replacement therapy (0-18 years) in: - Primary humoral immunodeficiencies (PID) - Secondary Immunodeficiency Syndromes (SID)- severe/recurrent infections, ineffective antimicrobial treatment and either proven specific antibody failure or serum IgG level of <4 g/l Immunomodulation (0-18 years) in: - Primary immune thrombocytopenia (ITP) - Guillain-Barré syndrome - Kawasaki disease - Chronic inflammatory demyelinating polyneuropathy (CIDP) - Multifocal motor neuropathy (MMN)	Rapidly progressive/refractory JDM.	**PID**: Starting dose: 0.4–0.8 g/kg, Maintenance dose: 0.2- 0.8 g/kg every 3–4 weeks. **SID** –0.2- 0.4 g/kg, every 3 – 4 weeks. **ITP**: There are two alternative treatment schedules: - 0.8 to 1g/kg given on day 1; this dose may be repeated once within 3 days - 0.4 g/kg given daily for 2 to 5 days. **Guillain-Barré syndrome:** 0.4 g/kg bw/day over 5 days Kawasaki disease: 2 g/kg as a single dose; in association with acetylsalicylic acid. **CIDP**: 2g/kg divided over 2 to 5 consecutive days followed by maintenance doses of 1 g/kg over 1 to 2 consecutive days every 3 weeks. **MMN**: Starting dose: 2 g/kg given over 2-5 consecutive days. Maintenance dose: 1 g/kg every 2 to 4 weeks or 2 g/kg every 4 to 8 weeks.
Iloprost	Synthetic prostacyclin analogue	Not licensed in children	Idiopathic or familial pulmonary arterial hypertension (PAH) and Raynaud's	**PAH** (8-17 years): Initially 2.5 micrograms for 1 dose, increased to 5 micrograms for 1 dose, increased if tolerated to 5 micrograms 6–9 times a day, adjusted according to response; reduced if not tolerated to 2.5 micrograms 6–9 times a day, reduce to lower maintenance dose if high dose not tolerated. **Raynaud's** (12-17 years): Initially 0.5 nanogram/kg/minute, increased to 1–2 nanograms/kg/minute given over 6 hours daily for 3–5 days, dose increase should be performed gradually.

Table 2: Biologic DMARDs and biosimilars licensed for use in children.

Legend: CAPS – Cryopyrin-Associated Periodic Syndromes; CNS – central nervous system; CTLA4 - cytotoxic T-lymphocyte-associated antigen 4; EMA – European Medicines Agency; EOW – every other week; EW – every week; FDA – Food and Drug Administration, USA; FMF – Familial Mediterranean Fever; GPA – Granulomatosis with Polyangiitis; HLH - hemophagocytic lymphohistiocytosis; IV – intravenously; JIA – Juvenile Idiopathic Arthritis; JPsA – juvenile psoriatic arthritis; MAS – macrophage activation syndrome; MKD – Hyperimmunoglobulin D Syndrome (HIDS)/Mevalonate Kinase Deficiency; MPA – Microscopic Polyangiitis; SC – subcutaneously; TRAPS – Tumour Necrosis Factor Receptor (TNF) Associated Periodic Syndrome; pJIA – polyarticular juvenile idiopathic arthritis; Q4W- every 4 weeks; Q8W- every 8 weeks; Q12W – every 12 weeks.

Synthetic targeted small molecules Mechanism of action/type of molecule	Clinical indications the treatment is licensed for in children	Off-license use in children	Dosage recommendation	Side-effects
Tofacitinib JAK 1/3 inhibition	pJIA or JPsA (≥ 2 years of age)	Refractory JDM Moderate/severe alopecia areata Refractory uveitis/scleritis	• 10 kg ≤ body weight < 20 kg: 3.2 mg (3.2 mL oral solution) twice daily. • 20 kg ≤ body weight < 40 kg: 4 mg (4 mL oral solution) twice daily. • Body weight ≥ 40 kg: 5 mg (one 5 mg tablet or 5 mL oral solution) twice daily.	Described more in JIA: Abdominal pain; anaemia; cough; fever; gastrointestinal disorders; headache influenza; joint disorders; nausea; pharyngitis; vomiting. Described in all ages: increased risk of infection; diarrhoea; dyspepsia; fatigue; sinusitis; skin reactions; hypertension. Contraindicated during conception, pregnancy, and breastfeeding.
Baricitinib JAK 1/2 inhibition	pJIA (RF+ or RF-) Extended oligoJIA ERA or JPsA Moderate/severe alopecia areata (≥ 2 years of age).	Refractory/severe JDM Autoinflammatory interferonopathies	**JIA** 10-30 kg: 2mg/day once daily. ≥ 30kg: 4mg/day once daily. **Monogenic interferonopathies** <20Kg: 2mg 4 times a day. 20-40Kg: 4 mg twice daily. >40Kg: 6 mg am, 4 mg pm (10 mg/day).	Abdominal pain; dyslipidaemia; headache; herpes zoster (interrupt treatment); increased risk of infection; nausea; skin reactions; thrombocytosis. Dose reduction is required if GFR <120 ml/min/1.73m^2. Contraindicated during conception, pregnancy, and breastfeeding.
Upadacitinib Selective JAK 1 inhibition	Active pJIA, JPsA (≥ 2 years of age) Refractory, moderate/severe atopic dermatitis, (≥ 12 years of age)	N/A	**pJIA/JPsA** 10 kg to less than 20 kg- 3 mg (3 mL oral solution) twice daily. 20 kg to less than 30 kg- 4 mg (4 mL oral solution) twice daily. 30 kg and greater - 6 mg (6 mL oral solution) twice daily. **Atopic Dermatitis** Body weight ≥ 40 kg -15 mg once daily.	Abdominal pain; anaemia; cough; dyslipidaemia; fatigue; fever; headache; increased risk of infection; lymphopenia; nausea; neoplasms; neutropenia; skin reactions; weight gain. Contraindicated during conception, pregnancy, and breastfeeding.

