Biologic disease modifying antirheumatic drugs and Janus kinase inhibitors in paediatric rheumatology – what we know and what we do not know from randomized controlled trials

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Abstract

**Background:** Biologic disease modifying antirheumatic drugs (bDMARDs) and Janus Kinase (JAK) inhibitors are prescribed in adult and paediatric rheumatology. Due to age-dependent changes, disease course, and pharmacokinetic processes paediatric patients with inflammatory rheumatic diseases (PiRD) differ from adult rheumatology patients.

**Methods:** A systematic literature search for randomized clinical trials (RCTs) in PiRD treated with bDMARDs/JAK inhibitors was conducted on Medline, clinicaltrials.gov, clinicaltrialsregister.eu and conference abstracts as of July 2020. RCTs were included if (i) patients were aged ≤ 20 years, (ii) patients had a predefined rheumatic diagnosis and (iii) RCT reported predefined outcomes. Selected studies were excluded in case of (i) observational or single arm study or (ii) sample size ≤ 5 patients. Study characteristics were extracted.

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Results: Out of 608 screened references, 65 references were selected, reporting 35 unique RCTs. All 35 RCTs reported efficacy while 34/35 provided safety outcomes and 16/35 provided pharmacokinetic data. The most common investigated treatments were TNF inhibitors (60%), IL-1 inhibitors (17%) and IL-6 inhibitors (9%). No RCTs with published results were identified for baricitinib, brodalumab, certolizumab pegol, guselkumab, risankizumab, rituximab, sarilumab, secukinumab, tildrakizumab, or upadacitinib. In patients with juvenile idiopathic arthritis (JIA) 25/35 RCTs were conducted. The remaining 10 RCTs were performed in non-JIA patients including plaque psoriasis, Kawasaki Disease, systemic lupus erythematosus and non-infectious uveitis. In JIA-RCTs, the control arm was mainly placebo and the concomitant treatments were either methotrexate, non-steroidal anti-inflammatory drugs (NSAID) or corticosteroids. Non-JIA patients mostly received NSAID. There are ongoing trials investigating abatacept, adalimumab, baricitinib, brodalumab, certolizumab pegol, etanercept, guselkumab, infliximab, risankizumab, secukinumab, tofacitinib and tildrakizumab.

Conclusion: Despite the FDA Modernization Act and support of major paediatric rheumatology networks, such as the Pediatric Rheumatology Collaborative Study Group (PRCSG) and the Paediatric Rheumatology International Trials Organization (PRINTO), which resulted in drug approval for PiRD indications, there are limited RCTs in PiRD patients. As therapy response is influenced by age-dependent changes, pharmacokinetic processes and disease course it is important to consider developmental changes in bDMARDs/JAK inhibitor use in PiRD patients. As such it is critical to collaborate and conduct international RCTs to appropriately investigate and characterize efficacy, safety and pharmacokinetics of bDMARDs/JAK inhibitors in paediatric rheumatology.

Keywords: Randomized controlled trials, Paediatric rheumatology, Monoclonal antibodies, Efficacy, Safety, Pharmacokinetics

Background
Paediatric inflammatory rheumatic diseases (PiRDs) are complex rare chronic inflammatory conditions with risk of chronic morbidity and mortality affecting infants, children and adolescents [1]. PiRDs include different heterogeneous disease groups, such as the juvenile idiopathic arthritis (JIA), connective tissue diseases (CTD), systemic lupus erythematosus (SLE), vasculitis, uveitis and autoinflammatory diseases (AID). JIA is one of the most common PiRD groups and can be divided into different subgroups according to the International League of Associations for Rheumatology (ILAR) [2, 3]. In paediatric rheumatology, (i) responsive and valid instruments to assess disease activity and (ii) standardized outcome measurements are important to achieve defined treatment aims, to avoid disease burden and to optimize patients care [4–7]. Treatment aims in PiRD patients include control of systemic inflammation, prevention of structural damage, avoidance of disease comorbidities and drug toxicities, improvement of physiological growth and development, increase of the quality of life and enabling participation in social life. To achieve these treatment goals, treat-to-target (T2T) strategies similar to those used in adult rheumatology have been implemented in PiRD management [8–10]. To reach the defined treatment targets, different levels of disease activity require different treatment selections and dose adjustments [11]. The cytokine modulating effects of biologic disease modifying antirheumatic drugs (bDMARDs) or Janus kinase (JAK) inhibitors have enabled T2T strategies, since they allow important inflammatory disease pathways to be targeted [12–15]. Over the past 15 years, bDMARDs use has become essential in paediatric rheumatology and has markedly improved clinical outcomes [13, 15–19]. However, off-label use in PiRD patients is still common [20–26]. Although some rheumatologic diseases occur in paediatric and adult patients, considerable differences in disease symptoms, disease course and disease activity might exist [27–32]. Moreover, some PiRDs are not common or well known in adulthood [33–36]. For example, the JIA associated uveitis is the most frequent and potentially the most devastating extra-articular manifestation of the JIA, commonly affecting children aged 3 to 7 years [37]. Additionally, Kawasaki Disease (KD) is an acute inflammatory febrile vasculitis of mainly medium-sized arteries that typically affects children younger than 5 years [38]. Furthermore, PiRD patients differ from adult rheumatology patients in several physiological aspects, due to age-dependent changes, maturation processes, differences in body composition and pharmacokinetic (PK) processes, such as drug absorption, distribution, metabolism, and excretion [39–45]. All these aspects are important factors to consider in diagnosis and treatment. This highlights that paediatric drug development cannot simply mimic development strategies for adults, but has to respect paediatric pathophysiology and specific paediatric disease characteristics [46]. Nevertheless, it is common to use the same bDMARDs and JAK inhibitors in paediatric and adult rheumatology, and most paediatric trials and dosing regimens are performed on the basis of existing adult data [47]. The goal of this review is to assess the current state of knowledge obtained from previously performed
randomized controlled trials (RCTs) in PiRD patients treated with bDMARDs and JAK inhibitors. In addition, an overview of approved bDMARDs and JAK inhibitors from the Food and Drug Administration (FDA) and European Medicines Agency (EMA) in paediatric and adult rheumatology is provided.

