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TESI DI DOTTORATO

PHARMACOVIGILANCE IN JUVENILE IDIOPATHIC ARTHRITIS PATIENTS (PHARMACHILD) TREATED WITH BIOLOGIC AGENTS AND/OR METHOTREXATE. A PEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION (PRINTO)/PEDIATRIC RHEUMATOLOGY EUROPEAN SOCIETY (PRES) REGISTRY

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ABSTRACT

Introduction: Pharmacovigilance in Juvenile Idiopathic Arthritis Patients Treated with Biologic Agents and/or Methotrexate (Pharmachild) is an international registry involving 86 centres in 32 countries from the Paediatric Rheumatology INternational Trials Organisation (PRINTO)/ Paediatric Rheumatology European Society (PReS). The registry was set up in 2011 to evaluate long term safety and efficacy profile of immunosuppressive treatments in children with Juvenile Idiopathic Arthritis (JIA).

Objectives: To present data coming from the Pharmachild/PRINTO registry and analyze infections, with a main focus on opportunistic, also evaluating the relationship between infections and biologic and synthetic Disease-Modifying Anti-Rheumatic Drugs (DMARDs) in children affected by JIA.

Methods: We provided descriptive statistics for demographic, clinical data, drug exposure, adverse events (AE) and events of special interest (ESI). Data from Pharmachild were combined with those coming from two national registries: BiKeR from Germany and the Swedish registry. The analysis was then focused on infections. A panel of specialists in infectious and rheumatologic diseases, identified as Safety Adjudication Committee (SAC), elaborated and approved by consensus, through three Delphi steps, a list of opportunistic pathogens for use in immunosuppressed children. Primary objective of the SAC was to adjudicate the infectious events encountered by the patients in Pharmachild with particular attention on opportunistic infections (OI).

Results: Data from 8,274 patients were reported from the Pharmachild registry, and combined with those from 3,990 and 3,020 patients from the Germany and the Swedish registries, respectively, for a total of 15,284 patients. The main differences between Pharmachild and the other two registries were found in the age of onset, in the distribution of the different categories of AIG and in the use of biological drugs. The most frequently reported AE in Pharmachild resulted to be infections, adjudicated by the SAC mostly as common (88.4%). A high percentage (17.4%) of OI was reported. Among all infectious events, herpes zoster and mycobacterial infections were the most frequent. A list of OI in pediatrics was identified for subjects with JIA.

Conclusions: Registries represent a powerful tool to address important issues on safety in children with JIA treated with immunosuppressive therapy. Their value can be increased by combining individual patient data from different national and international registries. The analysis of the AE in JIA patients has showed that infections are the most frequent event. However they are usually common and not life-threatening.

OUTLINE

- The present thesis has been divided into 5 chapters. Except for chapter 3, all chapters correspond to papers recently published on pediatric rheumatology journals by Dr. Gabriella Giancane during her PhD course.

- Chapter 1 and 2 describe the recent advances in different categories of juvenile idiopathic arthritis (JIA) in order to introduce the reader to the disease, its therapy and the possible safety implications for treatment.

- Chapter 3 provides a general description of the Pharmachild registry.

- Chapter 4 and 5 describe the results from the Pharmachild registry with a focus on infections.

CHAPTER 1

OLIGOARTICULAR AND POLYARTICULAR JUVENILE IDIOPATHIC ARTHRITIS

ABSTRACT

In the last two decades, the management of juvenile idiopathic arthritis (JIA) has been revolutionized by the increased tendency toward early aggressive interventions and the availability of the novel biologic medications. In 2017, three novel randomized controlled trials have evaluated the effectiveness and tolerability of golimumab and tocilizumab in polyarticular JIA, and have shown that the combination with methotrexate may increase and prolong the effect of intra-articular corticosteroid injection in children with oligoarthritis. A more rational approach to the management of JIA is being fostered by the recent publication of therapeutic recommendations, consensus treatment plans and advice for the optimal care. A few months ago, an international consensus effort has led to the development of the recommendations for the treat-to-target in JIA. The application of this strategy in routine care may improve disease outcome. Because the potential of attaining inactive disease in children with JIA has increased markedly, there is an urgent need for randomized controlled trials, analyses of clinical datasets, and expert advice to guide discontinuation of medications once complete disease quiescence has been achieved.

Introduction

The term juvenile idiopathic arthritis (JIA) embraces a heterogeneous group of illnesses, all displaying joint inflammation, but with distinct clinical phenotypes, disease courses, outcomes, and presumably, genetic background and pathophysiology (1). The current disease classification, based on the criteria created by the Pediatric Task Force of the International League of Associations for Rheumatology (ILAR), outlines seven disease categories, defined on the basis of the clinical and laboratory features present in the first 6 months of illness (2). JIA is the most common rheumatic disease of childhood and a leading cause of acquired disability in the pediatric age group.

In the past two decades, the management of JIA has been revolutionized by the tendency toward earlier introduction of methotrexate (MTX), the more widespread use of intra-articular corticosteroids (IACs), and, most importantly, the availability of biologic disease-modifying antirheumatic drugs (DMARDs) (3). This advance has made disease remission an achievable objective for most children with JIA. Complete disease control is regarded as the ideal therapeutic goal because its attainment was found to lead to better long-term outlook (4).

In recent years, the information on the efficacy and safety of drug therapies for JIA has been enriched through the accomplishment of new randomized controlled trials (RCTs) of traditional medications and biologic DMARDs. In addition, a more rational therapeutic approach has been fostered by the promulgation of therapeutic recommendations and consensus treatment plans. Most recently, a multinational collaborative effort has led to develop the recommendations for the treat-to-target (T2T) strategy in JIA. There is currently an increasing interest for an international consensus and evidence-based information to establish the optimal time for discontinuation of medication therapies in children with JIA who achieve sustained clinical remission.

The aim of the present review is to summarize the results of the RCTs conducted in the last year in oligoarticular and polyarticular JIA, to examine the therapeutic recommendations and consensus treatment plans proposed for the same disease subsets, and to discuss the rationale that underlies the implementation of the T2T strategy in JIA. In addition, the results of a recent survey aimed to assess the

attitudes and strategies of pediatric rheumatologists toward withdrawing medications in children with clinically inactive JIA are discussed.

Recent therapeutic advances in oligoarticular and polyarticular juvenile idiopathic arthritis

Oligoarthritis, which is defined as an arthritis that affects four or fewer joints during the first 6 months of illness, is the most common JIA category in Caucasian children in North America and Europe (5). Although articular damage and physical disability in oligoarthritis are generally less common and severe than those seen in other forms of JIA, children with this disease may develop significant musculoskeletal abnormalities, such as flexion contractures, valgus deformities, and localized disturbance of bone growth (1). Furthermore, a sizeable proportion of them experience a spread of joint disease over time (so-called extended oligoarthritis). In this subgroup, the prognosis is guarded (6,7).

In contrast to the numerous RCTs that have been performed in polyarticular and systemic JIA (3), only a few evidence-based data are available to guide the treatment of oligoarthritis (8–11). As a result, the management of this condition is largely empirical and likely variable among pediatric rheumatologists (12).

IAC injections are widely used in the treatment of children with oligoarthritis (13). However, the role of methotrexate (MTX), which is a key medication in the therapeutic regimen of polyarticular JIA, in this disease subset are still unclear. Ravelli and co-workers (14) addressed the question of whether the concomitant administration of MTX to children with oligoarticular JIA who undergo IAC therapy augments the frequency and duration of remission of joint disease. This multicenter RCT conducted in Italy compared IAC injections alone versus IAC injections plus oral MTX in children with oligoarticular JIA. Although in the intention-to-treat analysis of the primary outcome (remission of arthritis symptoms in all injected joints at 12 months) the difference between the two therapeutic groups was not significant, post-hoc multivariable analysis and Cox proportional hazards model suggested that concomitant administration of MTX may prolong and, to a lesser extent, augment the effectiveness of IAC therapy. The assessment of safety did not show an appreciable increase in serious toxicity.

The results of this study suggest that, owing to its high remitting potential, the combination of IAC injections and MTX could play a major role in T2T strategies for children with chronic arthritis. An unexpected finding was that he addition of MTX did not reduce the prevalence of new-onset of arthritis in previously unaffected joints, which highlights the need of future studies aimed to scrutinize the capability of therapeutic interventions to prevent arthritis extension in children with oligoarticular-onset JIA.

Previous RCTs have evaluated the efficacy and safety of three TNF inhibitors in polyarticular JIA: etanercept (15), infliximab (16) and adalimumab (17). Etanercept and adalimumab are presently licensed for use in JIA. A recent three-part randomized double-blinded placebo-controlled withdrawal trial (GO-KIDS study) assessed a fourth TNF blocker, golimumab, in active polyarticular-course JIA (18). Golimumab is a fully human, anti-TNF-α monoclonal antibody that can be administered either intravenously or subcutaneously. The objectives of this study were to evaluate the efficacy, safety and pharmacokinetics of subcutaneous golimumab in children with active polyarticular JIA despite MTX therapy.

During Part 1 (weeks 0–16), all patients received open-label golimumab (30 mg/m^2 of body surface area; maximum: 50 mg/dose) every 4 weeks, together with weekly MTX. Patients with at least 30% improvement per American College of Rheumatology (ACR) Pediatric (Pedi) 30 in Part 1 entered the double-blinded Part 2 (weeks 16–48), after 1:1 randomization, to continue golimumab or switch to placebo. In Part 3, golimumab was continued or could be restarted as in Part 1. The primary outcome was disease flares in Part 2; secondary outcomes included ACR Pedi 50,70 and 90 responses, clinical remission, PK and safety.

Of the 173 patients enrolled, 89.0% had an ACR Pedi 30 response and 79.2%, 65.9% and 36.4% demonstrated ACR Pedi 50, 70 and 90 responses, respectively, in Part 1. At week 48, the primary endpoint was not met as treatment groups had comparable frequency of disease flares (41% in the golimumab group vs 47% in the placebo group; p=0.41), and the rates of clinical remission were also comparable (12.8% in the golimumab group vs 11.8% in the placebo group). Frequency of adverse events and serious adverse events were similar in the treatment groups

during Part 2. Injection site reactions occurred in less than 1% of all injections. PK analysis revealed that the dosing of golimumab was correct.

The authors concluded that although the primary endpoint was not met, golimumab led to quick and clinically relevant improvement that was maintained over time even in patients who received placebo after week 16, and was well tolerated. Possible explanations for the failure to meet the primary endpoint include the long half-life of golimumab could have led to carry-over effects, with sustained disease control in patients who received placebo in part 2 and consequent delayed flare events in the placebo group; the low inflammatory burden of the study population; and the mandatory MTX background therapy that might have helped maintain disease control. Despite these negative results, it is widely thought that golimumab is effective in chronic arthritis and should be added to the therapeutic armamentarium for children with JIA (19).

Tocilizumab (TCZ) is a humanized, monoclonal, antihuman interleukin (IL)-6 receptor (IL-6R) antibody that binds to membrane and soluble IL-6R, blocking IL-6-mediated signaling (20,21). Two RCTs have shown that tocilizumab is efficacious and well tolerated in the management of children with systemic JIA (22,23).

Brunner and colleagues evaluated the efficacy and safety of TCZ for the treatment of patients with polyarticular-course JIA (24). This three-part, randomized, placebo-controlled, double-blind withdrawal study (CHERISH) enrolled patients who had active disease for a minimum of 6 months and inadequate responses to MTX. Part 1 was a 16-week, active-treatment, open-label, lead-in period, during which patients whose body weight (BW) was $\geq$ 30 kg received TCZ 8 mg/kg and patients weighting less than 30 kg were randomly assigned 1:1 to receive TCZ at 8 mg/kg or 10 mg/kg. The drug was administered intravenously every 4 weeks. At week 16, patients with at least ACR Pedi 30 response entered a 24-week, double-blind part 2 after randomization 1:1 to placebo or TCZ (stratified by MTX and corticosteroid use) for evaluation of the primary end point, which was disease flare, compared with week 16. Patients flaring or completing part 2 were given open-label TCZ in the part 3 of the study (64 weeks).

Of the 188 patients who were entered in part 1, 15 (7.9%) did not achieve an ACR Pedi 30 response and were discontinued from the study. Of the 163 patients who entered part 2, the 82 received TCZ and 81 were switched to placebo. The primary endpoint at week 40 was met as there were significantly more disease flare in the placebo group that in patients remaining on TCZ (48.1% versus 25.6%; p=0.0024). At the end of part 2, 64.6% and 45.1% of patients receiving TCZ had ACR Pedi 70 and ACR Pedi 90 responses, respectively. Response rates were numerically lower among patients weighting less than 30 kg who received 8 mg/kg TCZ than in the other two groups. The rates per 100 patient-years of adverse events (AEs) and serious AEs (SAEs) were 480 and 12.5, respectively; infections were the most common SAE (4.9/100 patient-years).

This study showed that TCZ at monthly dosing of 8 mm/kg in patients weighting 30 kg or more and 10 mg/kg in patients weighting less than 30 mg/kg provided sustained and clinically meaningful improvement for patients with polyarticular-course JIA. The frequency of neutropenia and the rate of serious infection were both lower than those observed in a previous trial of TCZ in systemic JIA (3.7% versus 16.9% and 4.9/100 patient-year versus 11.0/100 patient-year, respectively) (23). An interesting observation of this study was that biological-naïve patients had a lower incidence of flare regardless of assignation to TCZ of placebo, which is in keeping with the notion that patients previously treated with biologic medications could be more treatment-resistant. Also importantly, concomitant MTX administration was associated with fewer flare episodes both in TCZ and placebo subgroups.

Treatment recommendations and consensus treatment plans

In 2011, the ACR published a set of recommendations aimed to assist physicians in selecting the safest and most effective treatment for JIA (25). These recommendations were created following the Research and Development/University of California at Los Angeles (RAND/UCLA) Appropriateness Method and in accordance to the principles of the Appraisal of Guidelines for Research and Evaluation instrument (AGREE; www. agreecollaboration.org). The therapeutic choices are based on a step-up approach,

which dictates the prescription of medications with greater potency once the preceding treatment has failed. Instead of considering the ILAR categories, children with JIA were grouped into individual ‘treatment groups’. Recommendations were proposed for five treatment groups and were shaped according to the grade of disease activity and the presence of features of poor prognosis specific for each group (Tables 1 and 2). Three levels of disease activity were defined: low, moderate, and high. The state of inactive disease/clinical remission was not considered. Tapering or discontinuation of medications for patients with inactive disease was also not addressed. In addition to the recommendations regarding treatment effectiveness, guidance for the safety monitoring of the medications used in JIA was provided. (26)

We provide herein a summary of the recommendations outlined for JIA patients with a history of arthritis of 4 or fewer joints or 5 or more joints.

Table 1. American College of Rheumatology Recommendations for the treatment of juvenile idiopathic arthritis: features of poor prognosis and disease activity for a history of arthritis of 4 or fewer joints (*adapted from ref.* (25))

FEATURES OF POOR PROGNOSIS (must satisfy 1)
-Arthritis of the hip or cervical spine
-Arthritis of the ankle or wrist AND marked or prolonged inflammatory marker elevation
-Radiographic damage (erosions or joint space narrowing by radiograph)
DISEASE ACTIVITY LEVELS
<u>Low disease activity (must satisfy all)</u>
-1 or fewer active joints
-Erythrocyte sedimentation rate or C-reactive protein level normal
-Physician global assessment of overall disease activity <3 of 10
-Patient/parent global assessment of overall well-being <2 of 10
<u>Moderate disease activity (does not satisfy criteria for low or high activity)</u>
-1 or more features greater than low disease activity level AND fewer than 3 features of high disease activity
<u>High disease activity (must satisfy at least 3)</u>
-2 or more active joints
-Erythrocyte sedimentation rate or C-reactive protein level greater than twice upper limit of normal
-Physician global assessment of overall disease activity ≥7 of 10
-Patient/parent global assessment of overall well-being ≥4 of 10

Table 2. American College of Rheumatology Recommendations for the treatment of juvenile idiopathic arthritis: features of poor prognosis and disease activity for a history of arthritis of 5 or more joints (a*dapted from ref.* (25))

FEATURES OF POOR PROGNOSIS (must satisfy 1)
-Arthritis of the hip or cervical spine
-Positive rheumatoid factor OR anti–cyclic citrullinated peptide antibodies
-Radiographic damage (erosions or joint space narrowing by radiograph)
DISEASE ACTIVITY LEVELS
Low disease activity (must satisfy all)
-4 or fewer active joints
-Erythrocyte sedimentation rate or C-reactive protein level normal
-Physician global assessment of overall disease activity <4 of 10
-Patient/parent global assessment of overall well-being <2 of 10
Moderate disease activity (does not satisfy criteria for low or high activity)
-1 or more features greater than low disease activity level AND fewer than 3 features of high disease activity
High disease activity (must satisfy at least 3)
- 8 or more active joints
-Erythrocyte sedimentation rate or C-reactive protein level greater than twice upper limit of normal
-Physician global assessment of overall disease activity ≥7 of 10
-Patient/parent global assessment of overall well-being ≥5 of 10

History of arthritis of 4 or fewer joints

First-line NSAID monotherapy was recommended as one treatment approach for patients with low disease activity, without joint contracture and without features of poor prognosis. However, continuation of NSAID monotherapy for more than 2 months was felt inappropriate for patients with continued active arthritis, independently of poor prognostic features.

IAC injections were recommended for all patients with active arthritis, irrespective of disease activity level, prognostic features, or joint contracture. Triamcinolone hexacetonide was indicated as the preparation of choice. A duration of clinical improvement shorter than 4 months after local injection therapy may prompt the escalation of systemic therapy. However, IAC injections that result in clinical improvement of arthritis for at least 4 months may be repeated as needed.

Initiation of MTX was recommended as initial treatment for patients with high disease activity and features of poor prognosis. After a previous IAC injection, MTX start was recommended for patients with high disease activity without features of poor prognosis and for patients with moderate disease activity and features of poor prognosis. Following repeated IAC injections, initiation of MTX was recommended for patients with moderate disease activity without features of poor prognosis and for patients with low disease activity and features of poor prognosis.

Initiation of a TNF inhibitor was recommended for patients who have received IAC injections and at least 3 months of MTX and have moderate or high disease activity and features of poor prognosis. Anti-TNF therapy was also recommended for patients who have received IAC injections and 6 months of MTX and have high disease activity without features of poor prognosis.

History of arthritis of 5 or more joints

The indication of NSAID monotherapy was uncertain for patients with active arthritis. Continuation of NSAID monotherapy for longer than 2 months was considered inappropriate for patients with active arthritis, irrespective of poor prognostic features.

Initial MTX therapy was recommended for patients with high disease activity, irrespective of poor prognostic factors, and for patients with moderate disease activity and features of poor prognosis. Following approximately 1 month of NSAIDs, initiation of MTX was recommended for patients with low disease activity and features of poor prognosis. After 1 to 2 months of NSAIDs, initiation of MTX was recommended for patients with moderate disease activity without features of poor prognosis.

The use of methotrexate is favored over that of leflunomide, owing to the greater general experience with methotrexate. Nevertheless, initiation of leflunomide was highlighted as suitable initial treatment approach for patients with high disease activity and features of poor prognosis. Following a brief trial of NSAIDs, initiation of leflunomide was recommended as one treatment approach for patients with high disease activity without features of poor prognosis and for patients with moderate disease activity with features of poor prognosis.

Initiation of a TNF inhibitor was recommended for patients who have received MTX or leflunomide for 3 months and have moderate or high disease activity, irrespective of poor prognostic features. Anti-TNF therapy was also recommended for patients who have received MTX or leflunomide for 6 months and have low disease activity, irrespective of poor prognostic features.

Switching from one TNF inhibitor to another was considered indicated for patients who have received the current TNFα inhibitor for 4 months and have moderate or high disease activity, irrespective of poor prognostic features. Switching to a TNF inhibitor was recommended as one treatment approach for patients who have received abatacept for 3 months and have high disease activity and features of poor prognosis and for patients who have received abatacept for 6 months and have moderate or high disease activity, irrespective of prognostic features.