			If an adequate response is not achieved, the dose may be increased to 30 mg once daily.	
Apremilast Phosphodiesterase type-4 inhibitor	Paediatric psoriasis, (≥ 6 years of age and above 20kg)	JPsA Ulcers associated with BD	20 mg twice daily for those weighing 20 kg to <50kg. 30 mg twice daily for those weighing 50 kg or more.	Headache, diarrhoea, stomach pain; vomiting; weight loss; signs of a common cold; back pain; joint pain; allergic reactions; increased risk of infection; insomnia. Contraindicated during conception, pregnancy, and breastfeeding.
Dapaglifozin SGLT-2 inhibitor	Type II diabetes	LN	10 mg daily From age 10 years	Contraindicated in ketoacidosis; back pain; cystitis; dizziness; dyslipidaemia; hypoglycaemia (in combination with insulin or sulfonylurea); increased risk of infection; prostatitis; skin reactions; urinary and vulvovaginal disorders. The treatment should be discontinued when pregnancy is detected, not recommended for the 2nd and 3rd trimester of pregnancy.
Other treatments used off-license in paediatric rheumatology				
Pilocarpine Muscarinic receptor agonist (M1, M2, M3)	Not licensed in children	cSjD with symptoms of dryness	5 mg daily, increased to twice/three times daily based on effect and tolerability	Diarrhoea; headache; hyperhidrosis; hypersalivation; nausea; skin reactions; vision disorders; vomiting. Risk in pregnancy not known.
Sildenafil Phosphodiesterase type 5 (PDE-5) inhibitor	Pulmonary hypertension from 1 month of age	Severe Raynaud's Digital ulcers	Child 1–17 years (body-weight up to 20 kg) 10 mg 3 times a day. Child 1–17 years (body-weight 20 kg and above) 20 mg 3 times a day.	Alopecia; anaemia; anxiety; cough; diarrhoea; dizziness; fluid retention; gastrointestinal discomfort; gastrointestinal disorders; headaches; increased risk of infection; insomnia; nasal complaints; nausea; night sweats; pain; skin reactions; tremor; vasodilation; vision disorders
Bosentan Dual endothelin receptor antagonist	Pulmonary hypertension from 1 month of age	Severe Raynaud's Digital ulcers	Child 2–17 years (body-weight 10–20 kg) Initially 31.25 mg once daily for 4 weeks, then increased to 31.25 mg twice daily. Child 2–17 years (body-weight 20–40 kg) Initially 31.25 mg twice daily for 4 weeks, then increased to 62.5 mg twice daily.	Anaemia; abnormal liver function tests; diarrhoea; erythema; fluid retention; flushing; gastro-oesophageal reflux disease; headache; hypotension; nasal congestion; oedema; palpitations; syncope; leukopenia; neutropenia; thrombocytopenia;