Methods
Information sources and search
A systemic literature search was conducted on Medline via PubMed, the US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov), and the EU Clinical Trials Register (www.clinicaltrialsregister.eu). The MeSH terms used for electronic search on PubMed and ClinicalTrials.gov are detailed in the supplementary material (supplementary data S1). Similar search terms were used for the EU Clinical Trials Register. The statistical and clinical sections of the New Drug Approval (NDA) web pages of regulatory authorities in the US and Europe were reviewed for approved drugs (www.fda.gov, www.ema.europa.eu). Abstract searches were conducted after conferences, including the American College of Rheumatology (ACR), the European League Against Rheumatism (EULAR), the International Society of Systemic Auto-Inflammatory Diseases (ISSAID), Société Francophone pour la Rhumatologie et les Maladies Inflammatoires en Pédriatrie (SOFREMIP) and the Pediatric Rheumatology European Society (PRES). Additionally, relevant studies were identified by manual search of the bibliographies of references retrieved from PubMed. For all literature sources, only English articles were screened.

Eligibility and exclusion criteria
RCTs of patients aged 20 years and younger treated with predefined bDMARDs/JAK inhibitors were included if the sample size was at least five patients, and if PiRD diagnosis had been confirmed. The PiRDs included are listed in Table 1. The drugs and drug classes reviewed included the following: (i) Anti-CD20 agents: rituximab; (ii) CD80/86 inhibitors: abatacept; (iii) IL-1 inhibitors: anakinra, canakinumab, rilonacept; (iv) IL-6 inhibitors: tocilizumab, sarilumab; (v) IL-12/23 inhibitors: ustekinumab; (vi) IL-23 inhibitors: guselkumab, risankizumab, tildrakizumab; (vii) IL-17 inhibitors: secukinumab, ixekizumab, brodalumab; (viii) Tumour necrosis factor (TNF) inhibitors: adalimumab, etanercept, golimumab, infliximab, certolizumab pegol; (ix) BAFF inhibitors: belimumab; (x) JAK inhibitors: baricitinib, tofacitinib, upadacitinib. Studies must have at least included a relevant primary or secondary efficacy endpoint/outcome as detailed in the supplementary material (supplementary data S3). Consequently, studies were excluded if (i) the indication was not relevant, (ii) the population was not relevant, including studies which enrolled both adults and children with PiRD, (iii) the study design was not relevant including observational studies, single arm studies, reviews, meta-analyses and pooled analysis of multiple RCTs, (iv) treatment was not that as predefined, (v) the endpoint/outcome was not relevant, and/or (vi) the report was a duplicate of prior published results without any additional information.

Study selection and data collection process
Initial screening, based on retrieved abstracts, as well as the eligibility assessment based on full-text publications were performed by two independent review authors according to a review protocol (supplementary data S2). One scientist was responsible for the execution and documentation, and the other provided support as therapeutic area expert. Any discrepancies were resolved through discussion or consultation with a third independent reviewer. The primary reason for exclusion was documented for each excluded reference. Aggregate (summary) level data were extracted from each included trial by two independent review authors. The defined extracted variables for each RCTs included baseline demographic and clinical characteristics such as study design, location, patient population, sample size, age criteria, treatment and primary outcome/endpoint.

Results
Study selection
A systematic literature search was performed on July 26, 2020 using the predefined search criteria. A total of 608 references were screened, and 65 references for 35 uniquely identified RCTs performed in PiRD patients were selected for inclusion (Fig. 1). Of the references excluded, the large majority were due to irrelevant indication (56%, 302/543) or population (31%, 169/543). In total, the majority of RCTs were performed for TNF inhibitors (60%), IL-1 inhibitors (17%) and IL-6 inhibitors (9%). Only one RCT was available for the BAFF inhibitor belimumab, the JAK inhibitor tofacitinib, the IL-12/23 inhibitor ustekinumab, the IL-17 inhibitor ixekizumab, the TNF inhibitor golimumab and the CD 80/86 inhibitor abatacept. No RCTs with published results were identified for the anti-CD20 agent rituximab, the TNF inhibitor certolizumab pegol, the IL-6 inhibitor sarilumab, the IL-17 inhibitors brodalumab and secukinumab, the IL-23 inhibitors guselkumab, risankizumab and tildrakizumab and the JAK inhibitors baricitinib and upadacitinib (Table 2). Currently, there are no recruiting RCTs for sarilumab but there are two ongoing single-arm PK studies in sarilumab, NCT02776735 and NCT02991469 (data not shown). For the JAK inhibitors three Phase III RCTs are investigating baricitinib, and one Phase III global RCT is investigating tofacitinib in JIA patients (Table 3). Furthermore, there are ongoing
studies for guselkumab, risankizumab, tildrakizumab, brodalumab, secukinumab and certolizumab pegol mainly in PiRD patients with psoriasis (Table 3). Additionally, some studies are recruiting to investigate adalimumab in JIA-associated uveitis, abatacept in OJIA, infliximab in KD and etanercept in OJIA and PJIA.

### Study characteristics
Approximately two-thirds (25 out of 35) of the identified RCTs were conducted in JIA patients and the remaining ten RCTs were performed in non-JIA patients, including KD, plaque psoriasis, SLE, and non-infectious uveitis (Tables 4 and 5). The mean/median age of children...
Fig. 1 Flow chart of study selection and reasons for study exclusion after literature search