Prescription of abatacept was recommended as one treatment approach for patients who have received a TNFα inhibitor for 4 months and have high disease activity, irrespective of features of poor prognosis, or moderate disease activity and features of poor prognosis. Introduction of abatacept was also considered suitable for patients who have received more than one TNF inhibitor sequentially and have

moderate or high disease activity, irrespective of poor prognostic features, or low disease activity with features of poor prognosis.

Rituximab was recommended as one treatment approach for patients who have received a TNFα inhibitor and abatacept sequentially and have high disease activity, irrespective of poor prognostic features, or have moderate disease activity and features of poor prognosis. Rituximab was felt to be more appropriate for patients who are positive for rheumatoid factor than for patients who are not.

Guidelines for the management of JIA were also promulgated by the German Society for Pediatric Rheumatology (27). In the paper that reports these guidelines, the authors emphasize the following differences with the ACR recommendations: 1) The ACR recommendations advise an early aggressive therapeutic approach. For instance, they recommend MTX as first-line treatment for patients with oligoarthritis and high disease activity. The German experts felt that MTX could be recommended in oligoarthritis in case of insufficient therapeutic effect of prior treatment with NSAIDs and/or corticosteroids. 2) The ACR recommendation of use of TNF blockers as escalation therapy in selected patients with ≤ 4 affected joints is based on studies conducted in patients with polyarthritis or extended oligoarthritis and not supported by evidence that these medications are safe and efficacious in patients with persistent oligoarthritis. 3) The German experts considered a brief trial of local or systemic administration of corticosteroids plus NSAIDs as a suitable first-line treatment for patients with polyarthritis. In this disease subset, the ACR recommends initial MTX therapy irrespective of disease activity. 4) Consensus was reached among German investigators about the use of corticosteroids as bridging therapy until full onset of the therapeutic effect of DMARDs is seen. The ACR recommendations do not provide any guide about the use of systemic corticosteroids for patients with oligoarthritis and polyarthritis, but only for patients with systemic arthritis. 5) Non drug-based therapy, including physical and occupational therapy, surgical interventions and psychological support, are not covered by the ACR recommendations.

In 2016, the Pediatric Committee of the Canadian Rheumatology Association published a Position Statement on the current management of JIA (28). Overall, the Canadian committee members endorsed the ACR recommendations for

pharmacologic management of JIA. In addition, they highlight the importance of exercise, physiotherapy and occupational therapy, discuss the role of imaging to monitor disease activity and damage, and incorporate the recommendations about uveitis screening and management. Notably, in the general treatment principles it is stated that the goal of treatment is to attain a state of inactive disease with full, pain-free function.

In 2010, the British Society for Paediatric and Adolescent Rheumatology (BSPAR) published the Standards of Care for children and young people with JIA, which were aimed to help the pediatric rheumatology teams to improve the service they provide by formulating a statement of the minimum set of standards of care for children, adolescents, and young adults with JIA (29). This advocacy statement emphasizes the importance of empowering children and their caregivers, facilitating early detection of JIA, prompt referral to a team of health professionals who are expert in the diagnosis and management of childhood rheumatic diseases, prompt access to all appropriate pharmacologic and biologic therapies, and regular followup and monitoring.

In 2014, the Childhood Arthritis and Rheumatology Research Alliance (CARRA) developed Consensus Treatment Plans (CTPs) for new-onset polyarticular JIA through a case-based survey administered to CARRA members. This survey identified significant variability among treatment approaches. Two face-to-face consensus conferences were carried out by employing a modified nominal group technique in order to define treatment strategies, operational case definition, endpoints and data elements to be collected. A core workgroup subsequently reviewed the relevant literature, refined plans and developed medication dosing and monitoring recommendations. The approved CTPs included a step-up plan (non-biologic DMARD followed by a biologic DMARD in case of inadequate response in 3-6 months), an early combination plan (non-biologic and biologic DMARD combined within a month of treatment initiation), and a biologic only plan (biologic DMARD started without initiation of non-biologic DMARD). These approaches were approved by 96% of the CARRA JIA Research Committee members attending the 2013 CARRA face-to-face meetings (30).

These plans were aimed to highlight the importance of a correct timing in the introduction of therapies, rather than to address the use of specific medications, with the ultimate goal of reducing variations in treatment choices. In addition, they provide advice about medication dosing and monitoring, including tapering of corticosteroids. A major point of discussion of the face-to-face meeting in 2013 was selection of the outcome to be used as primary endpoint and the time point of observation. In the end, an agreement was reached that the ACR Pedi 90 at 12 months is a robust, meaningful and realistic outcome in order to compare the three treatment strategies. It was also established that radiographic progression is a key outcome measure and that radiographs of at least 1 affected joint should be obtained at baseline and on a yearly basis.

Unlike the ACR recommendations, the CTPs were developed by sole expert consensus, are devoted only to treatment-naïve recent-onset patients, and reflect current therapeutic strategies used in polyarticular JIA instead of focusing on particular classes of medications.

A recently accomplished European Union-funded initiative, named SHARE (Single Hub and Access Point for Pediatric Rheumatology in Europe, has developed consensus guidelines for the optimal care of pediatric rheumatic diseases in European countries whose publication is under way (31).

Toward a treat-to-target strategy for JIA

As stated above, owing to the recent therapeutic advances, the achievement of disease remission has become a realistic objective in the management of children with JIA. As a result, the therapeutic aims in pediatric rheumatology settings are being moved toward the attainment of an inactive disease status (32–37). However, only scarce information about the potential of contemporary therapies to lead to disease remission is available. Indeed, inactive disease has seldom been included as a primary endpoint in RCTs of synthetic or biologic DMARDs in JIA. In addition, the goal of achievement of disease remission has not been uniformly formulated in the aforementioned therapeutic recommendations or guidelines. Considering that disease remission is now attainable for many, if not most, patients with JIA, it has been suggested that future treatment guidelines should incorporate as overriding

goal the achievement of clinical remission or, at least, minimal disease activity (38,39).

Studies in adult patients with rheumatoid arthritis (RA) have shown that the strategy of tight control, with frequent adjustments of therapy according to quantitative indices, leads to improved patient outcomes (40–42). As a consequence, the paradigm of explicitly defining a treatment target and applying tight control and necessary therapeutic adaptation to reach the target has been incorporated into the 'treat-to-target' (T2T) recommendations for RA (43,44) and spondyloarthritis, comprising psoriatic arthritis (45,46). This principle has also been endorsed in the recommendations for the management of RA (47–50).

In recent years, standardized and well validated quantitative clinical measures for JIA have been published. They include the ACR Pedi response criteria (51), the definitions of clinical inactive disease (32,34) and minimal (or low) disease activity (52), and the Juvenile Arthritis Disease Activity Score (JADAS) (53,54). Cut-offs in the JADAS that correspond to the states of inactive disease and low, moderate and high disease activity have been established (55–57). The composition of the measures of inactive disease and low disease activity and the respective definitions are shown in Table 3.

Table 3. Criteria for clinical inactive disease and low (minimal) disease activity in JIA

	Items included							
	PhGA	Pa/ChGA	AJC	ESR/CRP	Systemic features	Uveitis	Morning stiffness	Requirements for classification as CID or LDA
Criteria for CID								
Wallace's preliminary criteria(34)	X		X	X	X	X[§]		Normal ESR/CRP and all other items at zero or not present
ACR preliminary criteria(32)	X		X	X	X	X[£]	X	Normal ESR/CRP, morning stiffness ≤15 min and all other items at zero or not present
JADAS criteria(55)	X	X	X	X				JADAS ≤ 1
cJADAS criteria(56)	X	X	X					cJADAS ≤ 1
Criteria for LDA								
Magni-Manzoni criteria – Oligo(52)	X		X					PGA ≤ 2.5, AJC = 0

Magni-Manzoni criteria – Poly(52)	X	X	X		PGA ≤ 3.4, Pa/PtGA ≤ 2.1, AJC ≤ 1[$]
JADAS criteria(55)	X	X	X	X	Oligoarticular course: JADAS ≤ 2.0 Polyarticular course: JADAS ≤ 3.8
cJADAS criteria(56)	X	X	X		Oligoarticular course: cJADAS ≤ 1.5 Polyarticular course: cJADAS ≤ 2.5

[§]Inactive uveitis was not defined

[£]Inactive uveitis as defined by the Standardization of Uveitis Nomenclature working group

[$]In systemic arthritis, absence of systemic features is required

ACR: American College of Rheumatology; AJC: active joint count; CID: clinical inactive disease; cJADAS: clinical JADAS; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; JADAS: Juvenile Arthritis Disease Activity Score; JIA: juvenile idiopathic arthritis; LDA: low disease activity; PGA: physician's global assessment of overall disease activity; Oligo: persistent oligoarthritis; Pa/ChGA: Parent's/child's global assessment of child's overall well-being; Poly: extended oligoarthritis, polyarthritis and systemic arthritis.

All these tools constitute suitable targets to implement therapeutic strategies aimed at tight disease control in pediatric rheumatology settings. Recently, the preliminary definition of inactive disease in JIA (32,34) has been used as primary outcome measure in a randomized, double-blind, placebo-controlled trial of two aggressive treatment strategies in children with early JIA (58). Recently, the importance of applying the T2T strategy in childhood arthritis has been emphasized, as this may lead to improve patient outcomes (59,60). However, this approach has not hitherto been implemented in routine management of JIA.

In 2017, an international Task Force of expert pediatric rheumatologists was convened to discuss this issue and to reach a consensus on a set of recommendations aimed at defining a T2T strategy for JIA. This effort was preceded a comprehensive systematic literature review (SLR), which was aimed to provide for consensus on the definition of treatment targets.

It was decided that the SLR should primarily explore the current evidence regarding the following aspects: whether the treat-to-target strategy is preferable to a non-steered management; the time that should be waited to escalate treatment in patients with active disease; the best tool to be used as target; the potential role of biomarkers in decision-making; the influence of disease duration and JIA heterogeneity on the strategy and choice of the target; the evidence that a longer time spent in inactive disease leads to better long-term outcome; the impact of treat-to-target in terms of cost, safety and treatment burden; the effect of treat-to-target on co-morbidities, including uveitis, psoriasis, depression, infections and adverse events; the evidence that improved patient/parent understanding on the disease improves the outcome; and the impact of treat-to-target on functional status, health-related quality of life and burden of disease on patient's family life.

The results of the SLR were analyzed by the expert Task Force at a consensus conference, which was held in Munich, Germany on August 24-25. After extensive discussion, numerous amendments and repeated voting, the experts formulated a set of recommendations in line with the European League Against Rheumatism (EULAR) standardized operating procedures (61). The individual statements that received a positive vote by the qualified majority of the expert committee members were retained and constituted the overarching principles and recommendations that

will guide the implementation of the T2T in JIA. These recommendations are in progress of publication (Ravelli A *et al*, manuscript in preparation).

Treatment discontinuation after disease remission

As discussed above, owing to the current therapeutic progresses, a high percentage of patients achieves an inactive disease status with contemporary therapies. Once complete disease quiescence has been achieved, it would be desirable to discontinue ongoing treatment to avoid prolonged exposure of the child to the potential of adverse effects. This goal should be balanced with the risk of disease flare after withdrawal of therapy. However, currently no guidelines or recommendations are available concerning appropriate discontinuation of medications after attainment of inactive disease status. As a result, treatment practices vary widely and remain empiric and physician-dependent.

Several studies have examined the effect of discontinuing treatment in children with JIA who had achieved a state of clinical remission (*reviewed in* (62)). Overall, the relapse rate after termination of both methotrexate and TNF antagonists was substantial. However, no consistent predictors of the risk of flare were identified.

Horton and co-workers (63) recently surveyed the members of CARRA to gain insights into the attitudes and strategies of pediatric rheumatologists toward withdrawing medications in children with non-systemic JIA who had achieved clinically inactive disease. Of the 388 practitioners, 124 (32%) provided their feed-back. As expected, there was marked variability in the approaches regarding when and how to withdraw medications. The most highly ranked factors in making decisions about drug discontinuation was duration of inactive disease, although this factor was valued less by more experienced physicians. Other reported factors were a history of drug toxicity, patient and family preferences, duration of JIA before inactive disease, failure of multiple prior synthetic or biologic DMARDs, presence of joint damage, a history of previous disease flare, and evidence of subclinical inflammation on imaging. The JIA category was also important, with diagnoses of pJIA RF+ and persistent oligoarthritis making respondents less likely and more likely, respectively, to stop medications.

About three-quarters of respondents would wait for a minimum of 6–12 months of inactive disease before tapering or discontinuing medications, whereas about two-third would wait for at least 12 months. There was a wide variability in the policy for decreasing or stopping or decreasing MTX or biologic therapies. stopping MTX or biologics. For children receiving combined administration of MTX and biologics, most clinicians preferred to stop MTX first.

Most respondents reported using imaging only seldom or sometimes to guide decision making, but most were also reluctant to withdraw medications in the presence of asymptomatic imaging abnormalities suggestive of subclinical inflammation. This likely reflected the uncertainty about the prognostic significance of the finding of subclinical synovitis on ultrasound and MRI in children with JIA in clinical remission (64).

Conclusions

In the last year, the therapeutic armamentarium for JIA has been enriched by the evaluation of the effectiveness and safety of two biologic DMARDs, golimumab and tocilizumab, in polyarthritis. In addition, evidence has been provided that the association with methotrexate may increase the effectiveness of IACs in children with oligoarthritis. Altogether, these RCTs provide the clinicians with adjunctive evidence-based information that may help to augment the likelihood of reaching the desired therapeutic objectives.

A more rational approach to the management of JIA has been fostered by the publication of therapeutic recommendations, consensus treatment plans and advice for the best standard of care for children with JIA. These efforts offer a valuable platform to better harmonize the protocols for disease treatment and monitoring in pediatric rheumatology centers throughout the world.

There is now compelling evidence that the incorporation of a T2T strategy may improve the outcomes in children with JIA. A recent international consensus effort has led to the promulgation of the recommendations for the implementation of the T2T approach in the management of JIA. The recommendations are primarily aimed at pediatric rheumatology practitioners and other health professionals involved in the care of patients with JIA. However, they will likely encounter the

interest of clinical trialists and regulators, owing to the increasing interest of pharmaceutic industries for strategic trials. Parents and patients are another important audience that should be informed on these statements and their potential role in preventing or minimizing damage and disability.

There is now an intense debate regarding whether targeting therapy to biomarkers or imaging measures provides better outcomes compared to treating to clinical targets alone. The studies performed thus far on these alternative targets do not allow to state their superiority. However, it is anticipated that the T2T approach aimed at clinical, biomarker or imaging remission in JIA will constitute a major area for research in the upcoming future.

Because the potential of attaining inactive disease in children with JIA has increased markedly, there is an urgent need for randomized controlled trials, analyses of clinical databases, and expert recommendations to guide discontinuation of medications once complete disease quiescence has been achieved. Another important matter for future studies is to identify predictors of disease flare after treatment discontinuation. Thus far, immunologic biomarkers, particularly the myeloid-related proteins MPR8/14, appear more promising than demographic and clinical parameters and ultrasound. However, well designed prospective studies must be conducted to recognize all potential predictors.

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CHAPTER 2

SYSTEMIC JUVENILE IDIOPATHIC ARTHRITIS

ABSTRACT

Systemic juvenile idiopathic arthritis (sJIA) is the form of childhood arthritis whose treatment is most challenging. The demonstration of the prominent involvement of interleukin (IL)-1 in disease pathogenesis has provided the rationale for the treatment with biologic medications that antagonize this cytokine. The three IL-1 blockers that have been tested so far (anakinra, canakinumab and rilonacept) have all been proven effective and safe, although only canakinumab is currently approved for use in sJIA. The studies on IL-1 inhibition in sJIA published in the past few years suggest that children with fewer affected joints, higher neutrophil count, younger age at disease onset, shorter disease duration, or, possibly, higher ferritin level may respond better to anti-IL-1 treatment. In addition, it has been postulated that use of IL-1 blockade as first-line therapy may take advantage of a "window of opportunity", in which disease pathophysiology can be altered to prevent the occurrence of chronic arthritis. In this review, we analyze the published literature on IL-1 inhibitors in sJIA and discuss the rationale underlying the use of these medications, the results of therapeutic studies, and the controversial issues.

Introduction

Systemic juvenile idiopathic arthritis (sJIA) is the most severe form of childhood arthritis and the most difficult to treat. Until recently, sJIA was considered a therapeutic orphan, since the most effective treatment was corticosteroids, whose long-term administration is associated with a wide range of side effects, including an increased risk of vertebral fractures, cataracts, growth retardation, and susceptibility to infection. Traditional disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate, have limited efficacy for the joint disease and virtually no impact on the systemic features. Poor responses have also been reported with the newer anti-tumor necrosis factor (TNF) agents (65–68), although these medications may be effective in the later afebrile disease phase, characterized by chronic arthritis (69,70). Recently, anti-TNF therapy was found to restore normal levels of vasculoprotective and proangiogenic endothelial progenitor cells in children with JIA (71). Several experimental studies have suggested a major pathogenetic role for cytokines such as interleukin (IL)-6 (72) and, more recently, IL-1 (73). These findings have opened the way to the successful treatment of sJIA with biologic agents that antagonize selectively these cytokines.

In the present review, we provide a brief overview of the main clinical features of sJIA and summarize the recent advances in therapy with IL-1 inhibitors.

Clinical characteristics of sJIA

sJIA accounts for 5-15% of all children with chronic arthritis in Europe and North America and is rather distinct from the other forms of JIA, owing to the association of arthritis with a severe systemic illness (74,75). It is considered the childhood-onset equivalent of adult-onset Still's disease. Children with sJIA typically present with a quotidian, high-spiking fever, often accompanied by an erythematous, salmon pink, macular rash, which tends to be migratory and is strikingly evanescent. Myalgias and abdominal pain may be intense during fever peaks. Other systemic manifestations include diffuse lymphoadenopathy, hepatosplenomegaly, and serositis, especially pleuritis and pericarditis. Arthritis is more often symmetrical and polyarticular, but may be absent at onset and develop

during the disease course weeks, months, or, rarely, years after the occurrence of extra-articular symptoms. At disease presentation, particularly when arthritis is not yet present, children often require an accurate diagnostic work-up to exclude other potential diagnoses, such as infections and malignancy. Characteristic laboratory features include anemia (usually hypochromic and microcytic), leukocytosis, thrombocytosis, elevated immunoglobulins, increased erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), and hypoalbuminemia. The International League for Associations of Rheumatology (ILAR) criteria for the classification of sJIA are shown in Table 1.

Table 1. ILAR criteria for sJIA.

Arthritis with, or preceded by, daily fever of at least 2 weeks' duration that is documented to be
quotidian for at least 3 days, and accompanied by one or more of the following:
1) evanescent, non-fixed, erythematous rash
2) generalized lymphadenopathy
3) hepatomegaly or splenomegaly
4) pericarditis, pleuritis and/or peritonitis
Exclusion criteria
- Psoriasis or a history of psoriasis in patient or first-degree relative
- Arthritis in HLA-B27–positive male > 6 years of age
- HLA-B27 associated diseases such as ankylosing spondylitis, enthesitis-related arthritis, sacroiliitis with inflammatory bowel disease, reactive arthritis, or acute anterior uveitis; or history of these in a first-degree relative
- Positive rheumatoid factor test on 2 occasions ≥ 3 months apart

Adapted from Petty RE et al. J Rheumatol 2004;31:390-2.

It has recently been argued that there are patients not classifiable as sJIA by current criteria who present with the same systemic features seen in classic sJIA, but never develop arthritis (74). The similarity of clinical manifestations suggest that their illness is closely related to sJIA, despite the absence of arthritis. This subgroup of patients, which nowadays lacks a taxonomic designation, would meet the criteria for adult-onset Still's disease, which do not require the presence of arthritis for diagnosis (76). These considerations have led to propose to include these patients in the sJIA category, and to rename sJIA as Still's disease in order to harmonize the terminology with that of the adult counterpart (77). A recent analysis of initial clinical features of 136 children with sJIA through a Web-based registry has shown that the ILAR criteria identified only 30% of sJIA patients at disease presentation (78).