			Child 12–17 years (body-weight 40 kg and above) Initially 62.5 mg twice daily for 4 weeks, then increased to 125 mg twice daily (max. per dose 250 mg).	angioedema; abdominal pain; fever; increased risk of infection; pulmonary oedema; vision blurred; vomiting. Contraindicated during conception, pregnancy, and breastfeeding.
Pamidronate **Zolendronate** Bisphosphonates, synthetic analogues of pyrophosphate, which are adsorbed onto hydroxyapatite with role in reducing the rate of bone turnover	Not licensed for use in children	CRMO Low bone density and fractures, as well as osteogenesis imperfecta	Pamidronate: 15–60 mg IV, as a single infusion or in divided doses over 2–4 days, dose adjusted according to body weight; maximum 90 mg per course. Most experience in CRMO – 1 mg/kg, max 60 mg per dose monthly or 1 mg/kg/dose, 3 consecutive days, every 3 months Zolendronate: initial 0.0125-0.025mg/kg/dose every 6 months, can be increased to 0.05mg/kg/dose (max 4 mg) (dependent on age) for CRMO, osteogenesis imperfecta and juvenile osteoporosis	Hypocalcaemia; flu-like symptoms; alopecia; anaemia; appetite decreased; arthralgia; constipation; diarrhoea; dizziness; dysphagia; electrolyte imbalance; eye inflammation; fever; gastritis; gastrointestinal discomfort; headache; influenza like illness; malaise; myalgia; nausea; oesophageal ulcer (discontinue); oesophagitis (discontinue); pain; peripheral oedema; renal impairment; skin reactions; taste altered; vomiting. Where exposure has occurred, either prior to or during pregnancy, skeletal development and neonatal calcium levels may be warranted.
Avacopan Complement 5a receptor (C5aR) antagonist	Not licensed for use in children	To be considered in active AAV (off-license) to reduce GC-toxicity	Dose recommended in adults with AAV: 30 mg BD Paediatric trial ongoing.	Abdominal pain upper; abnormal liver function tests; diarrhoea; headache; increased risk of infection; leukopenia; nausea; neutropenia; vomiting; angioedema. Contraindicated during conception, pregnancy, and breastfeeding.

Table 3: Targeted synthetic DMARDs and other small molecules

Legend: BD - Behçet's Disease; CRMO – chronic recurrent multifocal osteomyelitis; cSjD - childhood-onset Sjogren's Disease; ERA – enthesitis related arthritis; JDM – juvenile dermatomyositis; JPsA – juvenile psoriatic arthritis; pJIA – polyarticular juvenile idiopathic arthritis; PsA – psoriatic arthritis; SGLT-2 - sodium-glucose cotransporter-2

Interventional medicinal product being tested	Mechanism of action	Trial registration reference	Phase	Indication	Paediatric population/dose regimens tested
cDMARDs vs. standard of care					
Voclosporin VOCAL	Calcineurin inhibitor	NCT05288855 (completed)	Phase III	Lupus nephritis.	12 to 18 years Different doses are tested: 15.8 mg BID, 23.7 mg BID and 31.6 mg BID, in addition to standard of care with mycophenolate mofetil and steroids.
Voclosporin VOCAL -EXT	Calcineurin inhibitor	NCT05962788	Extension study Phase III	Lupus nephritis.	As per dose decided by the VOCAL study.
Small molecules vs. standard of care					
Apremilast	PDA4 inhibition	NCT04804553 NCT05767047	Phase III Phase III	Active JPsA with inadequate response/intolerance ≥ one DMARD (including bDMARDS). JPsA associated with oral ulcers.	5 to < 18 years No data available regarding the study dose/s.
Avacopan	Complement 5a receptor (C5aR) antagonist	NCT06321601	Phase III	Active ANCA-associated vasculitis (AAV) Treatment used in combination with a rituximab or a cyclophosphamide-containing regimen.	6 years to < 18 years of age.
Bariticinib (JUVE-BASIS)	JAK 1/2 inhibition	NCT03773978 (completed)	Phase III	Active JIA (polyarticular, extended oligoarticular, enthesitis-related JIA, JPsA) with an inadequate response to at least one conventional or biologic DMARD.	2 years to less than 18 years 2 mg QD for children <9 years of age 4 mg QD for adolescent participants (12 to <18 years of age) and children ≥9 years of age.
Baricitinib	JAK 1/2 inhibition	NCT03773965	Phase III	JIA patients including JPsA who have completed a previous baricitinib study (NCT03773978).	1 year to 18 years.
Baricitinib	JAK 1 inhibition	NCT04088396	Phase III	sJIA with at least 2 active joints.	1 year to less than 18 years No data available regarding the study dose/s.
Filgotinib	JAK 1 inhibition	NCT06222034	Phase I	JIA (polyarticular, extended oligoarticular, ERA, JPsA, sJIA with active arthritis without active systemic features or with stable active systemic features for at least 6 months).	8 years to 18 years old No data available regarding the study dose/s.
Deucravacitinib	TYK2 inhibitor	NCT06869551	Phase III	Active JPsA with inadequate response/intolerance ≥ one csDMARD and/or bDMARD.	5 years to 17 years old No data available regarding the study dose/s.
Upadacitinib (SELECT-YOUTH)	ATP-competitive JAK inhibitor	NCT03725007	Phase I	Polyarticular course JIA (rheumatoid factor-positive or rheumatoid factor-negative	2 years to 17 years No data available regarding the study dose/s.