Table 2 Overview of completed randomized controlled trials performed in paediatric rheumatology patients treated with bDMARDs/JAK inhibitors (July 2020)

| Drug Class      | Drug            | Studies | Arms | Patients | Indications                          | Populations                                      |
|-----------------|-----------------|---------|------|----------|--------------------------------------|--------------------------------------------------|
| Anti-CD 20 agent| rituximab       | 0       |      |          |                                      |                                                  |
| CD80/86 inhibitor| abatacept       | 1       | 2    | 190      | JIA                                  | PJJIA, SJIA (without systemic features), extended OJIA |
| IL-1 inhibitor  | anakinra        | 2       | 4    | 110      | JIA                                  | PJJIA, SJIA                                      |
|                 | canakinumab     | 2       | 4    | 261      | JIA                                  | SJIA                                             |
|                 | rilonacept      | 2       | 5    | 95       | JIA                                  | SJIA                                             |
| IL-6 inhibitor  | sarilumab       | 0       |      |          |                                      |                                                  |
| IL-12/23 inhibitor| tocilizumab     | 3       | 6    | 356      | JIA                                  | PJJIA, extended OJIA, SJIA                        |
| IL-12/23 inhibitor| ustekinumab     | 1       | 3    | 110      | Psoriasis                           | Plaque psoriasis                                  |
| IL-23 inhibitor | guselkumab      | 0       |      |          |                                      |                                                  |
|                 | risankizumab    | 0       |      |          |                                      |                                                  |
|                 | tildrakizumab   | 0       |      |          |                                      |                                                  |
| IL-17 inhibitor | brodalumab      | 0       |      |          |                                      |                                                  |
|                 | ixekizumab      | 1       | 3    | 201      | Psoriasis                           | Plaque psoriasis                                  |
|                 | secukinumab     | 0       |      |          |                                      |                                                  |
| TNF inhibitor    | adalimumab      | 6       | 13   | 485      | JIA, psoriasis, uveitis              | ERA, JIA-associated uveitis, PJJIA, plaque psoriasis |
|                 | etanercept      | 8       | 17   | 746      | JIA, psoriasis, vasculitis           | PJJIA, OJJIA, PsA, ERA, SJIA, plaque psoriasis, KD |
|                 | golimumab       | 1       | 2    | 154      | JIA                                  | PJJIA, SJIA (without systemic features), PsA    |
|                 | infliximab      | 6       | 13   | 576      | JIA, uveitis, vasculitis             | PJJIA, non-infectious uveitis, KD                |
|                 | certolizumab pegol | 0   |      |          |                                      |                                                  |
| BAFF inhibitor  | belimumab       | 1       | 2    | 93       | CTD                                  | SLE                                              |
| JAK inhibitor    | tofacitinib     | 1       | 2    | 225      | JIA                                  | ERA, PJJIA, PsA                                 |
|                 | baricitinib     | 0       |      |          |                                      |                                                  |
|                 | upadacitinib    | 0       |      |          |                                      |                                                  |

**Abbreviations:** IL interleukin, TNF tumour necrosis factor, JAK Janus Kinase, JIA juvenile idiopathic arthritis, CTD connective tissue disease, PJJIA polyarticular juvenile idiopathic arthritis, KD Kawasaki disease, SJIA systemic juvenile idiopathic arthritis, OJJIA oligoarticular juvenile idiopathic arthritis, ERA enthesitis-related juvenile idiopathic arthritis, PsA psoriatic juvenile idiopathic arthritis, SLE systemic lupus erythematosus
| Drug class   | Drug                          | Study                                      | Sponsor             | Population | Region          | Study duration     | Primary outcome/endpoint |
|-------------|-------------------------------|--------------------------------------------|---------------------|------------|------------------|---------------------|------------------------|
| CD 80/86 inhibitor | abatacept | Limit-JIA, NCT03841357 | Duke University     | OJIA       | United States   | 10/2019–12/2022 | Joint count, active anterior uveitis |
| IL-23 inhibitor | guselkumab | 9PROTOSTAR, NCT03451851 | Janssen             | Paediatric psoriasis | global   | 7/2018–6/2025 | PASI75, PGA ≤ 1 |
|              | risankizumab | M19–977, NCT04435600 | Abbvie               | Paediatric psoriasis | United States | 7/2020–6/2025 | PASI75, PGA ≤ 1 |
| IL-17 inhibitor | tildrakizumab | TILD-19-12, NCT03997786 | Sun Pharma Global FZE | Paediatric psoriasis | United States | 1/2020–11/2023 | PASI75, PGA ≤ 1 |
|              | brodalumab | 8EMBRACE 1, NCT04305327 | LEO Pharma          | Paediatric psoriasis | global   | 9/2020–11/2023 | PASI75 |
|              | secukinumab | CAIN457F2304, NCT03031782 | Novartis            | PsA, ERA   | global           | 5/2017–12/2020 | Disease flare |
|              |            | CAIN457A2310, NCT02471144 | Novartis            | Paediatric psoriasis | global   | 8/2018–9/2023 | PASI75, PGA ≤ 1 |
|              |            | CAIN457A2311, NCT03668613 | Novartis            | Paediatric psoriasis | global   | 9/2015–7/2023 | PASI75, PGA ≤ 1 |
| TNF inhibitor | adalimumab | 9ADJUST, NCT03816397 | UCSF                | JIA-associated uveitis | United States | 12/2019–12/2022 | Treatment failure |
|              | etanercept | STARS, EudraCT 2018–001931–27 | IRCCS Istituto Giannina Gaslini | OJIA, PJIA | Italy          | NA                  | Clinical inactive disease |
|              | infliximab | KIDCARE, NCT08063244 | UCSF               | Kawasaki disease | United States | 2/2017–9/2020 | Fever |
|              | certolizumab pegol | CIMcare, NCT04123795 | UCB Biopharma       | Paediatric psoriasis | North America | 1/2020–4/2023 | PASI75, PGA ≤ 1 |
| JAK inhibitor | baricitinib | 8JUVE-BRIGHT, NCT04088409 | Eli Lilly           | JIA-associated uveitis | Europe | 10/2019–7/2022 | Uveitis disease response |
|              |           | 8JUVE-BALM, NCT04088396 | Eli Lilly           | SIA        | global           | 2/2020–4/2023 | Disease flare |
|              |           | 8JUVE-BASIS, NCT03773978 | Eli Lilly           | PJIA, extended OJIA, ERA, PsA | global   | 12/2018–8/2021 | Disease flare |
|              | tofacitinib | A3921165, NCT03000439 | Pfizer             | SIA        | global           | 5/2018–8/2023 | Disease flare |