The course and prognosis of sJIA are variable (74,75). Around 40% of patients have a good long-term outcome, with a monocyclic course that enters a permanent remission with time. A small proportion of patients have an intermittent course, with relapses followed by periods of quiescence. In the remaining half of the patients, the disease pursues a more severe, persistent disease course. Among this unremitting subset, the sickest children have ongoing systemic symptoms, early destructive polyarthritis, growth failure, and are exposed to the serious side effects of corticosteroids. This particular disease phenotype represents the most disabling of all the different forms of JIA.

Children with sJIA are uniquely susceptible to develop a potentially fatal complication known as macrophage activation syndrome (MAS). MAS is characterized by an overwhelming inflammatory reaction due to an uncontrolled and dysfunctional immune response involving the continued activation and expansion of T lymphocytes and macrophages, with resultant massive hypersecretion of proinflammatory cytokines (79,80). Distinctive clinical features of MAS are high, nonremitting fever, hepatosplenomegaly, generalized lymphadenopathy, central nervous system dysfunction, hemorrhagic manifestations, and, in its most extreme forms, multiorgan failure. Characteristic laboratory abnormalities include pancytopenia, increased levels of ferritin, liver enzymes, lactate dehydrogenase, triglycerides, D-dimers, and soluble IL-2 receptor a (also known as soluble CD25),

and decreased fibrinogen levels. A characteristic histopathologic feature of MAS is the accumulation of well-differentiated macrophages exhibiting hemophagocytic activity in bone marrow biopsy specimens or aspirates (81). Although approximately 10% of sJIA patients develop overt MAS, up to 30% of children have evidence of subclinical MAS (82,83). MAS can result in progressive multi-organ failure and eventually a fatal outcome if unrecognized. Recent studies indicate a mortality rate of 8% (84,85). In 2016, classification criteria for MAS complicating sJIA have been published (Table 2). (86,87)

Table 2. 2016 classification criteria of MAS.

A febrile patient with known or suspected systemic juvenile idiopathic arthritis is classified as having macrophage activation syndrome if the following criteria are met:
Ferritin > 684 ng/ml
and any 2 of the following:
Platelet count ≤ 181 x 10^9/liter
Aspartate aminotransferase > 48 units/liter
Triglycerides > 156 mg/dl
Fibrinogen ≤ 360 mg/dl

Adapted from Ravelli A et al. Ann Rheum Dis 2016;75:481–489 and Arthritis Rheumatol 2016; 68: 566–76.

Interleukin-1 inhibitors in the management of sJIA

Anakinra

The first observation of successful treatment of sJIA with IL-1 inhibition dates back to 2004, when a remarkable response to the recombinant interleukin (IL)-1 receptor antagonist anakinra in two patients with severe and refractory disease manifestations was described (88).

In a landmark study published in 2005, Pascual et al (73) reported that the administration of anakinra to 9 children with active sJIA refractory to other therapies led to striking improvement in clinical symptoms and inflammatory markers. Seven patients achieved complete remission and the other 2 patients had a partial response. The rationale for the treatment was provided by the demonstration that patients' serum induced the transcription of innate immunity genes, included those of IL-1α and IL-1β, in healthy peripheral-blood mononuclear cells, and that patients' peripheral-blood mononuclear cells produced an excess of IL-1β upon activation.

A less impressive effectiveness was seen in a French multicenter, randomized, double-blind, placebo-controlled trial (ANAJIS trial), whose primary outcome was the achievement of an American College of Rheumatology Pediatric (ACR Pedi) 30 response at 1 month. At treatment endpoint, 8 of 12 patients (67%) in the anakinra group and only 1 of 12 patients (8%) in the placebo group were responders ($p=0.003$). However, no patient in both groups achieved a more robust improvement (i.e. a modified ACR Pedi 100 response). Furthermore, loss of response was observed in most patients over time. The authors attributed the frequent lack of sustained efficacy to the presence of severe polyarthritis and the absence of fever in most patients at enrolment, to the possible insufficient dosage in younger patients, and to the study design, which precluded the concomitant use of DMARDs and allowed early tapering of corticosteroids. Notably, a *de novo* type I interferon signature, which is not a feature of untreated sJIA, was induced in the majority of anakinra-treated patients, regardless of clinical response (89).

That anakinra could be less effective on arthritis symptoms than on systemic and laboratory features of inflammation was highlighted in a retrospective study by Gattorno and colleagues (90). By examining the pattern of response to anakinra in 22 children with sJIA, they identified two groups of patients: one group exhibited a dramatic response, with rapid improvement of arthritis and normalization of the CRP within the first week of treatment; the other group had no response or experienced only transient improvement of joint disease and CRP. The only difference between responders and nonresponders or incomplete responders was a lesser extension of arthritis and an increased absolute neutrophil count in the former

group. In vitro secretion of IL-1β and IL-18 by patient monocytes was not increased and was independent of both treatment outcome and disease activity. Other case series published around the same time also showed remarkable benefit among many, but not all, users of anakinra(91–93).

Recent observations suggest that initiation of anakinra early in the disease course may improve outcome. A multicenter retrospective cohort study of 46 patients who had received anakinra as part of initial corticosteroid-sparing regimen showed that around 60%, including 8 of 10 receiving anakinra monotherapy, attained a complete response without escalation of therapy. Almost all patients had rapid improvements in fever and rash, whereas a slower response of arthritis to treatment was seen, with persistently active synovitis in 39% of patients at 1 month, 27% of patients at 3 months, and 15% of patients at 6 months. Inflammatory markers normalized in most patients within one month. Evidence that early intervention with anakinra could prevent the development of persistent synovitis was obtained for 91% of 35 patients followed up for at least 6 months. Disease characteristics and treatment were similar in patients with partial or absent response and patients with complete response, except that that the former patients were markedly younger at disease onset (median age 5.2 years versus 10.2 years; P = 0.004). Notably, however, the median peak ferritin level was higher in complete responders than in partial or nonresponders (3,008 ng/ml versus 1,329 ng/ml). Although the difference was not significant, perhaps owing to the small size of the study population, this observation suggests that patients with more prominent activation of the monocyte/macrophage system are more responsive to IL-1 inhibition (94).

Vastert and co-workers (95) conducted the first prospective study of the use of an IL-1 antagonist as first-line therapy in sJIA. They started anakinra in 20 patients with new-onset sJIA who were corticosteroid-naïve. At 3 months, 85% of patients achieved an adapted ACR Pedi 90 response or had inactive disease; 75% of patients achieved this response while receiving anakinra monotherapy. In the majority of responding patients (73%), treatment could be stopped within 1 year, with remission being preserved during follow-up. However, in around one third of patients, concomitant therapy was required for maintenance of clinical response. IL-18 as

well as the myeloid-related proteins (MRP) S100A12 and S100A8/9 were found to be potential biomarkers for guiding the strategy of stopping treatment with IL-1 inhibitors.

A recent single-center experience with anakinra therapy in 25 patients with sJIA showed that 56% of patients attained inactive disease. The only baseline variable significantly associated with response was the time interval disease onset and treatment start, with earlier treatment being associated with better outcome. Once more, however, the median ferritin level tended to be higher in patients who reached inactive disease than in those who did not (1506 ng/ml versus 360 ng/ml). Importantly, the comparison of the dose administered with the ideal dose of anakinra in each individual patient did not show any relation with therapeutic response (96).

In spite of the demonstrations of its effectiveness, anakinra is not currently registered for the treatment of sJIA.

Canakinumab

A preliminary phase II, multicenter, open-label study evaluated dosing, efficacy and safety of the fully human anti-IL-1β antibody canakinumab in 23 children with sJIA and active systemic features. This analysis showed that the administration of 4 mg/kg was associated with rapid and sustained improvement in clinical response and enabled reduction or discontinuation of corticosteroids. In keeping with the findings of the aforementioned study by Gattorno et al (90), responders to canakinumab had fewer active joints and a higher white blood cell count at baseline than did nonresponders (97).

The results of this pilot study provided the basis for performing two double-blind placebo-controlled trials of canakinumab in a larger population of sJIA patients with active systemic features (98). In the first trial, 84% of patients receiving a single injection of canakinumab compared with only 10% of those receiving placebo achieved an ACR Pediatric 30 response with no fever ($p<0.001$). The frequency of inactive disease in the canakinumab group was as high as 33% after only 15 days. In the second trial, conducted with a withdrawal design, 73% of the patients demonstrated at least an ACR Pediatric 50 response and no fever and

31% had inactive disease at the end of the open-label phase, after a median of 113 days. In the randomized withdrawal phase, the frequency of flare was markedly lower in the canakinumab group than in the placebo group (74% of patients in the canakinumab group had no flare, versus 25% in the placebo group; P=0.003). At the end of the withdrawal phase, 62% of canakinumab-treated patients and 34% of patients in the placebo group had inactive disease. The average corticosteroid dose was reduced from 0.34 to 0.05 mg/kg/day and corticosteroids were discontinued in 33% of patients. Medication safety was overall good, although infections were more frequent with canakinumab than with placebo and 7 patients had MAS.

Canakinumab has been approved for the treatment for the treatment of active sJIA in children aged 2 years and older both in Europe and in the US.

Rilonacept

The efficacy and safety of the anti-IL-1 soluble decoy receptor protein, rilonacept, were evaluated in a pilot 3-phase trial consisting in a 23 months of open-label treatment preceded by a 4-week, double-blind, placebo-controlled phase. Although no significant differences in efficacy were observed between the rilonacept- and placebo-treated patients during the initial double-blind phase, fever and rash completely resolved by month 3 in all patients during the open-label treatment period and did not recur. The adapted ACR Pedi 30, 50, and 70 response rates at 3 months were 78.3%, 60.9%, and 34.8%, respectively, and were generally maintained over the study duration. In addition to declines in high-sensitivity CRP, reductions were seen in the levels of MRP-8/MRP-14 and D-dimer. In 22 of 23 patients, prednisone was tapered or discontinued. Treatment was not associated with serious adverse events (99).

A larger 24-week randomized trial of the same agent in 71 children with active arthritis in ≥2 joints, which incorporated a 4-week double-blind placebo phase, found a shorter time to response in the rilonacept arm than in the placebo arm (P=0.007). In a secondary analysis, 57% of the patients in the rilonacept arm had a response at week 4 compared with 27% of the patients in the placebo arm (P=0.016). No statistically significant association was observed between a poorer response at week 4 and absence of systemic manifestations or longer disease

duration. However, the median disease duration tended to shorter among patients who responded at week 4 compared to those who did not. The medication was generally well tolerated (100).

Thus far, rilonacept has not been approved for use in children with sJIA.

Open issues and future outlook

The advent of biologic agents that specifically inhibit IL-1 has dramatically improved clinical outcomes for many children with sJIA and confirmed the pathogenic role of this cytokine in disease processes. The demonstration of the prominent involvement of IL-1, together with the lack of HLA associations and autoantibodies and the strong implication of cells of the innate immune system, has led to the suggestion that sJIA is a distinct disease entity, with more similarities with autoinflammatory syndromes than with classic autoimmune diseases (77,101–103).

However, not all patients respond to IL-1 blockade (89,90,92,104). The varying susceptibility to anti-IL-1 therapy may be explained by the heterogeneity of sJIA. The aforementioned analysis of the pattern of response to anakinra identified two patient subsets, one with dramatic response, similar to that observed in cryopirin-associated autoinflammatory syndromes, and the other resistant or with an intermediate response. Patients responding to anti-IL-1 therapy had fewer affected joints and a higher neutrophil count (90). This observation has led to postulate that the group with bright response represents a separate entity in which autoinflammatory mechanisms play the leading pathogenetic role, whereas the group with more severe arthritis may also have autoimmune components (74). Other investigators have found evidence that anti-IL-1 treatment may be more effective for systemic features than for articular manifestations of the disease (99). However, in the canakinumab study, the response to treatment of children with polyarthritis was similar to those without polyarthritis. A differential therapeutic response based on the presence or absence of systemic features could not be evaluated in this trial because all children enrolled had ongoing fever (98).

The heterogeneous nature of sJIA has been further highlighted by Shimizu and co-workers (105), who delineated two distinct sJIA patient subsets based on their

serum IL-6 and IL-18 levels: an IL-6 dominant and an IL-18 dominant. The IL-6-dominant subset had a more severe polyarthritis and higher serum levels of matrix metalloproteinase (MMP-3), whereas the IL-18-dominant subset was more prone to develop MAS. Whether the differences in the predominant cytokine expression or in the susceptibility to anti-cytokine therapies dissect the spectrum of systemic JIA into clinically or pathogenetically distinct disease entities, remains to be established.

As noticed above, the tendency for ferritin level to be higher in responders to anakinra in some series suggests that patients with more pronounced activation of the monocyte system, which may predispose them to the progression to overt MAS, may be more susceptible to benefit from IL-1 inhibition. This hypothesis is in keeping with the recent reports of the effectiveness of anakinra in cases of MAS refractory to conventional therapies (79).

Another explanation for the inconsistent effectiveness of IL-1 inhibition could be the timing of therapy. Nearly all patients included in earlier open studies and in randomized clinical trials had long-standing disease and were still receiving systemic corticosteroids when treatment with IL-1 blocking agents was initiated. These characteristics may account for the partial or absent responses seen in a significant minority of patients. More favorable outcomes were obtained with the use of IL-blockade as first-line therapy, particularly in patients with new-onset disease and not yet exposed to corticosteroids or other DMARDs (94,95). Many patients achieved inactive disease rapidly and were able to stop anti-IL-1 therapy within one year, with sustained remission during follow-up (95). Of equal importance was the observation of a significant reduction in the proportion of children who developed the chronic polyarthritis manifestation of their disease (94).

The differential clinical responses in early versus late disease, coupled with data from animal models, have led to theorize a biphasic model of sJIA, in which the disease begins with a highly inflammatory febrile phase that, in more than half of the patients, converts over time to an afebrile phase characterized by chronic arthritis. The predominance of innate immune mechanisms in the early systemic stage, as opposed to the involvement of autoreactive T cells in the later induction of chronic arthritis, would explain why antagonism of IL-1 in new-onset disease is associated with better outcomes than those observed when this therapy is initiated

later in the disease course. Thus, early treatment with IL-1 inhibitors may take advantage of this "window of opportunity", in which disease pathophysiology can be altered to avoid the occurrence of chronic arthritis (106).

However, although this hypothesis is logical and attractive, its clinical background should be regarded in the light of some caveats. Because around 40% of patients with sJIA have a monocyclic course with spontaneous remission, results of open studies on patients with early disease may be biased toward patients destined to a milder course. Conversely, most patients enrolled in clinical trials had already had years of disease and, therefore, are unlikely to include patients with a monophasic course. In addition, the majority of these patients had proven refractory to other therapies. Thus, the observed different efficacy of IL-1 blockade between early and established sJIA could simply reflect the fact that the latter patient subset may be more challenging to treat. Nevertheless, although the hypothesis of a window of opportunity is far from proven, it should become the focus of further research into the pathophysiology of sJIA and, possibly, the objective of further multicenter trials in large populations, ideally combined with biomarker analyses.

Since there are now three IL-1 inhibitors on the market, the question arises about which of them is preferable. Not only they differ in the molecular structure, but the mechanism of action is slightly different: anakinra blocks both IL-1α and IL-1β, canakinumab inhibits only IL-1β, and rilonacept binds IL-1α, IL-1β, and IL-1 receptor antagonist. However, it is still unknown whether the different biding properties translate into differential clinical effects (107). Anakinra has been the first agent tested and is, thus, the one for which more experience has been gained (although it is not registered for the treatment of sJIA). It has a short half-life of 4-6 hours, which is advantageous for handling a major adverse event and provides a greater flexibility for the management of a medical emergency like MAS. However, the need of daily subcutaneous administrations, which are often associated with injection site reactions, may make it difficult to conduct therapy over long-term, particularly in younger children (89,92). The longer half-life of canakinumab, which enables its administration every 4 weeks, together with its blockage limited to IL-1β, makes this medication potentially better accepted and tolerated. Rilonacept could offer an alternative with its circulating half-life of 8.6 days, in contrast to the long

biologic activity of canakinumab (236 days), which could be a disadvantage in the setting of a serious toxic effect. Importantly, significant responses to canakinumab and rilonacept were seen in many patients who had previously been treated with anakinra, which suggests that failure of one anti-IL-1 therapy does not necessarily preclude use of another (99). Last but not least, the issue of cost may have a major impact on the choice of a particular molecule. The dosage, route of administration and half-life of the IL-1 inhibitors used in the management of sJIA is reported in Table 3.

Table 3. Characteristics of the IL-1 inhibitors used for the treatment of sJIA.

	Dosage	Route of administration	Half-life
Anakinra	1-4 mg/kg/day	Subcutaneous	4-6 hours
Canakinumab	≥2 years: 4 mg/kg/dose q 4 weeks Maximum dose: 300 mg	Subcutaneous	23-26 days
Rilonacept	Starting dose 4.4 mg/kg, then 2.2 mg/kg/week Maximum loading dose: 320 mg Maximum weekly dose: 160 mg/week	Subcutaneous	One week

Overall, all anti-IL-1 agents have proven safe and well tolerated. However, concerns have been raised regarding the risk of infection, neutropenia, and liver dysfunction (108–110). Furthermore, several instances of MAS during treatment with IL-1 inhibitors, some of which with a fatal outcome, have been seen in clinical practice, randomized controlled trials, and post-marketing experience (98,111). The

same phenomenon was reported during treatment with the IL-6 blocker tocilizumab (112,113). As discussed elsewhere, the occurrence of MAS during treatment with medications that inhibit proinflammatory cytokines implicated in its pathogenesis is a paradoxical phenomenon. Possible explanations include the increased rate of infections (which, in turn, may trigger MAS) associated with biologic therapies or the induction of an imbalance between up- and down-regulation of the various molecules that are part of the cytokine network (79,84). However, these episodes of MAS often abated after increasing the dose of biologic medications, which suggests a lack of causality and a real associative relationship in only a few instances.

Treatment targeting another cytokine implicated in the pathogenesis of sJIA, such as the IL-6 blocker tocilizumab, has also demonstrated efficacy in clinical trials (112,113). So far, however, there are no clinical data that allow either to compare the effectiveness and safety of IL-1 and IL-6 antagonists or to establish their relative indications in sJIA.

Additional investigations are needed to define the exact role of the currently available agents in the management of sJIA. Future studies will likely optimize the care of children with sJIA and further elucidate the disease pathogenesis.

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CHAPTER 3

THE PHARMACHILD REGISTRY

In order to establish the long-term safety and efficacy (response, joint erosion, damage, and treatment adherence) of biologic agents and MTX in JIA, i.e. the extent to which these drugs do more good than harm under the usual circumstances of healthcare practice in JIA, European Union supported in 2011 the project called "Pharmacovigilance in JIA patients treated with biologic agents and/or MTX" (Pharmachild), to implement an observational international registry including all children with JIA treated with any available MTX and biologic agents formulation.

Rationale

Aim of the project was to assess the long-term safety (primary goal) and effectiveness (magnitude of response, prevention or slowing of joint erosions, damage, and treatment adherence) of MTX and biologic agents in JIA.

Hypothesis to be tested

The overall hypothesis was to test whether biologic agents ± MTX were able to maintain an acceptable safety profile in the long term in children with different JIA categories while achieving clinical remission and prevent/stop joint erosion development over time

Primary objectives of the project

- To compare the long term incidence rates of emergent moderate, severe adverse events (AEs) and serious A (SAE) observed in paediatric subjects with JIA
- To assess the long-term efficacy (magnitude of response, prevention or slowing of joint erosion and damage, and treatment adherence) of biologic agents ± MTX in paediatric subjects with JIA.

To accomplish these objectives 3 different cohorts were established (treated with either MTX alone, biologics with or without concomitant MTX, or not treated with MTX or biologics). Patients either not receiving medication, or getting Non-Steroidal Anti-Rheumatic Drugs (NSAIDs) or intra-articular steroid injections were considered as control group.