				polyarticular JIA, extended oligoarticular JIA, or systemic JIA with active arthritis and without active systemic features).	
Monoclonal antibodies vs. standard of care					
Secukinumab	IL-17A blockade	NCT03769168	Phase III Extension study	JPsA/ERA patients included in the JUNIPERA trial. Long-term extension study.	Children and adults (≥2 years) Two dosing regimens studied, results under evaluation.
Ixekizumab	IL-17A blockade	NCT04527380	Phase III	Active JPsA or ERA. Active comparator adalimumab.	2 to 17 years W>50 kg - 80 mg SC Q4W, with a starting dose of 160 mg at Weeks 0, 4, 8 and 12; 25-50 kg- 40 mg SC Q4W 10-25 kg- 20 mg SC Q4W.
Ustekinumab U-POPS	IL-12/23 blockade	NCT05252533	Phase I	JPsA, paediatric psoriasis prescribed at a dose indicated by their clinician. PK study.	Children (≥5 to <12 years). Adolescents (≥12 to < 18 years). Dosing regimen needs to be determined in paediatric population.
Ustekinumab UNITED	IL-12/23 blockade	NCT05092269	Long-term extension study	JPsA patients who completed the dosing planned in the primary ustekinumab studies (CNTO1275CRD1001/PUC3001/CRD3004/ JPA3001).	2 to <18 years of age. No data available regarding the study dose/s.
Ustekinumab OR Guselkumab PSUMMIT-Jr	IL-12/23 or IL-23 blockade	NCT05083182	Phase III	JPsA or ERA with inadequate response/intolerance ≥ 1 DMARD (bDMARDs permitted, outside IL-23 inhibition).	5 to 17 years Dosing regimen needs to be determined in paediatric population.
Certolizumab PASCAL	TNF blockade	NCT01550003	Phase III	Active polyarticular JIA (including JPsA) with inadequate response/intolerance ≥ 1 DMARD (bDMARDs permitted).	2 to <18 years of age Two dosing regimen studied, results under evaluation.
Sarilumab SKYPP	IL-6 blockade	NCT02776735	Open Label Phase II (trial completed)	Polyarticular-course JIA	2 to 17 years Dosing regimen needs to be determined in paediatric population.
Anifrolumab	Type 1 IFN Receptor antagonist	NCT05835310	Phase III	Moderate to severe active SLE.	5 to < 18 years of age Dosing regimen needs to be determined in paediatric population.
Ianalumab SIRIUS-SLE 2	Dual mechanism of action: direct ADCC-mediated of	NCT05624749	Phase III	Moderate to severe active SLE.	12 to < 18 years of age Dosing regimen needs to be determined in paediatric population.

	B cells and BAFF-R blockade				
Head-to head trials of monoclonal antibodies					
Risankizumab vs. Adalimumab	IL-23 vs. TNF blockade	NCT06100744	Phase III	JPsA in patients who failed/were intolerant to ≥ 1 cDMARD.	5-18 years of age Risankizumab dosing regimen needs to be determined in paediatric population.
Ixekizumab vs. Adalimumab	IL-17A vs. TNF blockade	NCT04527380	Phase III	Active JPsA or ERA. Active comparator Adalimumab.	2 to 17 years Ixekizumab dosing regimen needs to be determined in paediatric population.
Cell-based therapies					
Chimeric antigen receptor(CAR) T cell -based therapies	CD-19 CAR-T therapy	NCT06839976 NCT06904729	Single-centre, single-arm, open-label phase 1/2 studies open in various centres, such as Seattle, Philadelphia, USA; Great Ormond Street Hospital, London, UK; Guangzhou, China	Refractory cSLE. including both LN and non-renal cSLE.	12-18 years of age.
Chimeric antigen receptor(CAR) T cell -based therapies	CD19 CAR-T therapy	NCT06569472	Phase I	Refractory JDM, intolerant or unresponsive to glucocorticoids and at least 2 immunosuppressants, rapidly progressive or associated with calcinosis and skin ulcers.	≥5 years and <17 years old.

Table 4: Ongoing clinical trials in paediatric populations with rheumatic conditions: ADCC - antibody-dependent cellular cytotoxicity; BAFF-R – B cell activating factor receptor; cSLE – childhood-onset systemic lupus erythematosus; ERA – enthesitis-related arthritis**;** IL – interleukin; JDM- juvenile dermatomyositis; JIA – juvenile idiopathic arthritis; JPsA – juvenile psoriatic arthritis; PK – pharmacokinetic; W – weight.

Source: https://clinicaltrials.gov, accessed in 16th of June 2025