Abbreviations: IL interleukin, TNF tumour necrosis factor, JAK Janus Kinase, ERA enthesitis-related juvenile idiopathic arthritis, JIA juvenile idiopathic arthritis, PsA, psoriatic juvenile idiopathic arthritis, OJIA oligoarticular juvenile idiopathic arthritis, PASI psoriasis area and severity index, PGA Physician global assessment, PJIA polyarticular juvenile idiopathic arthritis, SIA systemic juvenile idiopathic arthritis, NA not applicable.
Table 4 Overview and general characteristics of identified reviewed randomized controlled trials performed in JIA patients (July 2020)

| Drug class          | Drug                  | Dose                        | Study (phase) | Study time¹ | Population | N  | Age criteria | Age² | Background                      | Primary outcome/endpoint | Main conclusion |
|---------------------|-----------------------|-----------------------------|---------------|-------------|------------|----|--------------|------|---------------------------------|------------------------|-----------------|
| CD80/86 inhibitor   | abatacept             | 10 mg/kg q4w                | M101–033, NCT00095173 (III) [48–51] | 26 | P.JA, SJA (without systemic features), extended OJA | 190 | 6 to 17      | 12.4 | MTX, corticosteroids            | Disease flare            | Effective       |
| IL-1 inhibitor      | anakinra              | 1 mg/kg/d                   | [9900758–990779, NCT00037648 (II) [52, 53] | 16 | P.JA                      | 86  | 2 to 17      | 12  | MTX                            | Safety                 | Efficacy is inconclusive |
|                     |                       | 2 mg/kg/d                   | ANAJS, NCT00339157 (III) [53, 54] | 4.33 | SJA                      | 24  | 2 to 20      | 8.5 | NSAID, corticosteroids          | Modified ACR Pedi 30    | Effective       |
|                     | canakinumab           | 4 mg/kg single dose         | [β-SPECIFIC 1, NCT00886769 (III) [55–57] | 4.33 | SJA                      | 84  | 2 to 19      | 8   | MTX, NSAID, corticosteroids     | Modified ACR Pedi 30    | Effective       |
|                     |                       | 4 mg/kg q4w                 | [β-SPECIFIC 2, NCT00889863 (III) [55–57] | 120 | SJA                      | 177 | 2 to 19      | 8   | MTX, NSAID, corticosteroids     | Disease flare            | Effective       |
|                     | rilonacept            | 2.2 mg/kg qw                | RAPPORT, NCT00534495 (I) [58, 59] | 24  | SJA                      | 71  | 1 to 19      | 10  | NA                             | Modified ACR Pedi 30    | Effective       |
|                     |                       | 2.2 mg/kg qw, 4.4 mg/kg qw  | IL1-TA-0504, NCT01803321 (I) [60] | 104 | SJA                      | 24  | 4 to 20      | 12.6 | MTX, NSAID, corticosteroids     | ACR Pedi 30              | Not effective    |
| IL-6 inhibitor      | tocilizumab           | 8 mg/kg q4w, 10 mg/kg q4w   | CHERSH, NCT00988221 (III) [60–65] | 104 | P.JA, extended OJA       | 188 | 2 to 17      | 11  | MTX, corticosteroids            | Disease flare            | Effective       |
|                     |                       | 8 mg/kg q2w, 12 mg/kg q2w   | TENDER, NCT0042460 (III) [65–67] | 260 | SJA                      | 112 | 2 to 17      | 9.7  | MTX, corticosteroids            | Modified ACR Pedi 30    | Effective       |
|                     |                       | 8 mg/kg q2w                 | MRA316P, NCT00144599 (III) [68] | 18  | SJA                      | 56  | 2 to 19      | 8.3  | corticosteroids                 | ACR Pedi 30              | Effective       |
| TNF inhibitor       | adalimumab            | 24 mg/m2 q2w                | M113–328, NCT01166282 (III) [69–71] | 12  | ERA                      | 46  | 6 to 12      | 12.9 | MTX or SSZ, NSAID               | Joints with active arthritis | Effective       |
|                     |                       | 40 mg q2w                   | Horneff 2012, EudraCT 2007–003398-27 (III) [72] | 12  | ERA                      | 32  | 12 to 17     | 15.3 | NSAID, corticosteroids          | ASAS40                  | Effective       |
|                     |                       | 24 mg/m2 q2w                | EO038L, NCT001048542 (II) [73, 74] | 48  | P.JA                      | 171 | 4 to 17      | 11.2 | MTX, NSAID, corticosteroids     | Disease flare            | Effective       |
|                     |                       | 20 mg q2w, 40 mg q2w        | SYCAMORE, EudraCT 2010–0011-14 (NA) [75, 76] | 78  | JIA-associated uveitis   | 90  | 2 to 18      | 8.9  | MTX                            | Treatment failure       | Effective       |
|                     |                       | 24 mg/m2 q2w, 40 mg q2w     | ADJUVITE, NCT011385826 (III) [77] | 52  | JIA-associated uveitis   | 32  | >= 4         | 9.5  | MTX, corticosteroids (oral and topical) | LFP improvement >= 30% and no worsening on slit lamp | Effective       |
|                     | etanercept            | 0.8 mg/kg/qw                | Horneff 2015, EudraCT 2010–00384-5 (II) [78, 79] | 48  | ERA                      | 38  | 6 to 17      | 13.3 | SSZ, NSAID, corticosteroids     | Disease flare            | Effective       |
|                     |                       | 0.8 mg/kg/qw                | [160016 (NA) [79, 80] | 30.33 | P.JA                      | 69  | 4 to 17      | NA   | NSAID, corticosteroids          | Disease flare            | Effective       |
|                     |                       | 0.8 mg/kg/qw                | [20012616, NCT03780959 (III) [81] | 30.33 | P.JA                      | 69  | 4 to 18      | 10.5 | NSAID                           | Disease flare            | Effective       |
|                     |                       | 0.8 mg/kg/qw                | 20021628, NCT03781375 (III) [82] | 52  | P.JA                      | 25  | NA           | 10.1 | MTX                            | ACR Pedi 30              | NA              |
|                     |                       | 0.8 mg/kg/qw                | TREAT, NCT0043430 (NA) [83, 84] | 52  | P.JA                      | 85  | 2 to 17      | 10.5 | MTX                            | Clinical inactive disease | Not effective    |
|                     |                       | 0.8 mg/kg/qw, 1.6 mg/kg/qw  | [20021631, NCT00078006 (III) [85] | 39  | SJA                      | 19  | 2 to 18      | 9.1  | MTX, NSAID, corticosteroids     | Disease flare            | NA              |
| Drug class | Drug | Dose | Study (phase) | Study time | Population | N | Age criteria | Agea Background | Primary outcome/endpoint | Main conclusion |
|------------|------|------|---------------|------------|------------|---|--------------|----------------|-------------------------|----------------|
| JAK inhibitor | tofacitinib | 2–5 mg BID | ACUTE-JIA, NCT01015547 (II) [91] | 54 | P.JIA | 60 | 4 to 15 | 9.6 MTX, other DMARDs | ACR Pedi 75 | Effective |
| JAK inhibitor | tofacitinib | 2–5 mg | ACUTE-JIA, NCT02592434 (II) [92] | 44 | ERA, P.JIA, PsA | 225 | 2 to 17 | 13a NA | Disease flare | Effective |