Secondary objectives

- To identify predictors of safety (clinical or experimental, magnitude of response, remission)
- To assess potential risk factors (e.g. concomitant medications or diseases, medical history etc), which may modify the safety profile of biologic agents and MTX
- To evaluate efficacy in the different JIA categories, in terms of individual JIA core set variables, and using the ACR Paediatric 30, 50, 70, 90, 100 criteria for improvement, as well as Juvenile Disease Activity Score (JADAS-10, 27,71) and the achievement of clinical remission on and off medication as well as the occurrence of disease flare during biologic agents and MTX treatment course and after drug discontinuation, and the attainment of a status of minimal disease activity (MDA)
- To assess the number of children in which a biologic agent is added to the treatment
- To evaluate the progression of wrist joint erosion over time and abnormal growth/maturation in JIA subjects presenting a wrist involvement
- To assess the reasons for stopping drug treatment

Primary endpoint

<u>Safety</u>

- Proportion of JIA paediatric subjects with biologic agents and MTX -emergent moderate/severe and SAEs, referred as all moderate/severe AEs and SAEs belonging but not limited to events of special interest (ESI) such as malignancies and inflammatory bowel disease and other such as opportunistic

infections, autoimmune events, cardiovascular events, central nervous system involvement (e.g. optic neuritis, demyelinating disease), infertility, gastrointestinal bleeding, macrophage activation syndrome (MAS).

Efficacy

Secondary Endpoints

•Three to 10-year and longer probability of not experiencing AEs.

• Incidence rate of biologic agents and MTX-emergent moderate/severe AEs and SAEs in the 3 comparator groups.

• Treatment adherence and reasons of treatment withdrawal/change (e.g. lack of efficacy, AE and SAE or add-on therapy for inefficacy/intolerance, remission)

• Time to flare (as per standard PRINTO flare definition) during biologic agents and MTX treatment course and after biologic agents and MTX discontinuation.

• Joint space erosion over time (if part of routine care) according to the Poznanski score and erosion score according to the adapted versions of the Sharp/van der Heijde score at months 12 and 24.

• Baseline clinical and demographic predictors of safety (either clinically or laboratory), response, remission.

Study Design

This is an international, multicentre, observational, safety and efficacy study aimed to collect prospective safety, tolerability, efficacy, and treatment adherence information on JIA subjects exposed to any biologic agents and MTX, according to local standard of practice.

This is a non-interventional study, where the medicinal products are prescribed as per the investigator's decision. The assignment of the subject to a particular therapeutic strategy is not decided in advance by the study protocol, but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the subject in the study. No additional diagnostic or monitoring procedures are applied to the subjects and epidemiological methods will be used for the analysis of collected data.

Population

JIA (any ILAR category) after proper consent/assent. Two specific populations were enrolled:

- Prevalent cases: all patients under treatment or previously treated with biologic agents ± MTX, MTX alone or biologic agents alone or treated only with NSAIDs and/or steroid injection at the time of the project start were revised retrospectively to estimate moderate moderate/severe AEs and SAEs. The same patients continued to be followed over time after proper written informed consent.
- Incident cases: all cases newly treated with biologic agents ± MTX since the registry start.

From a time perspective the data collected derived from:

- Retrospective chart review of safety data

o Step 1: A census (e.g. collection of patient identification number, age, JIA type and type of treatment) was required from each centre before retrospective chart review of safety data initiation to avoid selection biases (e.g. to have the proper denominator against which evaluating the successful data collection).

o Step 2: Retrospective chart revision for the collection of moderate/severe AE and SAEs until the time of the last available visit. This retrospective chart review was considered successful if at least 70% of the patients listed in the census were retrieved. This step included also the integration in the Pharmachild project of data collected by other ongoing national registries (e.g. German, UK, French, Italian, USA etc).

- Prospective safety/efficacy data collection. This group included patients newly treated with biologic agents ± MTX and patients already on treatment and still followed at the participating centres and identified with the retrospective chart review.

Exposure

a) Medicinal Product (biologic agents ±MTX): prescribed according to treating physician's decision. Dose, frequency and route of administration comply with local standard of practice.

b) Co-medications: NSAIDs, systemic, intra-articular CS, and folic acid or its derivatives whose dose, frequency and route of administration comply with local standard of practice.

Inclusion criteria

- Signed written informed consent by subjects and /or parent or legally acceptable representative
- JIA (any ILAR category).
- Subjects receiving biologic agents ± MTX, MTX alone, or NSAIDs and/or steroid injections only as per physician discretion.

Choice of the comparator group

Three main groups of patients were identified, each one serving as comparator group for the remaining groups:

1. JIA patients treated with biologic agent alone or MTX alone;
2. JIA patients treated with a combination of biologic and MTX (including any other add on therapy e.g. cyclosporine, leflunomide etc);
3. JIA patients treated only with NSAIDs and/or steroid injections with at least 3 years follow-up.

Group 1 and 2 mainly refer to children with polyarticular course JIA treated with MTX ± biologics, while group 3 refers to children with mostly oligoarticular persistent course who are usually NOT treated with second line agents and have a more benign course. The 3 groups of children constitute the ideal comparator groups for any evaluation of the incidence rate of at least moderate and serious adverse events.

CHAPTER 4

PHARMACOVIGILANCE IN JUVENILE IDIOPATHIC ARTHRITIS PATIENTS TREATED WITH BIOLOGIC OR SYNTHETIC DRUGS: COMBINED DATA OF MORE THAN 15,000 PATIENTS FROM PHARMACHILD AND NATIONAL REGISTRIES.

ABSTRACT

Background: The availability of methotrexate (MTX) and the introduction of multiple biological agents have revolutionized the treatment of juvenile idiopathic arthritis (JIA). Several international and national drug registries have been implemented to monitor accurately the long-term safety/efficacy of these agents. This report aims to present the combined data coming from Pharmachild/PRINTO registry and the national registries from Germany (BiKeR) and Sweden.

Methods: Descriptive statistics for demographic, clinical data, drug exposure, adverse events (AE) and events of special interest (ESI). For the Swedish register, AE data were not available.

Results: A total of 15,284 patient's data were reported, 8,274 (54%) from the Pharmachild registry, 3,990 (26%) and 3,020 (20%) from the Germany and the Swedish registries, respectively. Pharmachild children showed a younger age (median of 5.4 years versus 7.6) at JIA onset and shorter disease duration at last available visit (5.3 versus 6.1-6.8) when compared to the other registries. The most frequent JIA category was the rheumatoid factor negative polyarthritis (range 24.6-29.9%). Methotrexate (61-84%) and etanercept (24%-61.8%) were the most frequently used synthetic and biologic disease-modifying anti-rheumatic drug (DMARD), respectively. There was a wide variability in glucocorticoid use (16.7-42.1%). Serious AE were present in 572 (6.9%) patients in Pharmachild versus 297 (7.4%) in BiKeR. Infection and infestations were the most frequent AE (29.4-30.1%) followed by gastrointestinal disorders (11.5-19.6 %). The most frequent ESI were infections (75.3-89%).

Conclusions: This manuscript is the first attempt to present a very large sample of data on JIA patients from different national and international registries and

represents the first proposal for data merging as the most powerful tool for future analysis of safety and effectiveness of immunosuppressive therapies in JIA.

Background

Juvenile idiopathic arthritis (JIA)(1) is the most common chronic paediatric rheumatic disease and an important cause of short and long-term disability and quality of life impairment(2-8). Although none of the available drugs for JIA has a curative potential, prognosis has greatly improved as the result of substantial progress in disease management with the introduction of biologics. Despite the good efficacy results of all phase III trials on biologic agents, the long-term safety profile needs to be further characterized. For example spontaneous reporting from countries with low incidence of tuberculosis suggested that tuberculosis might be problematic in patients treated with biologics(9). In August 2009, the Food and Drug Administration (FDA) announced through a Boxed Warning that an increased risk of certain cancers in children might occur and labeling for the TNF blocker products was updated.(10-14) A Cochrane review from February 2011 compared the adverse events (AE) of biologics and concluded that there is an urgent need for more research regarding their long-term safety of different biologics.(15) The availability of a large observational international and national registry could enable clinicians and regulatory agencies to monitor properly the long-term or rare safety events and effectiveness of these agents in the relatively low prevalent JIA.

The aim of this project is to presents the combined data of the "Pharmacovigilance in JIA patients treated with biologic agents and/or MTX" (Pharmachild) international registry and two consenting JIA national registries the "Biologics in Pediatric Rheumatology Registry" (BiKeR) from Germany and the JIA registry from Sweden. Secondary goal was to test a sharing system for future merging of data to address specific JIA scientific and clinical questions.

Methods

Registries description

The Pharmachild registry

Pharmachild is an observational international registry, started in 2011 with European Union initial funding support, which enrolled children from centers

members of the Paediatric Rheumatology INternational Trials Organisation (PRINTO).(16)

Inclusion criteria were children with JIA as per the International League of Associations for Rheumatology (ILAR) criteria(17) receiving biologics or other synthetic disease-modifying anti-rheumatic drugs (DMARDs), as per physician decision. The registry contains two specific populations. The first is a retrospective cohort of all patients under treatment or previously treated with DMARDs by one time clinical chart revision of safety events and complete drug exposure since disease onset to last available follow-up. The second is a prospective cohort including all cases newly treated DMARDs since the enrollment in the registry and cases still under treatment with any drug.To avoid selection biases each center performed a census for all the patients previously treated with DMARDs at that specific centre, used as the reference to evaluate the enrollment capability. In a second step, the center entered retrospective data, considered successful if they retrieved at least 70% of the patients listed in the census. Finally, in a third step, the prospective data collection started.

Data collection included full and complete details for ILAR classification criteria, demographic, clinical and laboratory information, efficacy (only for the prospective cohort) and safety data on a long-term basis. Centers reported the whole drug exposure of the patient, with dates of start and discontinuation of the drug, dosages, route of administration, reasons for discontinuation and possible correlation with the AEs. All the AEs of at least moderate/severe/very severe intensity and serious AE, using the latest release of the Medical Dictionary for Regulatory Activities (MedDRA) dictionary were reported; mild intensity was reported only for those AE which did not resolve and require a follow-up report. Some AEs were classified as by consensus of PRINTO members as events of special interest (ESIs).

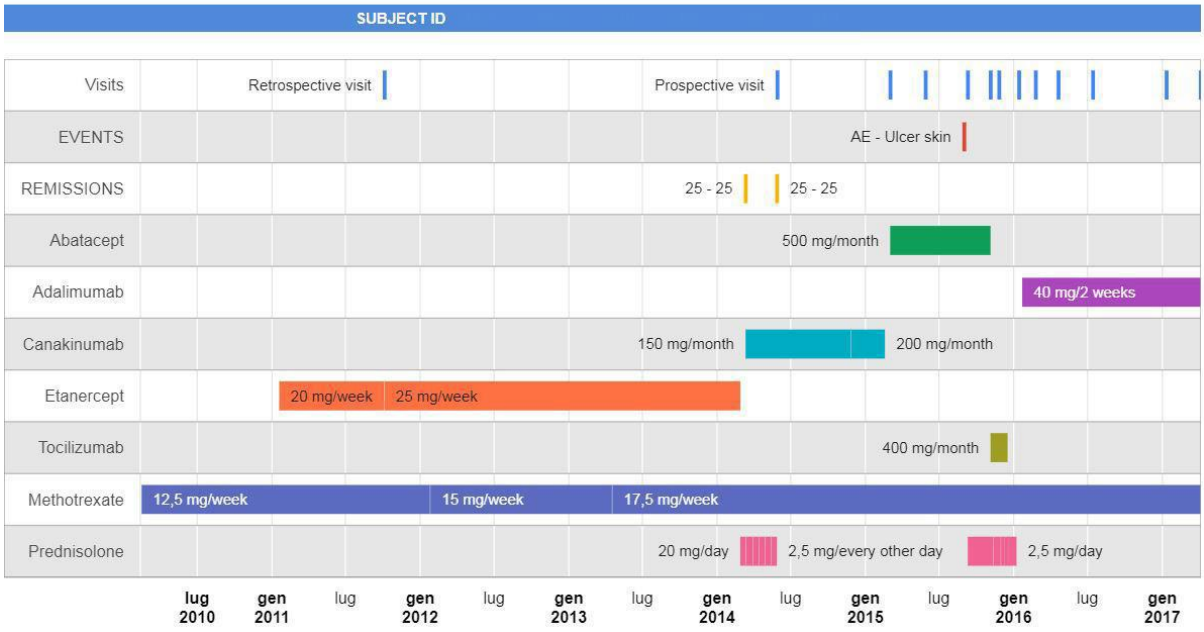
Efficacy data were collected in the prospective cohort through the JIA core set measures with whole joint count,(18) the disease activity status measured through the Juvenile Arthritis Disease Activity Score (JADAS), the annual evaluation of damage through the Juvenile Arthritis Damage Index (JADI) (19) and of growth and pubertal development and key information on imaging and bio-specimen local collection. As patient reported outcome (PRO) families completed online the Juvenile Arthritis Multidimensional Assessment Report (JAMAR)(20) before the scheduled clinic visit

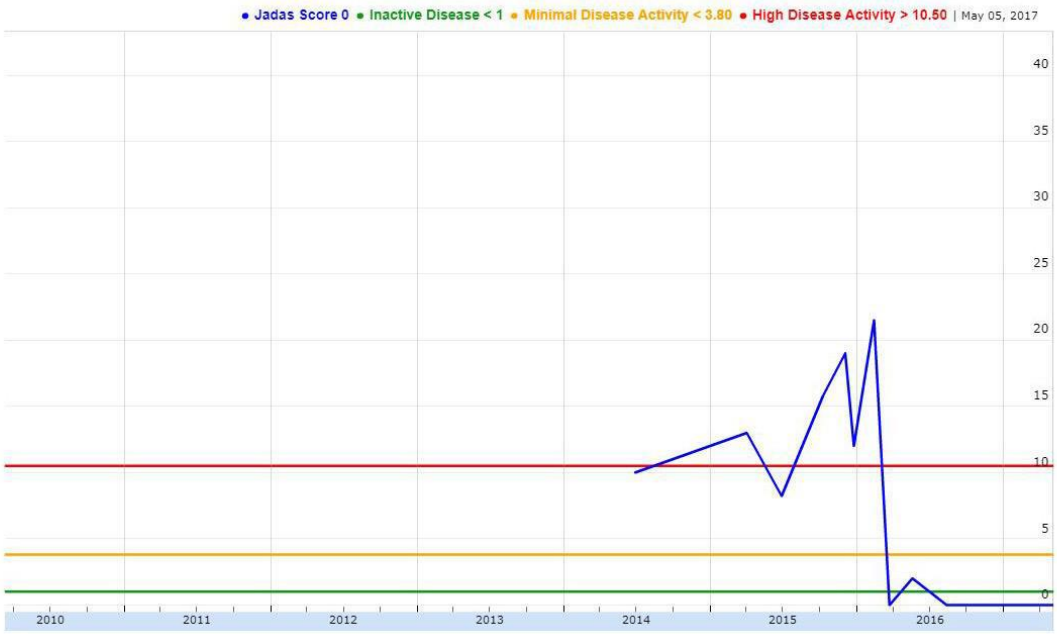
or in the hospital (on tablets or paper), in order to provide key notes to the treating physician before the clinical examination.

The system also provided data on drug exposure and occurrence of AEs (Figure 1) as a tool to discuss the health status of a patient with the family.

Figure 1. Pharmachild graphical depiction over time of the key efficacy and safety data. Drug exposure and adverse events are represented in parallel to JADAS pattern. The excel sheet with all the data could be downloaded automatically by all participating centres. In the present picture an example of a patient from an Italian centre is presented.

DRUG EXPOSURES AND JADAS

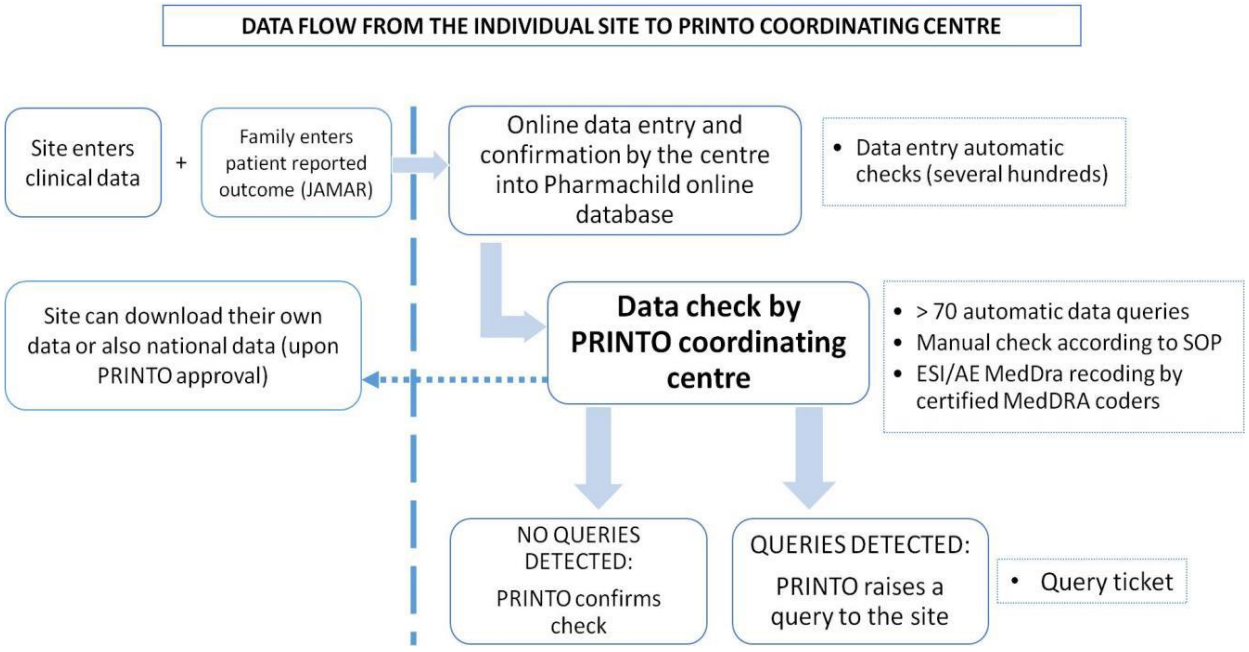




Visit date	29/05/2014	05/11/2015	26/11/2015	14/01/2016	05/04/2017
Physician global evaluation of disease activity (21 circle VAS)	1	4	2	5	0
Parents evaluation of child overall well-being (21 circle VAS)	8	9	8	9,5	0
ESR	20	30	7		10
CRP standardised	5	41	0,58	0,53	0,168
No. of joints with active arthritis	1	5	2	7	0
No. of joints with limitation of motion	1	5	2	7	0
JIA ACR inactive Disease	Active	Active	Active	Active	Inactive
JADAS10	10	19	12	21,5	0
JADAS inactive disease (<1)	N	N	N	N	Y
JADAS Minimal disease activity (< 3.80)	Y	N	Y	N	N
JADAS High disease activity (> 10.50)	N	Y	N	Y	N

Data collection was performed online via the secured PRINTO website on a dedicated server with a username and timely password on an https encrypted platform. English was the official language used for all forms completed by the physicians, while the PRO were available in the appropriate language spoken by parents/patients. The web system was designed to be user-friendly, modular and upgradable. During the data entry, several hundreds of automatic checks were in place to ensure data quality and consistency. In particular, safety events were checked for accuracy by the PRINTO certified MedDRA coders, which could go back to the center with electronic query tickets in case of missing or unclear information (Figure 2). A designated pediatric rheumatologist acted as Medical Monitor (JS), by performed an electronic check and revision of the AEs and ESIs; in addition for some ESI (e.g. infection) adjudicating committees were in place.

Figure 2. Data flow from the individual site to PRINTO coordinating centre.



The BiKeR registry

The BiKeR registry in Germany focused since 2001 on AE and efficacy data in patients treated with etanercept (ETN), the first biologic licensed in Germany.(21) Since then surveillance was extended to all biologics approved for JIA.(22-24) Information on biologics not approved for JIA was collected also for such patients who have been admitted for an approved biologic if patients were switched. The BiKeR registry is founded by pharmaceutical companies with independent bilateral contracts. BiKeR was approved by the ethics committee of the physician board Aerztekammer Nordrhein, Duesseldorf. BiKeR registry includes about 80 study sites and since its inception has followed more than 4000 patients in Germany and Austria aged 2 to 18 years, who meet the ILAR criteria for JIA. Written consent was obtained from patients and parents and repeated if patient became adult. Only pseudonymized data were collected.

Patient demographic characteristics, disease history, and previous treatments are documented at the time of patient enrollment. Details about relevant treatment and reasons for discontinuation, concomitant therapy, disease activity and AE are prospectively collected using standard case report forms (CRFs) at the start of treatment, at months 3 and 6, and every 6 months thereafter. Safety was analyzed based on adverse event reporting. All reported AE defined as any untoward medical occurrence in a subject administered a pharmaceutical product, even without a causal relationship with the treatment, were analyzed. Serious AE and ESI were defined as in Pharmachild. On site monitoring is performed in selected larger centers covering about 80% of admitted patients. In 2005, the register was extended to include a control group of 1500 biologic-naive JIA patients who started with the synthetic DMARD such as MTX to enable comparison of patients exposed to biologics to unexposed JIA cohorts.(25;26) The “Juvenile arthritis MTX/Biologics long-term Observation” (JUMBO) was launched in 2007, to include also data on long-term safety after transition to adulthood. (27) Actually 3,990 patients are included in the JUMBO registry.

The Swedish registry

In 2009, the Swedish JIA-registry begun to follow all children on biologics and later expanded to all patients treated with or without DMARDs. Reports from care givers, patients and medical records using JADAS, quality of life questionnaires and arthritis specific questions were included in the registry, that after 5 years, includes 1700 children (60% of the total JIA population and above 90 % of patients on cytokine modulators). Data on treatment, as well as disease course and efficacy were included, while data on safety were not available.(28)

Statistics

All registries and participating centers obtained approval from their respective ethics committee and obtained consent/assent based on national existing regulations.

Pharmachild, BiKeR and the Swedish registries reported cumulative summary data into predefined spreadsheet in order to provide baseline descriptive statistics of demographic and clinical data. Safety data were available only for Pharmachild and BiKeR. ESI common to both registries are reported.

For qualitative data, frequencies (%) were reported, while quantitative data were expressed in terms of medians with 1st and 3rd quartiles. No formal statistical comparisons were performed.

Results

Demographic characteristics and drug exposure

In Pharmachild a total of 11,796 patients were registered in the census registry as of January 2017 from 98 PRINTO centres in 32 countries. Clinical and safety data were provided for 8,274/11,796 (70.1%) patients belonging to 86 participating centres. Sixty/86 (61.2%) centres provided at least 70% safety data of their local JIA patients, with a median of 55 patients per centre. Prospective data were collected for a total of 3,070 patients.

Table 1 reports the demographic and clinical data for a total of 15,284 patient's data, 8,274 (54.1%) from the Pharmachild registry, 3,990 (26.1%) from the German BiKeR and 3,020 (19.8%) from Swedish registries. The patients included in the

German and Swedish registries were not overlapping with those in Pharmachild since the registries were created in different periods and included data from different patients with the same disease.

Patients coming from Pharmachild database showed a younger age (median of 5.4 years versus 7.6) at onset and shorter disease duration (5.3 versus 6.1-6.8) at the last available follow up visit with respect to the other registries. BiKeR reported a lower median number of children per centre (10.5 versus 52-55.5). ANA positivity was higher in BiKeR and missing in the Swedish register.

The JIA category distribution differed among registries, but the most frequent JIA category was the rheumatoid factor (RF) negative polyarthritis (range, 24.6%-29.9%). Oligoarticular JIA was more frequent in the Swedish registry (49.6% versus about 30.5%-37.1% in the other two registries), while in BiKeR the frequencies of oligo- and poly-articular JIA RF negative were similar (about 30%); Pharmachild depicted a higher frequency of systemic JIA (11% versus 4.7-6-7% in the German and Swedish registry).

Table 1. Demographic and clinical characteristics of the JIA patients from different registries. Data are medians (1^{st} –3^{rd} quartiles) or frequencies (%).

	Pharmachild N = 8,274	BiKeR N = 3,990	Sweden N = 3,020
N of countries	32	2#	1
N of centers	86	72	33
No of patients per center	55.5 (17-124)	10.5 (3-39.8)	52 (31-78)
Age at onset	5.4 (2.4-10.0)	7.6 (3.2-11.7)	7.6 (2.9-11.7)[1]
Age at JIA diagnosis	6.2 (2.8-10.9)	-	8.3 (3.5-12.8)[2]
Disease duration at last visit	5.3 (2.7-8.8)	6.1 (3.5-9.5)	6.8 (4.3-10.1)[3]
Female	5584 (67.5%)	2670 (66.9%)	1989 (65.9%)
Antinuclear antibodies (ANA)*	1767 (21.4%)	1900 (47.6%)	-
ILAR JIA category		[4]	[5]
Systemic	911 (11.0%)	267 (6.7%)	109 (4.7%)
Oligo	3071 (37.1%)	1215 (30.5%)	1148 (49.6%)
Oligo persistent	2011 (24.3%)	494 (12.4%)	-
Oligo extended	1060 (12.8%)	721 (18.1%)	-
Polyarticular RF-	2183 (26.4%)	1192 (29.9%)	568 (24.6%)
Polyarticular RF+	322 (3.9%)	243 (6.1%)	85 (3.7%)
Psoriatic arthritis	285 (3.4%)	296 (7.4%)	160 (6.9%)
Enthesitis related arthritis	924 (11.2%)	649 (16.3%)	185 (8.0%)
Undifferentiated arthritis	578 (7.0%)	127 (3.2%)	58 (2.5%)

*ANA at least 2 consecutively positive determinations according to local standards

Germany and Austria

[1] data available for 2,477 subjects [2] data available for 2,197 subjects

[3] data available for 2,479 subjects [4] data available for 3,989 subjects

[5]data available for 2,313 subjects

Table 2 reports the number of patients who ever received a drug from onset to last available follow-up visit, with the corresponding days of drug exposure per medication from the first day of drug administration to the last available follow-up visit, excluding the days off therapy for any reason.

There was a global trend to use MTX as a first-choice syntethic DMARD, and Etanercept as a first line biologic, but the Swedish registry used these drugs in a lower percentage of patients (MTX 61% versus about 84% in Pharmachild and BiKeR, Etanercept 24% versus 43.5% in Pharmachild and 61.8% in BiKeR). Despite the similar percentage of patients using these medications, children from BiKeR were exposed for a shorter period to the drugs compared to Pharmachild children, while the Swedish registry demonstrated a much longer drug exposure, with a wide range of variability among patients. Adalimumab, among the most frequently used biologics, was administered in a similar percentage of patients among all the three databases (about 21% patients). Systemic steroids were used in a similar percentage of patients and with the same drug exposure in BiKeR and Pharmachild, while the Swedish registry administered shorter cycles of steroids in a smaller number of patients (about 40% of patients in Pharmachild and BiKer versus 16.7% in the Swedish registry).

Table 2. Number of patients who ever received a drug from onset to last available follow-up visit, with the corresponding days of drug exposure per medication from the first day of drug administration to the last available follow-up visit. Data are numbers of patients with frequencies (%), and medians and 1st-3 rd quartiles of days of drug exposure.

Drug	**Pharmachild**	**BiKeR**	**Sweden**
	N = 8,274	N = 3,990	N = 3,020
	Days of drug exposure	Days of drug exposure	Days of drug exposure
Methotrexate	6963 (84.2%);	3344 (83.8%);	1842 (61%);
	924 (449-1747)	494 (173-957)	1198 (555-2127)
Sulfasalazine	861 (10.4%);	274 (6.9%);	95 (3%)
	360 (143-730)	174 (32-470)	443 (132-1042)
Cyclosporine	518 (6.3%);	113 (2.8%);	16 (0.5%);
	616 (235-1358)	186 (62-580)	584 (250-1452)
Leflunomide	372 (4.5%);	219 (5.5%);	2 (0.1%);
	434 (182-888)	267 (68-701)	840 (511-1169)
Hydroxychloroquine	279 (3.4%);	106 (2.7%);	32 (1.1%);
	486 (202-1022)	182 (1-535)	957 (311-1612)
Azathioprine	108 (1.3%);	155 (3.9%);	31 (1%);
	439 (187-973)	186 (26-494)	1171 (340-2179)
Thalidomide	35 (0.4%);	0	0
	290 (85-665)		
Systemic glucocorticoids	3299 (39.9%)	1680 (42.1%)	503 (16.7%)
	206 (67-648)	196 (81-449)	91 (35-437)

Etanercept	3600 (43.5%);	2467 (61.8%);	726 (24%);
	719 (300-1338)	489 (184-934)	827 (341-1666)
Adalimumab	1778 (21.5%);	810 (20.3%);	657 (21.8%);
	442 (174-927)	350 (117-755)	701 (292-1604)
Infliximab	705 (8.5%);	68 (1.7%);	189 (6.3%);
	425 (160-951)	213 (129-717)	825 (328-1738)
Tocilizumab	633 (7.7%);	281 (7%);	122 (4%);
	351 (126-742)	377 (127-730)	660 (193-1353)
Abatacept	420 (5.1%);	101 (2.5%);	80 (2.6%);
	342 (156-715)	190 (83-582)	378 (164-1125
Anakinra	339 (4.1%);	50 (1.3%);	48 (1.6%);
	299 (94-837)	304 (9-806)	422 (144-836)
Golimumab	161 (1.9%);	63 (1.6%);	93 (3.1%);
	270 (106-623)	344 (88-783)	796 (370-1743)
Canakinumab	145 (1.8%);	39 (1%);	7 (0.2%);
	351 (133-1032)	364 (214-733)	654 (604-1654)
Rituximab	103 (1.2%);	4 (0.1%);	20 (0.7%);
	42 (24-87)	15 (0-108)	129 (15-1550)
Certolizumab	33 (0.4%);	4 (0.1%);	8 (0.3%);
	166 (106-309)	49 (0-110)	984 (714-1538)
Other biologic	14 (0.2%);	4 (0.1%);	2 (0.1%);
agents	217 (54-432)	77 (25-149)	325 (223-426)

Safety data

Overall, the German registry showed a higher incidence of AEs, but with lower intensity. In Pharmachild 1,599/8,274 (19.3%) patients reported at least one moderate AE compared to 1,747/3,999 AE of any intensity (43.8%) patients in BiKeR. Indeed when the AEs of at least moderate intensity were compared between the 2 registries, the differences were less pronounced (18.5% for Pharmachild versus 10.2% in BiKeR). Serious AEs were present in 572 (6.9%) patients in Pharmachild versus 297 (7.4%) in BiKeR. Among them 13 deaths were reported in Pharmachild, 3 in BiKeR mainly due to severe infections and/or malignancies.

Table 3 reports a total of 5,173 AEs in Pharmachild and 5,013 in BiKeR, according to the MedDRA dictionary divided by system organ class (SOC). Infection and infestations resulted as the most frequent SOC in Pharmachild and BiKeR (29.4% versus 30.1% respectively) followed by gastrointestinal disorders (11.5% versus 19.6%) while all remaining SOCs occurred in less than 10% of the AE. In Pharmachild, more injuries, poisoning and complications, haematological, and hepatobiliary disorders were reported compared to BiKeR, which showed more investigations, general disorders and administration site conditions, neurological, and immune system disorders. The number of uveitis, included in “Eye disorders” category, resulted comparable in the two registries (5.2% versus 6.2% in Pharmachild and BiKeR, respectively).

These results were confirmed also by analyzing the distribution of AEs separately for the retrospective and the prospective visits. We identified a total of 1,050 AEs extracted from the prospective visits, and 4,123 events by the retrospective data, divided by SOC. In general, the hierarchy and frequency of AEs were similar, with Infections and Infestations being the most frequent events. (additional table 1)

Table 3. Total number of AE by MEDdra SOC ordered by decreasing frequencies. Data are absolute numbers and frequencies (%)

	Pharmachild N = 5,173	**BiKeR** N=5,013
Infections and infestations	1523 (29.4%)	1509 (30.1%)
Gastrointestinal disorders	595 (11.5%)	984 (19.6%)
Injury, poisoning and procedural complications	325 (6.3%)	152 (3.1%)
Blood and lymphatic system disorders	291 (5.6%)	99 (2%)
Investigations	285 (5.5%)	377 (7.5%)
Eye disorders	270 (5.2%)	309 (6.2%)
Skin and subcutaneous tissue disorders	256 (4.9%)	217 (4.3%)
General disorders and administration site conditions	245 (4.7%)	410 (8.2%)
Hepatobiliary disorders	233 (4.5%)	24 (0.5%)
Surgical and medical procedures	209 (4.1%)	98 (2%)
Nervous system disorders	151 (2.9%)	227 (4.5%)
Musculoskeletal and connective tissue disorders	147 (2.8%)	138 (2.7%)
Respiratory, thoracic and mediastinal disorders	112 (2.2%)	50 (1%)
Psychiatric disorders	105 (2.1%)	157 (3.1%)
Endocrine disorders	104 (2.0%)	6 (0.1%)
Metabolism and nutrition disorders	77 (1.5%)	34 (0.7%)

Renal and urinary disorders	66 (1.3%)	21 (0.4%)
Immune system disorders	33 (0.6%)	77 (1.5%)
Vascular disorders	30 (0.6%)	46 (0.9%)
Reproductive system and breast disorders	26 (0.5%)	13 (0.3%)
Congenital, familial and genetic disorders	22 (0.4%)	9 (0.2%)
Cardiac disorders	19 (0.4%)	13 (0.3%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	16 (0.3%)	29 (0.6%)
Ear and labyrinth disorders	13 (0.3%)	7 (0.1%)
Social circumstances	11 (0.2%)	0
Pregnancy, puerperium and perinatal conditions	9 (0.2%)	7 (0.1%)

Table 4 reports details for the 2,022 and 1,697 common ESI in Pharmachild and BiKeR, respectively. The most frequent ESIs were infections, which resulted the most prevalent in both registries (75.3% versus 89% in Pharmachild and BiKeR, respectively), followed by blood cells related ESIs. In Pharmachild infusion/injection related reactions were more frequent than in BiKeR (10.8% versus 1.4%).

There were 27 cases of tuberculosis reported in Pharmachild (52% from Asia, 37% from Europe, 11% from America) and none in BiKeR, while all serious/targeted infections were 674 (33.3%) and 171 (10.1%), respectively. 17 cases of tuberculosis were during biologic therapy, namely TNF inhibitors in 14 patients.

Few cases of malignancies were reported in a similar fashion in either registries. Beside the reported cases of haematological malignancies in Table 4, in Pharmachild we could observe 10 additional cases (neoplasm others), represented for one third by haemangioma, and with the remaining patients suffering from thyroid cancer, cervix neoplasm, skin tumors, breast fibroadenoma, colon adenoma and osteochondroma. The German registry reported in the same group similar malignancies, in particular of the genital apparatus (thyroid carcinoma, germ cell tumor, anaplastic ependymoma, cervix dysplasia).

Table 4. Total number of ESI ordered by decreasing frequencies. Data are absolute numbers and frequencies (%).

	Pharmachild N=2,022	**BiKeR** N=1,697
Infections	1523 (75.3%)	1509 (89%)
Serious/targeted infections (Epstein-Barr virus, cytomegalovirus, papilloma virus, herpes zoster primary and reactivation, and opportunistic infections)	674 (33.3%)	171 (10.1%)
Tuberculosis	27 (1,3%)	0
Other infections	822 (40.6%)	1338 (78.8%)
Infusion/injection related reactions	218 (10.8%)	24 (1.4%)
Infusion related reaction	144 (7.1%)	11 (0.6%)
Injection related reaction	74 (3.7%)	13 (0.8%)
Blood cells related ESI	188 (9.3%)	90 (5.3%)
Pancytopenia	6 (0.3%)	65 (3.8%)
Neutropenia	107 (5.3%)	14 (0.8%)
Macrophage activation syndrome	75 (3.7%)	11 (0.6%)
Aplastic anemia	0	0
Autoimmune ESI	50 (2.5%)	50 (2.9%)

	Pharmachild	BiKeR
	N=2,022	N=1,697
Inflammatory Bowel Disease (IBD)	21 (1.1%)	23 (1.3)
Other autoimmune diseases excluding IBD, uveitis and demyelinisation disorders	18 (0.9%)	24 (1.4%)
Lupus erythematosus systemic/lupus-like syndrome	4 (0.2%)	1 (0.1%)
Optic neuritis	4 (0.2%)	0
Multiple sclerosis	2 (0.1%)	0
Demyelination	1 (0.05%)	2 (0.2%)
Malignancies	16 (0.8%)	13 (0.8%)
Leukaemias	3 (0.1%)	2 (0.2%)
Lymphomas	2 (0.1%)	5 (0.3%)
Haematopoietic neoplasms (excluding leukaemias and lymphomas)	1 (0.05%)	2 (0.2%)
Neoplasm (other)	10 (0.5%)	4 (0.2%)
Others ESI	27 (1.3%)	11 (0.6%)
Gastrointestinal (GI) ulcer/GI bleed/GI	17 (0.8%)	4 (0.2%)

	Pharmachild	BiKeR
	N=2,022	N=1,697
perforation		
Pregnancy	9 (0.4%)	7 (0.4%)
Congestive heart failure	1 (0.05%)	0

Discussion

Since the 1990s, when the first immunomodulatory products for rheumatic diseases were introduced, the benefits of synthetic and biologic DMARDs became clear in the management of JIA. However, safety information for JIA is currently mainly derived from phase III clinical trials and more recent registries and administrative claims. Therefore little information exists on the long-term safety of these agents. A great scientific debate regarding the safety of TNF-blockers started in 2009 which lead the FDA to issue a warning regarding a possible association between the use of TNF-blockers and the development of lymphoma and other cancers in children and young adults with JIA(29). Until now, the effect of biological therapies on the risk to develop cancer or other risks such as infections in JIA is still controversial,(30) owing to confounding factors such as the use of concomitant immunosuppressants. Literature has provided evidence that an increased risk of malignancy exists among children with JIA when compared to the general population, irrespective of medication use. Conversely, other studies have not confirmed these findings, highlighting the need of further studies to estimate more accurately this risk.(11;13;31;32) In order to address more reliably this and other safety concerns several methods for pharmacovigilance could be implemented spanning from the results of phase II-III clinical trials, to post-marketing passive reporting or from registries (non for profit or sponsored by pharmaceutical companies).(10;33) With this purpose, several registries have been created in the last decade, and, in particular, the national pediatric rheumatology societies in

European countries and in North America initiated independent registries or registries in collaboration with pharmaceutical companies for the long-term evaluation of the safety and effectiveness mainly of biologic DMARDs.(26;28;33-37) Other research groups have concentrated their effort on the analysis of insurance claims. (30;38) PRINTO implemented Pharmachild in order to guarantee a critical mass of patients' data and to provide systematically-obtained evidence for provision of reliable scientific data for health professionals and health authorities. Aiming to avoid overlapping of data collection and to find an agreement on the proper way to share common data, a considerable number of European pediatric rheumatology societies (e.g. in France, Netherlands, Spain, Czech Republic primarily) agreed to use Pharmachild as their primary resource for data collection.

This manuscript is the first attempt to present a very large sample of data on JIA patients from different registries, providing an overview on the baseline characteristics from international and national registries. This analysis highlights some differences, but also similarities. An important difference that we could observe was the highest frequency of AEs in the German BiKeR registry, but associated with a lower intensity, which may reflect the different inclusion criteria of the two registries. Indeed, in Pharmachild, events of mild intensity, defined as transient or mild discomfort (<48 hours) and no medical intervention/therapy required are excluded. This difference is the trade-off implemented in Pharmachild in order to concentrate on more important safety events and facilitate data collection in the everyday busy clinical practice.

Similarities among registries regarding therapies and AEs could be identified. MTX was the most used synthetic DMARD. Etanercept was the most frequently used biologic agent in all registries considered, followed by Adalimumab. Drug exposure differentiated the three databases, since in BiKeR it was lower for almost all the medications, while in the Swedish registry much longer and with a wider range of exposure variability, despite the similar disease duration. The relatively high rate of Etanercept use in the BiKeR registry might be explained by the fact that this registry originally started as a registry for this specific drug, when Etanercept was the only approved biological drug in pediatric rheumatology and then extended to other medications after their approval. However, also in more

recent years in BiKeR, Etanercept is the first biologic in about two thirds of patients with non-systemic JIA. Systemic steroids were used much less in Sweden and for shorter periods, maybe due to the lower incidence of systemic JIA. About ESIs, infections were the most common event in both Pharmachild and BiKeR registries, while malignancies were reported in a limited number of patients. The overall frequency of the different AEs and ESIs was similar between Pharmachild and BiKeR. The major difference when comparing Pharmachild to BiKeR were an higher frequency of tuberculosis infection and infusion/injection related reactions in the first for a possible interviewer bias elicited by the Pharmachild case report forms which explicitly focus the attention of the clinicians to these AEs. The difference in the rate of tuberculosis infections may also reflect a different risk among European countries, and the need of higher awareness of this problem in some regions.