Abbreviations: Drug class: IL interleukin, TNF tumour necrosis factor, JAK Janus Kinase; Dose: mg milligram, kg kilogram, d per day, qw once per week, q2w once per every 2 weeks, q4w once per every 4 weeks, BID twice a day; Population: ERA enthesitis-related juvenile idiopathic arthritis, PsA psoriatic arthritis, OJIA oligoarticular juvenile idiopathic arthritis, PJIA juvenile Polyarticular idiopathic arthritis, RF rheumatoid factor negative, SJIA systemic juvenile idiopathic arthritis; Background: MTX methotrexate, HCQ hydroxychloroquine, NSAID non-steroidal anti-inflammatory drugs, DMARDS disease modifying antirheumatic drugs, SSZ sulfasalazine; Outcome: ACR Pedi 30 ACR Pedi 30% response criteria, ACR Pedi 75 ACR Pedi 75% response criteria, LFP laser flare photometry, ASAS40 assessment in ankylosing spondylitis response criteria 40%; NA not available

a median age, otherwise mean age across all arms of the study, b withdrawal study design instead of parallel, c duration in weeks, d Also registered under EudraCT 2005–000443-28; e Also registered under EudraCT 2013–002466-22; f Also registered under EudraCT 2008–005476-27; g Also registered under EudraCT 2008–005479-82; h Also registered under EudraCT 2009–011593-15; i Also registered under EudraCT 2007–00872-18; j Also registered under EudraCT 2009–017938-46; k Also registered under EudraCT 2011–01661-40; l Also registered under EudraCT 2010–019441-26; m Also registered under EudraCT 2009–015019-42; n Also registered under EudraCT 2015–001438-46; o same study
| Drug class       | Drug               | Dose                          | Study (phase) | Studytime\(^c\) | Population | N     | Age criteria | Age\(^a\) | Primary outcome/endpoint | Main conclusion |
|------------------|--------------------|-------------------------------|---------------|-----------------|------------|-------|--------------|----------|----------------------------|----------------|
| IL-12/23 inhibitor | ustekinumab        | 0.75 mg/kg, 22.5/45/90 mg     | \(^d\)CADMUS, NCT01090427 (III) \(^93\)\(^b\) | 60              | Plaque psoriasis | 110   | 12 to 17     | 15.2     | PGA ≤1                     | Effective       |
| IL-17 inhibitor  | ixekizumab         | 20 mg BW < 25 kg q4w, 40 mg BW 25–50 kg q4w, 80 mg BW > 50 kg q4w | \(^d\)IXORA-PEDS, NCT03073200 (III) \(^94\)\(^b\) | 12              | Plaque psoriasis | 201   | 6 to 17      | 13.5     | PASI75, PGA ≤1             | Effective       |
| TNF inhibitor    | adalimumab         | 0.4 mg/kg q2w, 0.8 mg/kg q2w  | \(^f\)M04–717, NCT01251614 (III) \(^95–98\)\(^b\) | 52              | Plaque psoriasis | 114   | 4 to 17      | 13       | PASI75, PGA ≤1             | Effective       |
|                  | etanercept         | 0.8 mg/kg/qw                  | \(^f\)EATAK, NCT00841789 (II) \(^99\)\(^b\) | 6               | KD         | 205   | 0 to 18      | 3.7      | Fever                      | Not effective   |
|                  |                    | 0.8 mg/kg/qw                  | \(^f\)20030211, NCT00078819 (III) \(^100–104\)\(^b\) | 48              | Plaque psoriasis | 211   | 4 to 17      | 13\(^a\) | PASI75                    | Effective       |
|                  | infliximab         | 5 mg/kg single dose           | Han 2018 (NA) \(^105\)\(^b\) | 0.571           | KD         | 154   | 0 to 4       | 2.2\(^a\) | Unclear                    | Effective       |
|                  |                    | 5 mg/kg single dose           | TA-650-22, NCT01596335 (III) \(^106\)\(^b\) | 8               | KD         | 31    | 1 to 10      | 3\(^a\)  | Defervescence              | Effective       |
|                  |                    | 5 mg/kg single dose           | Tremoulet 2014, NCT00760435 (III) \(^107, 108\) | 5               | KD         | 196   | 0 to 17      | 3\(^a\)  | Fever                      | Effective       |
|                  |                    | 5 mg/kg, 10 mg/kg q4w         | Pro000000057, NCT00589628 (N) \(^109\)\(^b\) | 39              | Non-infectious uveitis | 13    | 4 to 18      | NA       | Uveitis disease activity  | NA             |
| BAFF inhibitor   | belimumab          | 10 mg/kg qm                   | \(^g\)PLUTO, NCT01649765 (II) \(^110, 111\) | 52              | SLE        | 93    | 5 to 17      | 14       | SRI4                       | Effective       |