Next to reporting baseline data from a large sample of JIA patients, this study could not merge individual patient data because of the lack of homogeneous information. It can be seen therefore as a practical proposal for future studies that involve data merging. We propose for future studies a 3-step procedure. In step 1, the CRFs of the different registries should be compared to highlight the similarities and differences. Step 2 will verify the database technical characteristic (e.g. Sql server version 2005, Access 2010, etc) and the field coding (e.g. gender, int, 1=male; 2= female, etc). The third step related to the individual patient's data merging. An excel spreadsheet with the data specifications related to a specific manuscript will be shared with the participating registries. Each registry will have to add its own data related to the project. The coordinator of the project will merge the individual patients' data after proper coding transformation. A census (e.g. few demographic data of all patients in the registry) will be provided by each registry as preliminary step to check for a potential selection bias. The coordinator will then prepare a further spreadsheet to highlight the important missing information (query log) to be solved in a timely manner in order to proceed with the manuscript final analysis and drafting. The entire procedure may meet some obstacles due to the lack of homogeneous information among registries and ethical and data protection regulations that often inhibit the exchange of patient data. Nevertheless, this

methodology appears as a successful tool for future studies increasing the number of patients and data.

A possible limitation to our study is that a relevant part of clinical information comes from retrospective data with no efficacy results available. Nevertheless, as pointed out in the additional table 1, retrospective data in Pharmachild were mostly overlapping to prospective data, thus supporting the validity of these safety findings. This limitation becomes crucial when we consider efficacy data, which can be provided only by the prospective analysis. For this reason further work in the future will be focused on these patients in order to advance the use of JIA drugs through the study of the Pharmachild population. Future analytical work will have also to report accumulated patient years of treatment for each of the registries.

Conclusions

This manuscript is the first attempt to present a very large sample of data on JIA patients from different national and international registries and represents the first proposal for sharing of data from national and international registries as the most powerful tool for future analysis of safety and effectiveness, with the aim to address important questions on the current daily practice in paediatric rheumatology.

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CHAPTER 5

ADJUDICATION OF INFECTIONS IN JUVENILE IDIOPATHIC ARTHRITIS PATIENTS TREATED WITH SYTHETIC AND BIOLOGIC DRUGS: AN EVIDENCE BASED EVALUATION FROM THE PHARMACHILD REGISTRY

ABSTRACT

Background: Pharmachild is a pharmacovigilance registry on children with juvenile idiopathic arthritis (JIA). Little evidence exists in literature about the relationship between JIA and opportunistic infections (OI).

Objective: To analyse the OI in the Pharmachild population, through the work of an independent Safety Adjudication Committee (SAC).

Methods: The SAC (3 pediatric rheumatologists and 2 pediatric infectious disease specialists) elaborated and approved by consensus a list of OI for use in immunosuppressed children. Through a 5 step-procedure, all the at least severe and serious infectious events encountered by the patients in the Pharmachild registry, were retrieved and evaluated by the SAC. A final evidence-based listing of opportunistic pathogens/infection presentations was provided.

Results: We found 772 adverse events in 572 eligible patients, of which 335 as serious/severe/very severe non-OI and 437 as OI (any intensity or severity). 682/772 (88.3%) were adjudicated as infections, 603 (88.4%) common and 119 (17.4%) opportunistic. The SAC considered the treatment of infection appropriate in 77% of the cases, and the immunosuppressive therapy possibly related to the event in 76% of the cases. Herpes infection was the most frequent event, followed by mycobacterial infections. The role of the list in identifying OI in pediatrics was confirmed by the comparison with the events adjudicated by the panel.

Conclusions: We found a significant number of OI in JIA patients on immunosuppressive therapy. The approved list on the definition of OI in JIA patients, created by consensus and validated on the Pharmachild patients, makes future studies on pharmacovigilance easier to compare.

Introduction

With the advent of biologic disease modifying anti rheumatic drugs (DMARDs), in a chronic condition like juvenile idiopathic arthritis (JIA), regulatory authorities such as the Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have demanded to pharmaceutical companies and clinical researchers to evaluate the long term safety of drugs used in children enrolled in phase II-III clinical trials.(1-16) Due to the limited number of patients enrolled in these trials, (17) clinical researchers have devoted their work to the implementation of national and international registries, (18-28) or to the analysis of insurance claim data (29-32).

Children during their growth are subject to a natural higher rate of infections. Treatments in JIA with synthetic and biologic DMARDs are expected to increase the frequency of common infections and the risk of serious and opportunistic infections, (23;31-35) including especially tuberculosis in some geographic areas.(36;37;37;38) In order to tackle the long term safety and efficacy evaluations the Paediatric Rheumatology INternational Trials Organization (PRINTO) started in 2011 Pharmachild, an observational international registry, with European Union initial funding support, enrolling children internationally.(39;40)

Recent literature seems to confirm the likely high incidence of infections among JIA patients treated with immunosuppressants,(21) but conclusive data are not yet available, and in particular little evidence exists about the role of JIA or its immunosuppressive therapy in acquiring opportunistic infections (OI).

Several studies in literature have the objective to define and classify OI for example in HIV patients or in cancer (41-44), but Winthrop and colleagues (33) in 2015 were the first to convene a consensus meeting to review the published literature, on clinical trials and postmarketing surveillance, on OI in patients with immune-mediated diseases treated with biologic DMARDs, in order to provide consensus recommendations for their evaluation in the context of clinical trials and observational studies.

Primary objectives of this study were to derive a consensus based list of opportunistic pathogens for use in children with JIA and confirm its role in

identifying OI through the evaluation of the infectious events reported in Pharmachild by an independent Safety Adjudication Committee (SAC).

Patients and Methods

Pharmachild

Pharmacovigilance In Juvenile Idiopathic Arthritis Patients (Pharmachild) registry (project number 260353) involves 86 participating centres in 32 countries members of PRINTO (at www.printo.it) and the Paediatric Rheumatology European Society (PRES at www.pres.eu) with the aim to observe children with JIA to compare the long term incidence rates of moderate, severe, very severe adverse events (AE) and serious AE (SAE) and to assess the long-term efficacy of biologic and synthetic DMARDS in JIA. For the related details on this registry we refer to the recently published manuscript.(40)

Study design

The study was divided into 5 main steps (Supplementary Figure S1).

Step 1. Provisional listing of opportunistic pathogens/infection presentations

A study Steering Committee (SC) comprehended two PhD medical doctors (GG and JS), two certified Medical Dictionary for Regulatory Activities (MedDRA) coders (CP, LV), 3 biostatisticians (AP, FB, FB) and two Senior researchers (NW, NR).

The SAC was organized as an independent group of 5 physicians: 2 pediatric infectious disease specialists (EC and AG) and 3 pediatric rheumatologists (GH, HIH, DL), who have experience and expertise in the diagnosis and treatment of children with infectious or rheumatic diseases.

The SC starting point was the prior work by Winthrop et al,(33) an international consensus committee (infectious disease, public health and pulmonary physicians and rheumatologists) that through a systematic review in immune-mediated disorders also including JIA studies, and after a consensus process,

recommended a list of definite and probable OI. This list was discussed, modified and approved by the SAC by consensus, through three subsequent Delphi web rounds, with the final result of a list of opportunistic pathogens/presentations for use in immunosuppressed children with JIA. In the first round SAC members worked independently from each other, while at the second round they could revise the comments from the other members. Finally consensus was agreed through a dedicated teleconference (moderator NR).

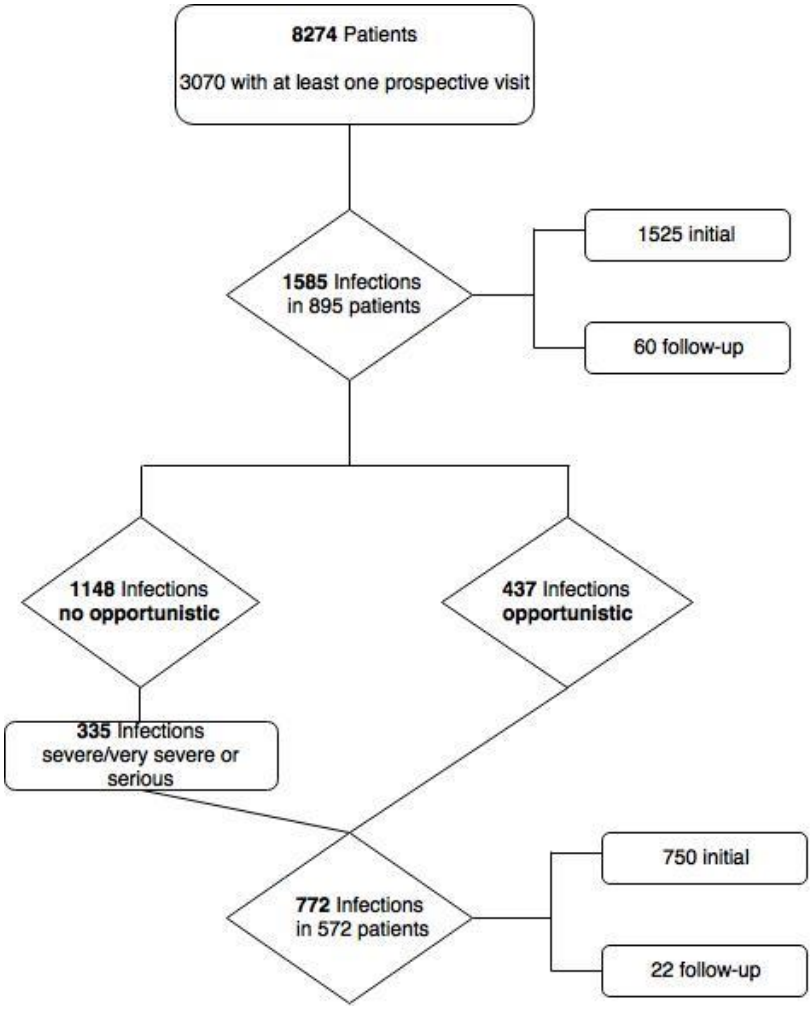
The SC then integrated the review of the literature with more recent evidence on OI in JIA (32;45;46) and prepared a provisional list of OI pathogens, then matched with the MedDRA Preferred Terms (PT) in order to properly retrieve cases in the Pharmachild database.

Step 2: Retrieval of infections in Pharmachild

For the Pharmachild study, the investigators reported online on the PRINTO database all AE from the disease onset to the last available follow-up visit. The MedDRA System Organ Class (SOC) "infections and infestations" was categorized in Pharmachild as Event of Special Interest (ESI), including two different groups of infectious events, classified as tuberculosis and targeted infections (Epstein-Barr virus, cytomegalovirus, papilloma virus, herpes zoster primary and reactivation, and opportunistic infections).

According to the Pharmachild protocol, all events (AEs and ESIs) of at least moderate intensity and all SAE were collected. AEs and ESIs were coded initially by the investigators during data entry using MedDRA dictionary, then recoded, if needed, by the PRINTO certified MedDRA coders and revised by the PRINTO medical monitor (JS), based on the most current version of MedDRA. All infectious events (both initial and follow-up) in the MedDRA system organ class (SOC) (Supplementary Figure S2) infection and infestations in Pharmachild at January 2017 were retrieved (Figure 1).

Figure 1. Flowchart of the Pharmachild population with infective events.



Step 3. Adjudication of infections by the SAC

A standard operating procedure (SOP) described the work to be done by the SAC. In brief, inclusion criteria for the SAC adjudication process were all the opportunistic events in the provisional list of OI derived by step 1 (any grade of severity) plus the non-opportunistic infections of at least severe intensity or all serious infections.

The list of the events to be adjudicated by the SAC was provided in a dedicated external area of the PRINTO/Pharmachild website, with access through secure personal username and password.

The SAC members who revised all eligible cases presented in alphabetical order were blinded to the provisional list of opportunistic pathogens/presentations (see Step 1), and did not participate to data collection in Pharmachild.

The full patients' data were available for the SAC members: 1. Demographic characteristics of the patient (with personal data encrypted); 2. ILAR category of JIA; 3. Laboratory and clinical information; 4. Complete drug therapy with whole drug exposure for synthetic and biologic DMARDs since disease onset to the last available observation; 5. Concurrent medications at the time of the infectious event; 6. Full AE report plus ESI specific form for infections. In addition, disease activity and damage measure were available for prospective visits. The SAC members had the possibility to access clinical information in its entirety through a read-only modality with no possibility to modify the original data. A numeric code allowed the patient inclusion, without any patient or center identifier and no a priori categorization of AE as OI or serious were provided so to decrease the biases in their adjudication exercise.

The SAC mandate was to evaluate each infectious case, based on the whole patient's history available in Pharmachild, by answering 5 questions: 1. Based on the information provided, do you confirm that this patient had an infection?; 2. Is this infection common?; 3. Is this an opportunistic infection?; 4. Was the treatment appropriate for the infection?; 5. Could the event be possibly related to any of the drug(s) taken at the time of the event? The study SC was available to provide any additional information related to the event and required by the SAC at any time.

The consensus among the SAC members was defined as an agreement of at least 3 out of 5 (60%) members, on the first 3 out of 5 prior adjudication questions ("Is this an infection?", "Is it common?", "Is it opportunistic?"). Initially the SAC members worked independently from each other while in the second step for all cases without consensus each member could access the evaluations by the other SAC members.

Step 4. Analysis of the Pharmachild registry

Step 4 was designed to evaluate, in an evidence-based fashion, the frequency of those events in the Pharmachild registry classified as infections by consensus

among the SAC, and to assign a final MedDRA code (HLT/PT) to the event. In case of discrepancies in the categorization, after PRINTO and MM (JS) check, a third examiner (GG) re-evaluated the individual case to assign the final MedDRA code (HLT/PT).

Step 5. Final evidence-based listing of opportunistic pathogens/infection presentations

In this step all the infectious events adjudicated by the SAC in Pharmachild were matched by MedDRA PT term with the provisional list of OI (see Step 1) and divided in three groups: "confirmed OI", whether there was full agreement between the SAC and the provisional list of OI; "confirmed non-OI" for those events adjudicated as non-OI by the SAC and missing in the provisional list; "possible/patient and/or pathogen related OI", for the remaining events in Pharmachild that could be possibly considered opportunistic depending on the physician's evaluation of the patient history and by the detection of the specific pathogen causing the disease.

Statistical analysis

Descriptive statistics were reported in terms of absolute frequencies and percentages for qualitative data. Quantitative data were described in terms of median values and inter-quartile range (IQR) values due to their non-normal (Gaussian) distribution.

Results

Step 1. Provisional list of opportunistic pathogens/presentations

After the three web Delphi rounds, the probable and definitive definitions of OI were agreed with one major change by 5/5 (100%) of the SAC. In particular, the definition of definite OI was confirmed, while for probable infections it was integrated with the following "In case of the unusually severe course of infection due to a common pathogen with usually mild disease the pathogen might

tentatively be considered opportunistic in a patient with impaired immune function. Two definite categories of pathogens/presentations were modified by the SAC, while twelve were added in the provisional list of probable OI from the literature and matched with the HLT/PT MedDRA dictionary; no infections already included in the list by Winthrop et al were deleted.

Supplementary table S1 shows the provisional list of pathogens/presentations, with the corresponding HLT terms according to MedDRA dictionary.

Step 2: Retrieval of infections in Pharmachild

Among the 8,274 patients enrolled in the Pharmachild registry at January 2017, 895 (10.8%) patients experienced 1,585 infections. A total of 772 events (48.7%) in 572 patients were eligible for the evaluation by the SAC, of which 437 resulted as preliminary OI and 335 as very severe/severe or serious non-OI affecting (Figure 1). The baseline characteristics of the 572/895 (63.9%) adjudicated patients are reported in Table 1 in comparison with those who were not adjudicated ones. The adjudicated group was represented by younger patients, with longer disease duration and higher frequency of systemic JIA.

Table 1. Demographic and clinical characteristic of the Pharmachild patients with infections evaluated or not evaluated by Safety Adjudication Committee (SAC). Data are n (%) or medians (m) with IQR range. Drugs refers to their administration at any time during the patient's history and are sorted by their descending frequencies.

	Patients Adjudicated (N=572)	**Patients not Adjudicated (N=323)**	**Patients with Infections (N=895)**
Females	388 (67.8%)	241 (74.6%)	629 (70.3%)
Age at onset, m	3.1 (1.7-6.7)	4.1 (2.1-8.5)	3.5 (1.9-7.3)
Age at diagnosis, m	3.7 (2.1-7.5)	4.9 (2.4-9.5)	4.1 (2.2-8.1)
Disease duration at last follow-up, m	7.6 (5.0-11.1)	5.8 (3.1-10.3)	7.1 (4.2-10.8)
JIA category			
Systemic	120 (20.9%)	37 (11.4%)	157 (17.5%)
Oligo persistent	101 (17.7%)	80 (24.8%)	181 (20.2%)
Oligo extended	100 (17.5%)	50 (15.5%)	150 (16.8%)
Polyarticular RF-	132 (23.1%)	84 (26.0%)	216 (24.1%)
Polyarticular RF+	19 (3.3%)	15 (4.6%)	34 (3.8%)
Psoriatic	25 (4.4%)	8 (2.5%)	33 (3.7%)
Enthesitis	36 (6.3%)	21 (6.5%)	57 (6.4%)
Undifferentiated	39 (6.8%)	28 (8.7%)	67 (7.5%)
Therapy			
Systemic glucocorticoids	336 (58.7%)	490 (54.7%)	154 (47.7%)
Synthetic DMARDs			
Methotrexate	532 (93.0%)	821 (91.7%)	289 (89.5%)
Cyclosporine	90 (15.7%)	103 (11.5%)	13 (4.1%)
Sulfasalazine	66 (11.5%)	94 (10.5%)	28 (8.7%)
Leflunomide	40 (7.0%)	68 (7.6%)	28 (8.7%)
Azathioprine	17 (3.0%)	23 (2.6%)	6 (1.9%)
Hydroxychloroquine	14 (2.4%)	23 (2.6%)	9 (2.8%)

	Patients Adjudicated (N=572)	Patients not Adjudicated (N=323)	Patients with Infections (N=895)
Thalidomide	7 (1.2%)	9 (1.0%)	2 (0.6%)
Biologic DMARDs			
Etanercept	298 (52.1%)	424 (47.4%)	126 (39.0%)
Adalimumab	178 (31.1%)	260 (29.1%)	82 (25.4%)
Tocilizumab	103 (18.0%)	122 (13.6%)	19 (5.9%)
Infliximab	84 (14.7%)	101 (11.3%)	17 (5.3%)
Anakinra	54 (9.4%)	82 (9.2%)	28 (8.7%)
Abatacept	39 (6.8%)	56 (6.3%)	17 (5.3%)
Canakinumab	28 (4.9%)	38 (4.2%)	10 (3.1%)
Rituximab	26 (4.5%)	29 (3.2%)	3 (0.9%)
Golimumab	14 (2.4%)	20 (2.2%)	6 (1.9%)
Certolizumab	4 (0.7%)	5 (0.6%)	1 (0.3%)
Other biologic agents	2 (0.3%)	3 (0.3%)	1 (0.3%)

Step 3. Adjudication of infections by the SAC

A total of 689/772 (89.2%) events achieved consensus (3/5 SAC members) on the first 3 adjudication questions and, of these, 682 (99.0%) were considered as infections by the SAC (Table 2). The majority of the infections were considered common (88.4%) with 119 infections (17.4%) classified as opportunistic by the SAC after evaluation of the whole patient's history. The last 2 questions were more difficult for consensus to be reached. Regarding the fourth question, about the appropriateness of the treatment for the infection, consensus was achieved for 484 (77.1%) events, while for 140 (22.3%) of the cases it was impossible to determine the suitability of the infection treatment.