Abbreviations: Drug class: IL interleukin, TNF tumour necrosis factor; Dose: mg milligram, kg kilogram, qw once per week, q2w once every 2 weeks, q4w once every 4 weeks, qm once every month; Population: KD Kawasaki disease, SLE systemic lupus erythematosus; Outcome: PASI psoriasis area and severity index, PGA Physician global assessment, SRI4 systemic lupus erythematosus response index 4, NA not available \(^\text{median age, otherwise mean age across all arms of the study, parallel study design, duration in weeks; in registered under EudraCT 2009–013072-52; Also registered under EudraCT 2009–014368-20, Also registered under EudraCT 2016–003331-38, Also registered under EudraCT 2011–000368–88.}\)
enrolled in the JIA RCTs ranged from 8 years to 15.3 years. In contrast, the non-JIA patients included in RCTs had a mean/median age range varying between 2.2 and 15.2 years, with KD patients being younger (range 2.2 to 3.7 years). In JIA RCTs, the control was mainly placebo, and the concomitant background treatments were usually either methotrexate, NSAID or corticosteroids, whereas in non-JIA trials the control arm was a mixture of placebo or standard of care treatments and patients received mostly NSAID as background treatments (data not shown for the control arm). The primary efficacy outcome/endpoint in the JIA RCTs was mainly ACR Pedi 30/modified ACR Pedi 30 or disease flare (Table 4). Other instruments to assess the primary outcome were count of joints with active arthritis, the assessment of Spondyloarthritis International Society 40% score (ASAS 40), inactive disease, treatment failure and improvement of laser flare photometry (Table 4). In non-JIA patients, efficacy outcomes/endpoints varied due to heterogeneous subgroups. The primary efficacy outcome/endpoint of RCTs in KD was mainly related to fever, whereas for plaque psoriasis the Psoriasis Area and Severity Index (PASI 75), or the Physician Global Assessment (PGA) was used (Table 5). The RCT addressing SLE used the SLR response index (SRI 4), whereas the primary outcome/endpoint in non-infectious uveitis was assessed with uveitis disease activity using the Standardization of Uveitis Nomenclature (SUN) criteria, AC cells and vitreous haze. The majority of the JIA RCTs were global studies or otherwise conducted in either Europe or the United States, with one study (NCT00144599) located in Japan (data not shown). The non-JIA RCTs took place either in North America, Europe or globally (data not shown). In particular, KD RCTs took place mainly in Asia or the United States. Details for JIA and non-JIA RCTs are shown in Tables 4 and 5. All non-JIA studies were of a parallel study design, while in JIA studies there was a mixture of parallel and withdrawal study designs (Tables 4 and 5). The main conclusion of the majority of the studies (in terms of meeting the primary endpoint/outcome) was that the bDMARDs evaluated were more effective in comparison to placebo or standard of care (Tables 4 and 5).

Approved bDMARDs and JAK inhibitors in paediatric and adult rheumatology

In March 2020, the FDA has approved all 23 reviewed drugs, including bDMARDs and JAK inhibitors for adult rheumatology, whereas the EMA has approved 22 (Table 6). For PiRD patients, 10 bDMARDs (EMA) and 11 (FDA) have been approved (Table 6). Not surprisingly, the more recently approved bDMARDs in adult rheumatology and the JAK inhibitors have mostly not yet been approved for PiRD patients. Infliximab is approved for several rheumatologic indications in adulthood including rheumatoid arthritis (RA), PsA, ankylosing spondylitis, and plaque psoriasis, but is not approved for any PiRD indication so far. In paediatrics, infliximab is still restricted for in-label use in paediatric chronic inflammatory bowel diseases. Furthermore, there are some differences between the FDA and EMA in bDMARDs and JAK approvals. For example, the FDA has approved rilonacept for the treatment of the Cryopyrin-associated periodic syndrome (CAPS) in adults and children aged 12 years and older, whereas EMA has not. Particularly relevant for the PiRD patients are the different age limitations for different bDMARDs, and varying age restrictions for different PiRD diagnoses. No bDMARDs are approved in children younger than 2 years with the exception of anakinra, which is approved by the EMA for the age ≥ 8 months. The age limitations have changed over the last couple of years, and today the common age categories are ≥ 2, ≥ 4, ≥ 6, or ≥ 12 years. A detailed overview about paediatric bDMARDs approvals, indications and age limitations by the EMA and FDA in March 2020 compared with adult rheumatology is given in Table 6.