Similarly for the fifth question about the possible relationship between the infection and the related JIA treatment(s), the lack of consensus increased up to 279 (41%). For 307/403 (76.2%) cases for which there was consensus, the SAC considered the drug(s) possibly related to the event. The administration of 1 biologic (more commonly etanercept or adalimumab) plus 1 synthetic DMARD

was the most frequent association with infection (32% of the cases), followed by methotrexate alone (21%), etanercept alone (20.3%) and finally by the association of either 1 biologic plus 1 synthetic DMARD plus systemic steroids (9%) or 1 synthetic DMARD plus systemic steroids (3.7%) (data not shown).

Table 2. Frequency of answers by the SAC. Consensus by the majority of the SAC members (3/5) was required on the first 3 questions. SAC: Safety Adjudication Committee. ID: impossible to determine.

Questions for the SAC adjudication	Yes	No	ID	Events with consensus
1. Based on the information provided, do you confirm that this patient had an infection?	682 (99%)	0	7 (1%)	689 (100%)
2. Is this infection common?	603 (88.4%)	78 (11.4%)	1 (0.2%)	682 (100%)
3. Is this an opportunistic infection?	119 (17.4%)	556 (81.5%)	7 (1%)	682 (100%)
4. Was the treatment appropriate for the infection?	484 (77.1%)	4 (0.6%)	140 (22.3%)	628 (92%)
5. Could the event be possibly related to any of the drug(s) taken at the time of the event?	307 (76.2%)	70 (17.4%)	2 (0.5%)	403[1] (59%)

[1] n=24 were events without answers by the panel

Step 4. Analysis of the infections according to MedDRA dictionary

The evaluation of the Pharmachild registry conducted by the SAC led to the adjudication of the 682 infections corresponding to 53 HLT and 153 PT. For 92 (60%) PTs, the SAC confirmed the same PT used by the Pharmachild Medical Monitor, while for the remaining 40% discrepancies were solved by the study SC after re-evaluation of the individual cases. The final number of HLT was 50, with corresponding 149 PTs, showed in details with the frequency of the events in Supplementary Table S2.

Step 5. Final evidence-based listing of opportunistic pathogens/infection presentations

After matching the adjudicated events with the provisional list of OI, among the 682 events, 106 (15.5%) for 22 PT were classified as "confirmed OI", 274 (40.2%) for 89 PT were classified as "confirmed non-OI", and 302 (44.3 %) for 38 PT were classified as "possible/patient and/or pathogen- related OI".

Table 3 shows the frequency of the "confirmed OI" by HLT/PT. Regarding pathogens, herpes viral infections resulted the most represented HLT/PT category, with 72 events (68% of the total confirmed OI), mostly represented by herpes zoster infection (66/72, 91.6%). Tuberculosis, Candida, Papilloma and Pneumocystis followed with a frequency higher than 3% among "confirmed OI". Of the total 29 tubercular infections in Pharmachild (Supplementary table S2), only 11/106 (10.4%) were "confirmed OI", mostly with pulmonary or disseminated presentations.

Table 3. Frequency of the 106 infections "confirmed OI" adjudicated by the SAC after evaluation of the cases available in Pharmachild with full agreement between the SAC and the list of provisional pathogens/presentations. Data are presented as per the MedDRA High Level and Preferred Term and sorted by frequencies in descending order.

HLT-PT NAME	"Confirmed OI" N=106
Herpes viral infections	**72 (68%)**
Herpes zoster	66 (91.6%)
Herpes ophthalmic	2 (2.8%)
Ophthalmic herpes zoster	2 (2.8%)
Herpes virus infection	1 (1.4%)
Herpes zoster oticus	1 (1.4%)
Tuberculous infections	**11 (10.4%)**
Pulmonary tuberculosis	6 (54.5%)
Disseminated tuberculosis	4 (36.4%)
Bone tuberculosis	1 (9.1%)
Candida infections	**9 (8.5%)**
Oral candidiasis	4 (44.4%)
Candida pneumonia	2 (22.2%)
Balanitis candida	1 (11.1%)
Candida sepsis	1 (11.1%)
Oesophageal candidiasis	1(11.1%)
Papilloma viral infections	**4 (3.8%)**
Vulvovaginal human papilloma virus infection	3 (75%)
Anogenital warts	1 (25%)
Pneumocystis infections	**4 (3.8%)**
Pneumocystis jirovecii pneumonia	4 (100%)
Cytomegaloviral infections	**3 (2.8%)**
Cytomegalovirus mononucleosis	1 (33.3%)
Cytomegalovirus viraemia	1 (33.3%)
Pneumonia cytomegaloviral	1(33.3%)
Aspergillus infections	**1 (0.9%)**
Bronchopulmonary aspergillosis	1 (100%)
Leprous infections	**1 (0.9%)**
Leprosy	1 (100%)
Infections NEC	**1 (0.9%)**
Infection in an immunocompromised host	1 (100%)

Table 4 reports the frequency of “confirmed non-OI” and “possible/patient and/or pathogen- related OI”, after removing 218 infections for which PTs did not include a specific pathogen (the complete list of “confirmed non-OI” and “possible/patient and/or pathogen- related OI” in supplementary table S2). Among the 274 infections classified as “confirmed non-OI, only 59 (21.5%) were related to a specific pathogen, while almost in all the infections classified as “possible/patient and/or pathogen- related OI” (299/302, 99%), a specific pathogen was identifiable.

As indicated in table 4, influenza virus, streptococcus, staphylococcus and Escherichia resulted the most frequent “non-confirmed OI”. Conversely, for the remaining infectious events, classified as “possible/patient and/or pathogen- related OI”, the suspicion of an opportunistic condition could be raised for herpes infections (193/299, 64.5%) with a different clinical presentation compared to the previous group of “confirmed OI”. In particular varicella resulted the most common herpes manifestation in this group, affecting 155/299 (51.8%) cases, then followed by herpes simplex presentations. Epstein-Barr viral infections were reported in 38/299 cases (12.7%), generically as infections in 22 cases (7.4%) and classified as infectious mononucleosis in 13 cases (4.3%). Latent tuberculosis accounted for 12/299 (4.1%) cases, followed by few cases of tuberculosis, also with lymph-node involvement included in this group. The remaining events of “possible/patient and/or pathogen- related OI” affected less than 3% of the cases.

Table 4. Frequency of the "confirmed non OI" and "possible/patient and pathogen related OI" adjudicated by the SAC after evaluation of the cases available in Pharmachild. Clinical presentations were removed because of the lack of the specified pathogen. Data are presented as per the MedDRA High Level Term and Preferred Term and sorted by frequencies in descending order.

HLT-PT NAME	"Confirmed Non-OI" N=59	"Possible/Patient and pathogen related OI" N=299
Herpes viral infections, N=193		
Varicella		128 (42.8%)
Oral herpes		30 (10.1%)
Varicella zoster virus infection		24 (8.1%)
Herpes simplex		4 (1.4%)
Varicella zoster pneumonia		3 (1%)
Exanthema subitum		1 (0.3%)
Genital herpes simplex		1 (0.3%)
Herpes dermatitis		1 (0.3%)
Ophthalmic herpes simplex		1 (0.3%)
Epstein-Barr viral infections, N=38		
Epstein-Barr virus infection		22 (7.4%)
Infectious mononucleosis		13 (4.3%)
Epstein-Barr viraemia		2 (0.7%)
Hepatitis infectious mononucleosis		1 (0.3%)
Tuberculous infections, N=18		
Latent tuberculosis		12 (4.1%)
Tuberculosis		3 (1%)
Tuberculosis of intrathoracic lymph nodes		3 (1%)
Candida infections, N=8		
Vulvovaginal candidiasis		6 (2.1%)
Anal candidiasis		1 (0.3%)
Candida infection		1 (0.3%)
Influenza viral infections, N=14		
Influenza	13 (22%)	
H1N1 influenza	1 (1.7%)	
Streptococcal infections, N=14		
Scarlet fever	4 (6.7%)	

Pharyngitis streptococcal	3 (5.1%)	
Erysipelas	2 (3.4%)	
Pneumonia pneumococcal	2 (3.4%)	
Streptococcal bacteraemia	1 (1.7%)	
Streptococcal infection	1 (1.7%)	
Streptococcal sepsis	1 (1.7%)	
Salmonella infections, N=9		
Gastroenteritis salmonella		6 (2.1%)
Salmonella bacteraemia		1 (0.3%)
Salmonellosis		1 (0.3%)
Typhoid fever		1 (0.3%)
Molluscum contagiosum viral infections,		
Molluscum contagiosum		7 (2.3%)
Cytomegaloviral infections, N=5		
Cytomegalovirus infection		5 (1.7%)
Campylobacter infections, N=5		
Campylobacter gastroenteritis		5 (1.7%)
Staphylococcal infections, N=5		
Staphylococcal sepsis	2 (3.4%)	
Furuncle	1 (1.7%)	
Pneumonia staphylococcal	1 (1.7%)	
Toxic shock syndrome staphylococcal	1 (1.7%)	
Escherichia infections, N=4		
Escherichia pyelonephritis	3 (5.1%)	
Cystitis escherichia	1 (1.7%)	
Papilloma viral infections, N=3		
Papilloma viral infection		3 (1%)
Skin structures and soft tissue infections,		
Impetigo	3 (5.1%)	
Bordetella infections, N=3		
Pertussis	2 (3.4%)	
Bordetella infection	1 (1.7%)	
Giardia infections, N=3		
Giardiasis		3 (1%)
Mycoplasma infections, N=3		
Mycoplasma infection	1 (1.7%)	
Pharyngitis mycoplasmal	1 (1.7%)	
Pneumonia mycoplasmal	1 (1.7%)	
Caliciviral infections, N=2		
Gastroenteritis caliciviral	1 (1.7%)	
Gastroenteritis norovirus		1 (0.3%)
Hepatitis viral infections, N=2		
Hepatitis B		1 (0.3%)
Hepatitis C		1 (0.3%)
Parvoviral infections, N=2		
Parvovirus B19 infection		2 (0.7%)
Rotaviral infections, N=2		

Gastroenteritis rotavirus		2 (0.7%)
Yersinia infections, N=2		
Gastroenteritis yersinia	1 (1.7%)	
Yersinia infection	1 (1.7%)	
Blastocystis infections, N=1		
Blastocystis infection	1 (1.7%)	
Bone and joint infections, N=1		
Osteomyelitis acute	1 (1.7%)	
Borrelial infections		
Lyme disease	1 (1.7%)	
Clostridia infections, N=1		
Clostridium difficile colitis	1 (1.7%)	
Coxiella infections, N=1		
Coxiella infection	1 (1.7%)	
Enteroviral infections NEC, N=1		
Enterovirus infection		1 (0.3%)
Fungal infections NEC, N=1		
Systemic mycosis		1 (0.3%)
Haemophilus infections, N=1		
Haemophilus infection	1 (1.7%)	
Helicobacter infections, N=1		
Helicobacter gastritis	1 (1.7%)	
Mycobacteria identification and serology,		
Tuberculin test positive	1 (1.7%)	
Pseudomonal infections, N=1		
Pseudomonal sepsis	1 (1.7%)	
Respiratory syncytial viral infections, N=1		
Respiratory syncytial virus infection		1 (0.3%)
Rubeola viral infections, N=1		
Pneumonia measles	1 (1.7%)	

Discussion

An evidence based-list of opportunistic pathogens with the related MedDRA classification in immunosuppressed children with JIA has been derived by the combination of consensus among a panel of pediatricians with expertise in rheumatology and infectious diseases, and the analysis of the Pharmachild international registry in JIA.(40) The final list of opportunistic infections/presentations could constitute a future reference for researchers, pharmaceutical companies and regulatory authorities dealing with pharmacovigilance issues.

The introduction of biologics in 2000s for the treatment of JIA has dramatically changed the prognosis of children affected by JIA, but has also raised concerns on the possible risk of infections and other safety events in these patients. Despite the widespread use of these drugs, there is still a lack of knowledge regarding the assessment of the long-term safety of the biologics in JIA. In this context, the role of national and international registries becomes an important source of data.(40;46-48).

The international registry Pharmachild has the advantage to combine information from different countries based on real clinical data. In Pharmachild infections occur in about 11% of patients with JIA(40), and among them it is of primary importance to identify the opportunistic ones, that may take advantage of a condition of immunosuppression like in children with JIA on therapy. This is not an easy task, because apparently there is a great gap between what pediatric rheumatologists feel can be considered as an OI and what a panel of experts adjudicates as such. While most serious infections occur in the general population, some events are more frequent or severe in case of immunosuppression. Conversely, some infections, such as tuberculosis, more common in immune compromised children, may affect also the general population, although usually less severely.(49) Considering these difficulties in correctly defining OI, we made an effort to produce a document defining OI specifically in children with JIA on immunosuppression, based on the example of a specialized Committee convened in the adult setting to define OI in adults with immune mediated diseases on biologics.(33) With the same approach, our panel of specialists voted, through a three-step Delphi procedure, for a correct definition of definite and probable OI, and subsequently produced a list of OI by cross matching the provisional list produced by consensus with the Pharmachild data. In a first phase of our study, among the Pharmachild patients, a considerable percentage of infections (17.4%) was adjudicated as opportunistic. When we matched the provisional list of OI with the patients' clinical information, it became clear that beside events with full agreement between the SAC and the list, which could be considered either "confirmed OI" (106/682, 15.5%) or "non-confirmed OI" (274/682, 40.2%), there was a considerable number (299/682, 43.8%) of debatable infections due to the

specific patient's history and/or the pathogen presentation, and classified as "possible/patient and/or pathogen- related OI". The most explanatory case is represented by herpes zoster infection. (Table 3 and 4) While zoster infection was included among the "confirmed OI", as stated in the majority of the literature in this issue,(50-52) its clinical presentation varicella, very frequent in our population (155/682, 22.7%), due to the high incidence in healthy non vaccinated children and its often non complicated presentation, was included among the "possible/patient and/or pathogen- related OI". This group of patients highlights the difficulties in defining OIs in JIA children on treatment, but also the critical importance of providing a reference document listing those infections that should always be considered as opportunistic in these category of patients, with possible implications for treatment or prophylaxis.

The current literature provides similar evidence, but remains controversial for the majority of OI. Beukelman et al. in 2012 reviewed US Medicaid data comparing the incidence of bacterial infections requiring hospitalization in children with and without JIA.(1;31) The infection rate was already twice high in patients with JIA not exposed to treatments, compared to children with attention-deficit hyperactivity disorder (ADHD) used as controls.(31) The same author one year later re-analyzed the same data by comparing the incidence rate of selected OI among children with and without JIA. Coccidioides, Salmonella and herpes zoster resulted increased in frequency among JIA patients.(30) Among the 15 pathogens they used to define their list of OI, all in our provisional OI list (supplementary table S1), only Herpes Zoster, Tuberculosis, Pneumocystis and Aspergillus were confirmed in our final list of "confirmed OI". The remaining cases were included in the "possible/patient and/or pathogen- related OI" list. Interestingly, the authors included primary varicella infection in the OI only if received critical care services during the hospitalization. An increased risk of herpes zoster infection was confirmed in many studies in literature, both in JIA (50) and in the adult rheumatoid arthritis(53). More recently, Aeschlimann et al. studied, through a meta-analysis, whether treatment with biologics during clinical trial study periods increases the risk of serious infections in children with JIA. On a total of 19 trials accounting for 21 individual studies, 17 serious infections were reported among

810 children, with bronchopulmonary and varicella being the most frequent events.(54) Beside this evidence, the role of other opportunistic pathogens still needs to be further investigated.

Conclusions

In conclusion almost 1/5 of all severe and/or serious infections in JIA patients on immunosuppressive therapy are opportunistic. The most frequent opportunistic pathogens were herpes virus (excluding non-complicated primary varicella), mycobacterial and Candida infections. We provided with our work a list of "confirmed OI" in children with JIA on immunosuppressive therapy, that could be used as possible reference document for future works on pharmacovigilance in children with JIA on immunosuppressive therapy, and a list of infections that could possibly display an opportunistic nature related to the patient's history and/or the pathogen presentation. More clarity in the understanding of OI in JIA children on immunosuppressant will help in deciding treatment or prophylaxis in this group of patients.

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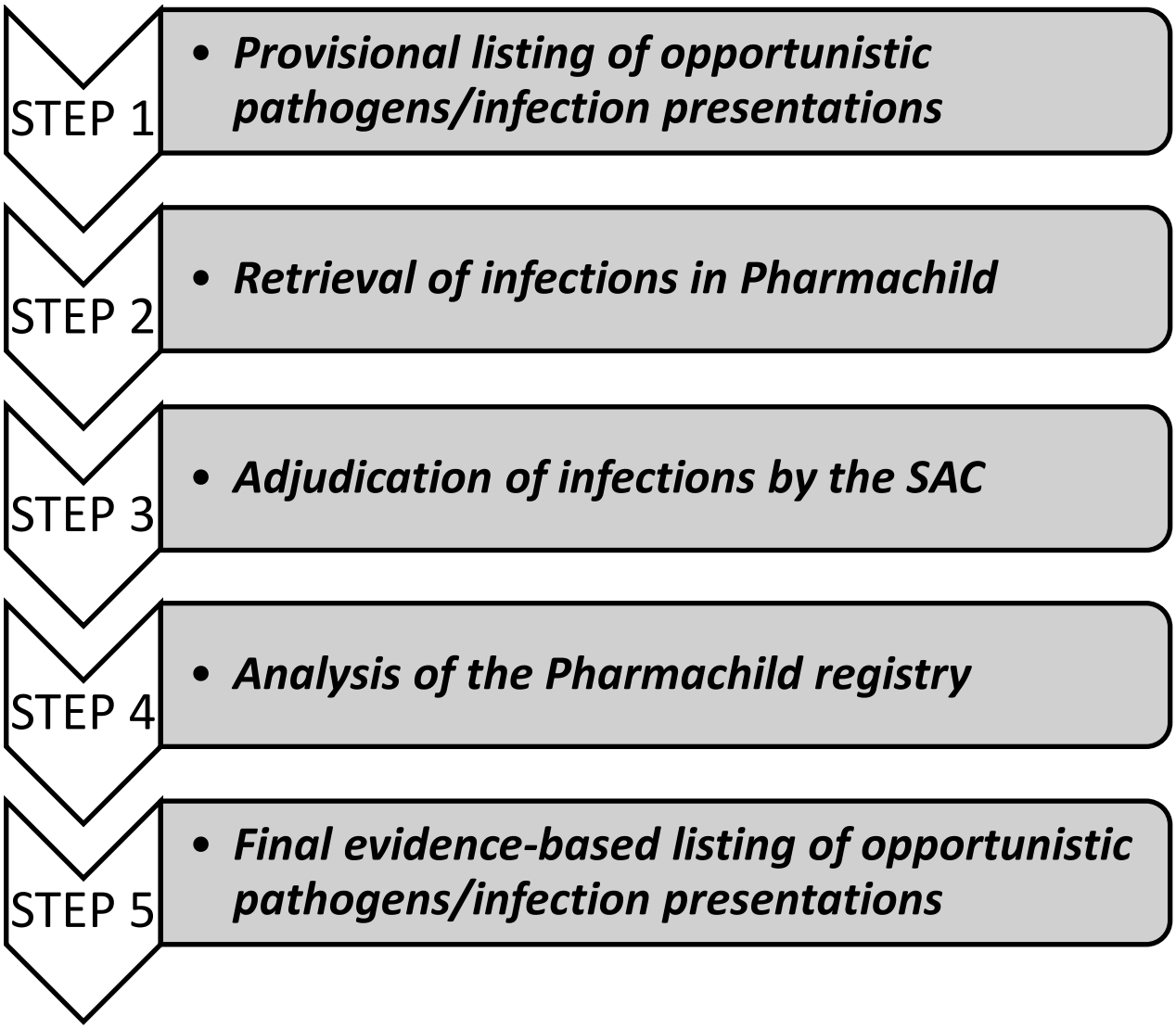
Supplementary Material

Supplementary Figure S1. Flow chart of the project.



Supplementary Figure S2. Hierarchy of MedDra clinically-validated international medical terminology

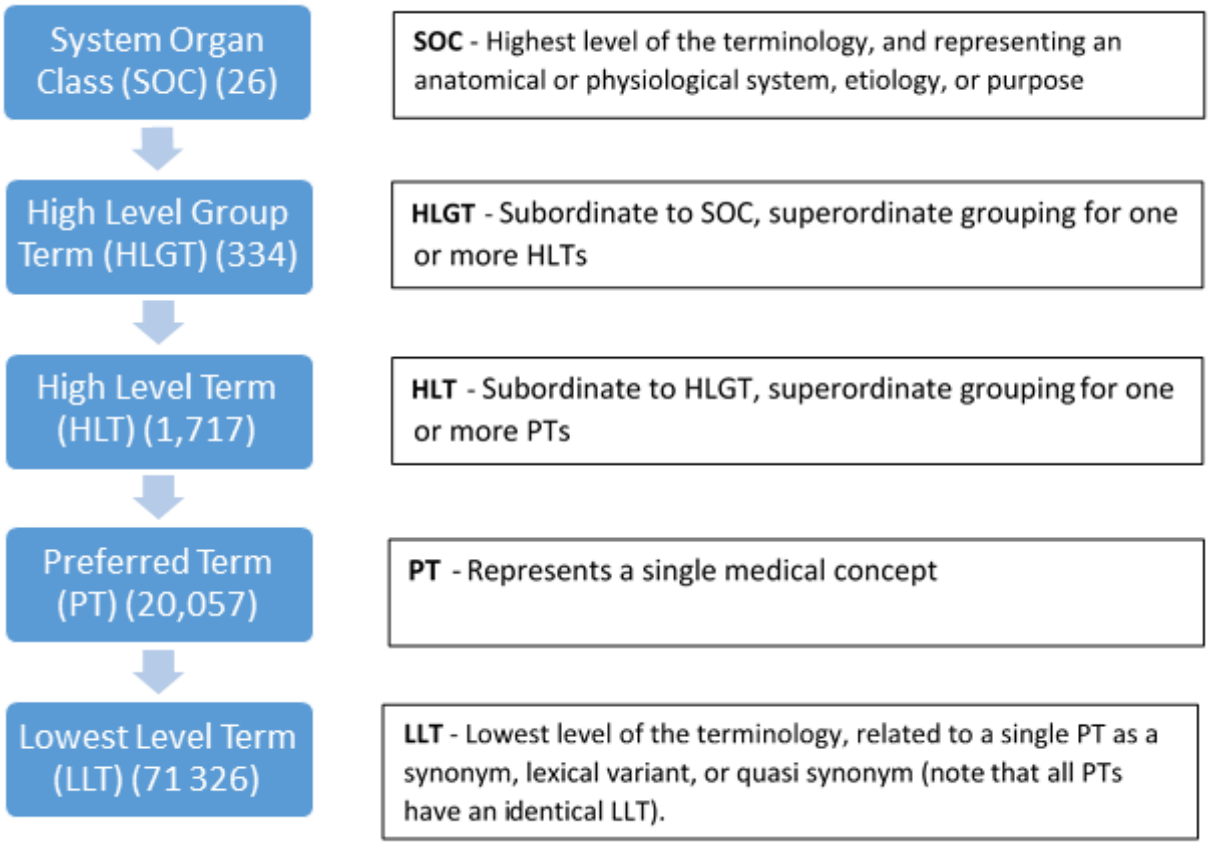


Table S1. Provisional list of pathogens/presentations and MedDRA HLT term approved by consensus by the SAC. Highlighted in red those pathogens/presentations modified by the SAC after consensus and literature review on the basis of Winthrop et al.'s paper. (33)

DEFINITION OF DEFINITE OPPORTUNISTIC INFECTION IN JIA CHILDREN	**HLT**
1. Generally does not occur in the absence of immunosuppression and whose presence suggests a severe alteration in host immunity **OR**	
2. Can occur in patients without recognized forms of immunosuppression, but whose presence indicates a potential or likely alteration in host immunity	
List of definite pathogens and/or presentations of specific pathogens	
Aspergillosis (invasive disease only)	Aspergillus infections
Bartonellosis (disseminated disease only)	Bartonella infections
BK virus disease including PVAN	BK virus infection
Blastomycosis	Blastomyces infections
Candidiasis (invasive disease or pharyngeal)	Candida infections
Coccidioidomycosis	Coccidioides infections/ Paracoccidioides infections
Cryptococcosis	Cryptococcal infections
Cytomegalovirus disease with onset at age > 1 month: pneumonia (CMV in BAL), colitis, CNS disease (CMV in CSF), liver (biopsy), retina (confirmed by ophthalmologist), nephritis, myocarditis, pancreatitis, others	Cytomegaloviral infections
HBV reactivation	Hepatitis viral infections
Herpes simplex (invasive disease only)	Herpes viral infections
Herpes zoster (any form)	Herpes viral infections
Histoplasmosis	Histoplasma infections
Legionellosis	Legionella infections
Listeria monocytogenes (invasive disease only)	Listeria infections
Nocardiosis	Nocardia infections

Non-tuberculous mycobacterium disease	Atypical mycobacterial infections
Other invasive fungi: Mucormycosis (zygomycosis) (Rhizopus, Mucor and Lichtheimia), Scedosporium /Pseudallescheria boydii, Fusarium	Fungal infections NEC
Pneumocystis jirovecii	Pneumocystis infections
Post-transplant lymphoproliferative disorder (EBV)	Epstein-Barr viral infections
Progressive multifocal leucoencephalopathy	Polyomavirus infections
Salmonellosis (invasive disease only)	Salmonella infections
Strongyloides (hyperinfection syndrome and disseminated forms only)	Nematode infections
Toxoplasmosis of central nervous system, onset at age ≥ 1 month; Disseminated toxoplasmosis, visceral toxoplasmosis	Toxoplasma infections
Tuberculosis	Tuberculous infections
DEFINITION OF PROBABLE OPPORTUNISTIC INFECTION	
Published data is currently lacking, but expert opinion believes that risk is likely elevated in the setting of biologic therapy. In case of the unusually severe course of infection due to a common pathogen with usually mild disease the pathogen might tentatively be considered opportunistic in a patient with impaired immune function. Below there is a non-exhaustive list of possible pathogens	
List of probable pathogens and/or presentations of specific pathogens	
Campylobacteriosis (invasive disease only)	Campylobacter infections
Cryptosporidium species (chronic disease only)	Cryptosporidia infections
Enterovirus chronic encephalitis	Enteroviral infections NEC
Giardia, Isospora: chronic (>1 month) diarrhea	Giardia infections/ Isospora infections
HCV progression	Hepatitis viral infections
Human Herpes Virus (HHV6-7): pneumonia, encephalitis	Herpes viral infections
Human Herpes Virus (HHV8): kaposi sarcoma	Herpes viral infections
Human metapneumovirus (hMPV): pneumonia, ARDS	Viral infections NEC
Human Papilloma Virus (HPV): extensive warts	Papilloma viral infections
Human respiratory syncytial virus (RSV): pneumonia with onset > 6 months of age	Respiratory syncytial viral infections

Legionellosis	Legionella infections
Leishmaniasis (Visceral only)	Leishmania infections
Microsporidiosis	Protozoal infections NEC
Molluscum contagiosa: chronic, disseminated	Molluscum contagiosum
Paracoccidioides infections	Paracoccidioides infections
Parvovirus B19: pure red cell aplasia	Parvoviral infections
Penicillium marneffei	Fungal infections NEC
Rota-Arena-Norovirus: chronic (> 1 month) diarrhea	Rotaviral infections/ Arenaviral infections/ Caliciviral infections
Shigellosis (invasive disease only)	Shigella infections
Sporothrix schenckii	Sporothrix infections
Trypanosoma cruzi infection (Chagas' disease) (disseminated disease only)	Trypanosomal infections
Varicella: encephalitis (excluding cerebellitis), hepatitis, pneumonia	Herpes viral infections
Vibriosis (invasive disease due to Vibrio vulnificus)	Vibrio infections
West Nile, Usutu: chronic encephalitis	Flaviviral infections

Supplementary Table S2. Complete table with the frequency of the 682 infections adjudicated by the SAC after evaluation of the cases available in Pharmachild compared to the pathogens/presentations in the provisional list approved by the SAC. Data are presented as per the MedDRA High Level Term (HLT) and Preferred Term (PT) sorted by frequencies in descending order (HLT and then PT). *For the definition see Step 5.

HLT-PT NAME	N	%	"Confirmed OI"*	"Confirmed Non-OI"*	"Possible patient and/or pathogen related OI"*
Herpes viral infections	**265**	**38.9%**			
Varicella	128	48.3%			x
Herpes zoster	66	24.9%	x		
Oral herpes	30	11.3%			x
Varicella zoster virus infection	24	9.1%			x
Herpes simplex	4	1.5%			x
Varicella zoster pneumonia	3	1.1%			x
Herpes ophthalmic	2	0.7%	x		
Exanthema subitum	1	0.4%			x
Genital herpes simplex	1	0.4%			x
Herpes dermatitis	1	0.4%			x
Herpes virus infection	1	0.4%	x		
Herpes zoster oticus	1	0.4%	x		
Ophthalmic herpes simplex	1	0.4%			x
Ophthalmic herpes zoster	2	0.7%	x		

HLT-PT NAME	N	%	"Confirmed OI"*	"Confirmed Non-OI"*	"Possible patient and/or pathogen related OI"*
Lower respiratory tract and lung infections	**49**	**7.2%**			
Pneumonia	41	83.6%		x	
Atypical pneumonia	2	4.1%		x	
Bronchitis	2	4.1%		x	
Infectious pleural effusion	2	4.1%			x
Lower respiratory tract infection	2	4.1%		x	
Upper respiratory tract infections	**44**	**6.4%**			
Upper respiratory tract infection	14	31.8%		x	
Tonsillitis	11	25%		x	
Pharyngitis	8	18.2%		x	
Sinusitis	3	6.8%		x	
Chronic sinusitis	2	4.5%		x	
Pharyngotonsillitis	2	4.5%		x	
Rhinitis	2	4.5%		x	
Adenoiditis	1	2.3%		x	
Laryngitis	1	2.3%		x	
Epstein-Barr viral infections	**38**	**5.6%**			
Epstein-Barr virus infection	22	57.9%			x
Infectious mononucleosis	13	34.2%			x
Epstein-Barr viraemia	2	5.3%			x
Hepatitis infectious mononucleosis	1	2.6%			x
Abdominal and gastrointestinal infections	**32**	**4.7%**			
Gastroenteritis	15	46.9%		x	

HLT-PT NAME	N	%	"Confirmed OI"*	"Confirmed Non-OI"*	"Possible patient and/or pathogen related OI"*
Appendicitis	12	37.5%		x	
Appendicitis perforated	3	9.4%		x	
Anal abscess	1	3.1%		x	
Gastrointestinal infection	1	3.1%		x	
Tuberculous infections	**29**	**4.2%**			
Latent tuberculosis	12	41.4%			x
Pulmonary tuberculosis	6	20.7%	x		
Disseminated tuberculosis	4	13.8%	x		
Tuberculosis	3	10.3%			x
Tuberculosis of intrathoracic lymph nodes	3	10.3%			x
Bone tuberculosis	1	3.4%	x		
Bacterial infections NEC	**27**	**4%**			
Pneumonia bacterial	11	40.8%		x	
Cellulitis	2	7.4%		x	
Nail bed infection bacterial	2	7.4%		x	
Upper respiratory tract infection bacterial	2	7.4%		x	
Urinary tract infection bacterial	2	7.4%		x	
Wound infection bacterial	2	7.4%		x	
Ear infection bacterial	1	3.7%		x	
Lymphadenitis bacterial	1	3.7%		x	
Otitis externa bacterial	1	3.7%		x	
Peritonitis bacterial	1	3.7%		x	
Pharyngitis bacterial	1	3.7%		x	

HLT-PT NAME	N	%	"Confirmed OI"*	"Confirmed Non-OI"*	"Possible patient and/or pathogen related OI"*
Pyomyositis	1	3.7%		x	
Infections NEC	**21**	**3.1%**			
Respiratory tract infection	12	57.1%		x	
Abscess limb	2	9.5%		x	
Postoperative wound infection	2	9.5%		x	
Wound infection	2	9.5%		x	
Infection in an immunocompromised host	1	4.8%	x		
Injection site infection	1	4.8%		x	
Lymph node abscess	1	4.8%		x	
Ear infections	**18**	**2.6%**			
Otitis media acute	8	44.4%		x	
Otitis media	5	27.7%		x	
Ear infection	3	16.7%		x	
Otitis externa	1	5.6%		x	
Otitis media chronic	1	5.6%		x	
Candida infections	**17**	**2.5%**			
Vulvovaginal candidiasis	6	35.3%			x
Oral candidiasis	4	23.5%	x		
Candida pneumonia	2	11.7%	x		
Anal candidiasis	1	5.9%			x
Balanitis candida	1	5.9%	x		
Candida infection	1	5.9%			x
Candida sepsis	1	5.9%	x		

HLT-PT NAME	N	%	"Confirmed OI"*	"Confirmed Non-OI"*	"Possible patient and/or pathogen related OI"*
Oesophageal candidiasis	1	5.9%	x		
Influenza viral infections	**14**	**2.1%**			
Influenza	13	92.9%		x	
H1N1 influenza	1	7.1%		x	
Streptococcal infections	**14**	**2.1%**			
Scarlet fever	4	28.6%		x	
Pharyngitis streptococcal	3	21.4%		x	
Erysipelas	2	14.3%		x	
Pneumonia pneumococcal	2	14.3%		x	
Streptococcal bacteraemia	1	7.1%		x	
Streptococcal infection	1	7.1%		x	
Streptococcal sepsis	1	7.1%		x	
Salmonella infections	**9**	**1.3%**			
Gastroenteritis salmonella	6	66.7%			x
Salmonella bacteraemia	1	11.1%			x
Salmonellosis	1	11.1%			x
Typhoid fever	1	11.1%			x
Urinary tract infections	**9**	**1.3%**			
Pyelonephritis	5	55.6%		x	
Urinary tract infection	2	22.2%		x	
Cystitis	1	11.1%		x	
Pyelonephritis acute	1	11.1%		x	
Cytomegaloviral infections	**8**	**1.2%**			

HLT-PT NAME	N	%	"Confirmed OI"*	"Confirmed Non-OI"*	"Possible patient and/or pathogen related OI"*
Cytomegalovirus infection	5	62.5%			x
Cytomegalovirus mononucleosis	1	12.5%	x		
Cytomegalovirus viraemia	1	12.5%	x		
Pneumonia cytomegaloviral	1	12.5%	x		
Molluscum contagiosum viral infections	**7**	**1.1%**			
Molluscum contagiosum	7	100%			x
Papilloma viral infections	**7**	**1.1%**			
Papilloma viral infection	3	42.8%			x
Vulvovaginal human papilloma virus infection	3	42.8%	x		
Anogenital warts	1	14.4%	x		
Sepsis, bacteraemia, viraemia and fungaemia NEC	**7**	**1.1%**			
Device related sepsis	2	28.6%		x	
Sepsis	2	28.6%		x	
Sepsis syndrome	2	28.6%		x	
Viraemia	1	14.3%			x
Campylobacter infections	**5**	**0.7%**			
Campylobacter gastroenteritis	5	100%			x
Staphylococcal infections	**5**	**0.7%**			
Staphylococcal sepsis	2	40%		x	
Furuncle	1	20%		x	
Pneumonia staphylococcal	1	20%		x	

HLT-PT NAME	N	%	"Confirmed OI"*	"Confirmed Non-OI"*	"Possible patient and/or pathogen related OI"*
Toxic shock syndrome staphylococcal	1	20%		x	
Viral infections NEC	**5**	**0.7%**			
Viral upper respiratory tract infection	3	60%		x	
Gastroenteritis viral	2	40%		x	
Escherichia infections	**4**	**0.6%**			
Escherichia pyelonephritis	3	75%		x	
Cystitis escherichia	1	25%		x	
Pneumocystis infections	**4**	**0.6%**			
Pneumocystis jirovecii pneumonia	4	100%	x		
Skin structures and soft tissue infections	**4**	**0.6%**			
Impetigo	3	75%		x	
Subcutaneous abscess	1	25%		x	
Bordetella infections	**3**	**0.4%**			
Pertussis	2	66.7%		x	
Bordetella infection	1	33.3%		x	
Dental and oral soft tissue infections	**3**	**0.4%**			
Tooth abscess	2	66.7%		x	
Sialoadenitis	1	33.3%		x	
Giardia infections	**3**	**0.4%**			
Giardiasis	3	100%			x
Mycoplasma infections	**3**	**0.4%**			
Mycoplasma infection	1	33.3%		x	
Pharyngitis mycoplasmal	1	33.3%		x	

HLT-PT NAME	N	%	"Confirmed OI"*	"Confirmed Non-OI"*	"Possible patient and/or pathogen related OI"*
Pneumonia mycoplasmal	1	33.3%		x	
Caliciviral infections	**2**	**0.3%**			
Gastroenteritis caliciviral	1	50%		x	
Gastroenteritis norovirus	1	50%			x
Eye and eyelid infections	**2**	**0.3%**			
Conjunctivitis	2	100%		x	
Hepatitis viral infections	**2**	**0.3%**			
Hepatitis B	1	50%			x
Hepatitis C	1	50%			x
Parvoviral infections	**2**	**0.3%**			
Parvovirus B19 infection	2	100%			x
Rotaviral infections	**2**	**0.3%**			
Gastroenteritis rotavirus	2	100%			x
Yersinia infections	**2**	**0.3%**			
Gastroenteritis yersinia	1	50%		x	
Yersinia infection	1	50%		x	
Aspergillus infections	**1**	**0.1%**			
Bronchopulmonary aspergillosis	1	100%	x		
Blastocystis infections	**1**	**0.1%**			
Blastocystis infection	1	100%		x	
Bone and joint infections	**1**	**0.1%**			
Osteomyelitis acute	1	100%		x	
Borrelial infections	**1**	**0.1%**			

HLT-PT NAME	N	%	"Confirmed OI"*	"Confirmed Non-OI"*	"Possible patient and/or pathogen related OI"*
Lyme disease	1	100%		x	
Clostridia infections	**1**	**0.1%**			
Clostridium difficile colitis	1	100%		x	
Coxiella infections	**1**	**0.1%**			
Coxiella infection	1	100%		x	
Enteroviral infections NEC	**1**	**0.1%**			
Enterovirus infection	1	100%			x
Fungal infections NEC	**1**	**0.1%**			
Systemic mycosis	1	100%			x
Haemophilus infections	**1**	**0.1%**			
Haemophilus infection	1	100%		x	
Helicobacter infections	**1**	**0.1%**			
Helicobacter gastritis	1	100%		x	
Leprous infections	**1**	**0.1%**			
Leprosy	1	100%	x		
Muscle and soft tissue infections	**1**	**0.1%**			
Psoas abscess	1	100%		x	
Mycobacteria identification and serology	**1**	**0.1%**			
Tuberculin test positive	1	100%		x	
Pseudomonal infections	**1**	**0.1%**			
Pseudomonal sepsis	1	100%		x	
Respiratory syncytial viral infections	**1**	**0.1%**			
Respiratory syncytial virus infection	1	100%			x

HLT-PT NAME	N	%	"Confirmed OI"*	"Confirmed Non-OI"*	"Possible patient and/or pathogen related OI"*
Rubeola viral infections	**1**	**0.1%**			
Pneumonia measles	1	100%		x	

DECLARATIONS

Ethics approval and consent to participate

All registries and participating centers obtained approval from their respective ethics committee and obtained consent/assent based on national existing regulations.

Availability of data and material

Data from the registries included in chapter 4 were elaborated from Pharmachild, BiKeR and the Swedish registry.

Pharmachild registry is registered at Clinicaltrials.gov (NCT01399281) and at the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP; http://www.encepp.eu/encepp/viewResource.htm?id=19362)

BiKeR registry is registered at ENCePP (http://www.encepp.eu/encepp/viewResource.htm?id=20591)

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- Nicolino Ruperto, MD, MPH PRINTO Senior Scientist

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