Discussion

This review indicates that reported data from RCTs characterizing efficacy, safety and/or PK, remains limited for several prescribed bDMARDs and JAK inhibitors in PiRD patients. As RCTs are robust research methods to determine cause-effect relationships between intervention and outcome, they are important to generate evidence in basic, translational and clinical research and can improve management of patients [112]. In the past, several clinical trials were conducted in PiRD with support of research networks in paediatric rheumatology, such as the Pediatric Rheumatology Collaborative Study Group (PRCSG) and the Paediatric Rheumatology International Trials Organisation (PRINTO) resulting in bDMARDs approval for some PiRD indications [19, 113]. This review indicates that TNF inhibitors are the most studied bDMARDs in PiRD patients, particularly in the JIA group. JIA is one of the most commonly diagnosed PiRDs with a prevalence of 16/100,000 to 150/100,000 [3]. In several JIA sub-groups, treatment with TNF inhibition is recommended, particularly when conventional disease modifying antirheumatic drugs (cDMARDs) cannot achieve the defined target [114, 115]. One of the first FDA-approved TNF inhibitors for polyarticular JIA treatment was etanercept in 1999, followed by adalimumab in 2008. This might explain why a majority of RCTs were performed for etanercept. Up to now, no JAK inhibitor is approved for PiRD patients. JAK inhibitors can be administered orally and therefore this treatment approach might be of particular interest in paediatric rheumatology,
| Drug class          | Drug (brand name) | Adults | Children |
|---------------------|-------------------|--------|----------|
|                     | Approved by FDA (date) | Approved by EMA (date) | Approved by FDA (date) | Current FDA age criteria | Approved by EMA (date) | Current EMA age criteria |
| Anti-CD20 agent     | rituximab (MabThera, Rituxan) | RA (2006), WS/MPA (2011) | RA (2006), GPA/MPA (2013) | GPA/MPA (2019) | ≥2 years | GPA/MPA (2020) | ≥2 years |
| CD80/86 inhibitor   | abatacept (Orencia) | RA (2005), PSA (2017) | RA (2007), PSA (2017) | P.JA (2008) | ≥2 years (sc); ≥6 years (iv) | P.JA (2009) | ≥2 years |
| IL-1 inhibitor      | anakinra (Kineret) | CAPS (2009), TRAPS/FM/FMK (2016) | CAPS (2009), AOSD (2016), TRAPS/FM/FMK (2016) | CAPS (2009), SJIA (2013), TRAPS/FM/FMK (2016) | ≥4 years CAPS/ SJIA (2013), TRAPS/FM/FMK (2016) | ≥2 years |
|                     | canakinumab (Ilaris) | RA (2010) | not approved | not approved | CAPS (2008) | ≥12 years | not approved | ≥2 years |
| IL-6 inhibitor      | tocilizumab (RoActemra/Actemra) | Plaque psoriasis (2017) | Plaque psoriasis (2017) | P.JA (2008) | ≥2 years | P.JA (2013) | ≥2 years |
|                     | sarilumab (Kevzara) | RA (2017) | not approved | not approved | RA (2017) | not approved | not approved |
| IL-12/23 inhibitor  | ustekinumab (Stelara) | Plaque psoriasis (2013) | Plaque psoriasis (2013) | not approved | not approved |
| IL-23 inhibitor     | guselkumab (Tremfya) | Plaque psoriasis (2017) | Plaque psoriasis (2017) | not approved | not approved | not approved | ≥6 years |
|                     | risankizumab (Skyrizi) | Plaque psoriasis (2018) | Plaque psoriasis (2018) | not approved | not approved | ≥6 years | ≥6 years |
| IL-17 inhibitor     | brodalumab (Siliq, Kyntheum) | Plaque psoriasis (2015), PSA (2016), AOS (2017), AOS (2019) | Plaque psoriasis (2015), PSA (2016), AOS (2017) | not approved | not approved | not approved | ≥6 years |
|                     | ixekizumab (Taltz) | Plaque psoriasis (2017) | Plaque psoriasis (2017) | not approved | not approved | not approved | ≥6 years |
| TNF inhibitor       | adalimumab (Humira) | RA (2002), PSA (2005), AS (2006), plaque psoriasis (2008), non-infectious intermediate, posterior and panuveitis (2016) | RA (2003), PSA (2005), PSA (2006), plaque psoriasis (2007), non-radiographic axial spondyloarthritids (2012), non-infectious intermediate, posterior and panuveitis (2016) | P.JA (2008) | ≥2 years | P.JA (2008), ERA (2014), non-infectious anterior uveitis (2017) | ≥2 years |
|                     | certolizumab pegol (Cimzia) | RA (2009), PSA (2013), AOS (2013), plaque psoriasis (2018), non-radiographic axial spondyloarthritids (2019) | RA (2009), PSA (2013), plaque psoriasis (2018), non-radiographic axial spondyloarthritids (2019) | not approved | not approved | ≥2 years |
|                     | etanercept (Enbrel) | RA (1998), PSA (2002), AS (2003), plaque psoriasis (2004) | RA (2000), PSA (2002), AOS (2004), plaque psoriasis (2004), non-radiographic axial spondyloarthritids (2014) | P.JA (1999), plaque psoriasis (2016) | ≥2 years PL.A | ≥4 years plaque psoriasis | ≥2 years |
|                     | golimumab (Simponi) | RA/PSA/AS (2009) | RA/PSA/AS (2009), non-radiographic axial spondyloarthritids (2015) | not approved | not approved | P.JA (2016) | ≥2 years |
|                     | infliximab (Remicade) | RA (1999), AS (2004), PSA (2005), plaque psoriasis (2004) | RA (2000), AS (2003), PSA (2004), plaque psoriasis (2005) | not approved | not approved | ≥2 years | ≥2 years |
| BAFF inhibitor      | belimumab (Benlysta) | SLE (2011) | SLE (2011) | SLE (2011) | ≥2 years | SLE (2019) | ≥2 years |
| Drug class | Drug (brand name) | Adults | FDA date | EMA date | Children | FDA date | EMA date |
|------------|-------------------|--------|----------|----------|----------|----------|----------|
| JAK inhibitor | tofacitinib® (Xeljanz) | RA (2012), PsA (2017) | RA (2017), PsA (2018) | not approved | not approved | not approved | not approved |
|             | baricitinib (Olumiant) | RA (2018) | RA (2016) | not approved | not approved | not approved | not approved |
|             | upadacitinib (Rinvoq) | RA (2019) | RA (2019) | not approved | not approved | not approved | not approved |

*Also approved to treat Non-Hodgkin’s Lymphoma, chronic lymphatic leukemia and pemphigus vulgaris; †Also approved to treat giant cell arteritis, cytokine release syndrome (≥2 years); ‡Also approved to treat ulcerative colitis (FDA only), Crohn’s disease; §Also approved to treat ulcerative colitis, Crohn’s disease (≥6 years), hidradenitis suppurativa (age ≥12 years); ¶Also approved to treat Crohn’s disease (FDA only); ‖Also approved to treat ulcerative colitis; ‖‖Also approved to treat Crohn’s disease (≥6 years), ulcerative colitis (≥6 years); "Also approved to treat ulcerative colitis (FDA only)

Abbreviations: AOSD adult-onset Still’s disease, AS ankylosing spondylitis/spondylitis, CAPS cryopyrin-associated periodic syndrome, CINCA chronic infantile neurologic, cutaneous, and arthritis, EMA European Medicines Agency, ERA enthesitis-related juvenile idiopathic arthritis, FDA Food and Drug Administration, FMF familial mediterranean fever, GPA granulomatosis with polyangiitis, IL interleukin, MKD mevalonate kinase deficiency, MPA microscopic polyangiitis, NA not applicable, NOMID neonatal-onset multisystem inflammatory disease, PJIA polyarticular juvenile idiopathic arthritis, PsA psoriatic arthritis/psoriatic juvenile idiopathic arthritis, RA rheumatoid arthritis, SJIA systemic juvenile idiopathic arthritis, SLE systemic lupus erythematosus, TNF tumor necrosis factor receptor-associated periodic syndrome, TRAPS tumour necrosis factor receptor-associated periodic syndrome, WG Wegner’s Granulomatosis
explaining why several RCTs are currently performed for JAK inhibitors. For several bDMARDs, a latency in drug approval for PiRD patients can be observed with a delay ranging between 1 year to 9 years. However, around 50% of reviewed therapeutic drugs are currently not approved for PiRD patients. Off-label and unlicensed drug use is frequent in paediatric patient populations [116, 117] and a considerable number of PiRD patients has to be treated with off-label bDMARDs or JAK inhibitors as no approved drugs are available for their age group, the PiRD indication or in general [20–23, 25]. Off-label use is often of great concern to the families of the affected children [17]. In addition, it seems that off-label and unlicensed drug use in children is associated with increased risk of medication errors and adverse events [118–120]. As infants and children with PiRD differ greatly from adult rheumatology patients the lack of paediatric PK data for bDMARDs and JAK inhibitors, can result in over- and under-dosing [42, 47, 121]. While under-dosing/low drug concentrations can result in drug-antibodies and drug insufficiency with uncontrolled chronic inflammation and disease burden, over-dosing can be associated with serious short- and long-term safety events [122–124]. There are data suggesting that based on the body weight, the clearance of several drugs is higher in paediatrics than in adults [39]. In PiRD patients, particularly in infants and younger children, there are data for bDMARDs and JAKs indicating a need for more frequent drug administration due to shorter half-life or the need for higher weight based drug dosages to achieve the defined therapy target [121, 125–127]. Moreover, it seems that subcutaneously administered bDMARDs are absorbed faster in young children [44]. As the therapy outcomes in PiRD patients is influenced by these age-dependent PK processes and the disease course, it is crucial to understand the developmental changes to optimize bDMARDs and JAK inhibitor dosing in paediatric rheumatology [39–42, 44, 46, 47]. As a consequence, the FDA Modernization Act stimulates the conduct of dedicated clinical studies to enhance understanding of PK, efficacy-safety balance, and optimal dosing of drugs in paediatric patients [128]. Nevertheless, concern has been raised that trial discontinuation, and nonpublication with associated risk of publication bias, seems to be common in paediatric patients [129, 130]. Slow recruitment rates in rare paediatric diseases can be challenging for paediatric trials, and poor recruitment seems to be one of the major risks for early termination or discontinuation of such studies [130]. These observations highlight the value of established research networks in paediatric rheumatology, such as PRCSG and PRINTO, in conducting clinical studies in PiRD patients as efficacy, safety and PK data obtained from PiRD patients to optimize treatment are warranted.

This review has several limitations. Despite a comprehensive search strategy and independent reviewer processes, there might be a risk of a reporting bias as unpublished RCTs were not included. Furthermore, this review does not include observational studies, single arm studies or RCTs including both children and adults. We cannot rule out that not all conducted RCTs in PiRDs were identified, despite a rigorous screening and review process. We have included RCTs with patients aged 20 years and younger, although this upper age limit of 20 years constituted the risk of having studies performed mainly in adolescents and young adults. To address this bias we have reported for each analysed RCT the age criteria and the median/mean age. As several included RCTs had an upper age criteria between 17 to 20 years, we would have missed otherwise these studies if we have limited the search to the age criteria 16 or 18 years.

Conclusion

In summary, paediatric rheumatology patients differ from adult rheumatology patients in many aspects. As therapeutic drug response is influenced by age-dependent PK processes and disease course, it is important to consider developmental changes when prescribing bDMARDs or JAK inhibitors in PiRD patients. As such, it is critical to conduct international multicentre studies in PiRD patients to enroll a sufficiently high patient number in a reasonable period of time with the goal to appropriately investigate and characterize PK, efficacy and safety for bDMARDs and JAK inhibitors. More efficacy and safety data, ideally combined with PK data from PiRD patients will optimize bDMARDs and JAK inhibitor use in paediatric rheumatology.

Abbreviations

AID: Autoinflammatory diseases; cDMARDs: conventional disease modifying antirheumatic drugs; bDMARDs: Biologic disease modifying antirheumatic drugs; CTD: Connective tissue diseases; EMA: European Medicines Agency; ERA: Enthesitis-related juvenile idiopathic arthritis; ERAS: Enthesitis-related juvenile idiopathic arthritis; FDA: Food and Drug Administration; ILAR: International League of Associations for Rheumatology; IL: Interleukin; JAK: Janus kinase; JA: Juvenile idiopathic arthritis; KD: Kawasaki disease; NSAID: Non-steroidal anti-inflammatory drugs; OJIA: Oligoarticular juvenile idiopathic arthritis; PiRD: Pediatric inflammatory rheumatic diseases; PJIA: Polyarticular juvenile idiopathic arthritis; PtA: Psoriatic juvenile idiopathic arthritis; RA: Rheumatoid arthritis; RF: Rheumatoid factor; RCT: Randomized controlled trials; SJA: Systemic juvenile idiopathic arthritis; SLE: Systemic lupus erythematosus; TNF: Tumour necrosis factor; T2T: Treat to target

Supplementary Information

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Additional file 1: Supplementary data S1. Search terms. Supplementary data S2. Review protocol. Supplementary data S3. Outcome/Endpoint inclusion criteria for literature search.

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TW, CW, NZ, AW and MP have contributed to the design, data gathering and analysis. TW and CW performed the initial data screening and eligibility assessment. CW was responsible for the execution and documentation and TW provided support as therapeutic area expert. Any discrepancies were resolved through discussion or consultation with a third independent reviewer (MP). All authors (TW, CW, NZ, AW, MP) have contributed in preparation of the submitted manuscript. They were involved in drafting the work and critically revising. All authors have approved this version to be published and they agreed to be accountable for all aspects in the work in ensuring questions related to the accuracy or integrity of any part of the work appropriately investigated and resolved. All authors have agreed to the submission of this manuscript to Rheumatology.

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