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Original article

Burden of comorbid conditions in children and young people with juvenile idiopathic arthritis: a collaborative analysis of 3 JIA registries

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Abstract

Objectives. Burden of comorbidities are largely unknown in JIA. From 2000, national and international patient registries were established to monitor biologic treatment, disease activity and adverse events in patients with JIA. The aim of this analysis was to investigate in parallel, for the first time, three of the largest JIA registries in Europe/internationally—UK JIA Biologic Registers (BCRD/BSPAR-ETN), German biologic registers (BiKeR/JuMBO), multinational Pharmachild—to quantify the occurrence of selected comorbidities in patients with JIA.

Methods. Information on which data the registers collect were compared. Patient characteristics and levels of comorbidity were presented, focussing on four key conditions: uveitis, MAS, varicella, and history of tuberculosis. Incidence rates of these on MTX/biologic therapy were determined.

Results. 8066 patients were registered into the three JIA registers with similar history of the four comorbidities across the studies; however, varicella vaccination coverage was higher in Germany (56%) *vs* UK/Pharmachild (16%/13%). At final follow-up, prevalence of varicella infection was lower in Germany (15%) *vs* UK/Pharmachild (37%/50%). Prevalence of TB (0.1–1.8%) and uveitis (15–19%) was similar across all registers. The proportion of systemic-JIA patients who ever had MAS was lower in Germany (6%) *vs* UK (15%) and Pharmachild (17%).

Conclusion. This analysis is the first and largest to investigate the occurrence of four important comorbidities in three JIA registries in Europe and the role of anti-rheumatic drugs. Combined, these three registries represent one of the biggest collection of cases of JIA worldwide and offer a unique setting for future JIA outcome studies.

Key words: JIA, epidemiology, biologic therapy, DMARDs, outcome measures, viruses

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Rheumatology key messages

- This study investigated comorbidities over 8000 children and young people with JIA across three large registers.
- Rates of comorbidities were similar, although varicella vaccination in populations impacted comparability of varicella infections.
- This study showed how JIA registers can collaborate, with synchronized analyses, and can move towards harmonization.

Introduction

JIA, characterized by arthritis of unknown origin starting before 16 years old, is the most common form of childhood chronic rheumatic illness, with a prevalence varying between 16 and 150 per 100 000 [1, 2]. The ILAR has identified seven JIA categories with distinct clinical symptoms and disease courses [3]. Many children and young people (CYP) with arthritis will continue to have active disease as adults, some with severe disability despite the dramatically improved disease outcomes observed since the introduction of biologic therapy. Childhood arthritis is costly to society, in both personal and economic terms. Patients with JIA show an impairment in health status, and may require an extended period of care [4].

Many CYP with JIA suffer from comorbidities, defined as distinct additional diseases that exist prior to or during the clinical course of JIA [5], with some being transient, resolving medical conditions and others remaining active and persistent. These may be related to JIA itself, such as uveitis or macrophage activation syndrome (MAS) [6, 7], or to its treatment, such as an increase in serious infections [8, 9]. Other conditions may be coincidental or share risk factors with JIA itself. These can add to the complexity of the case, as the overall impact of the various diseases can contribute to the overall burden of illness for the patient (e.g. socio-economic, cultural, environmental, patient behaviour and psychological characteristics) [10]. In adults with RA, comorbidity is also common, with some studies suggesting that three-in-four patients will have a second or further diagnosis as well [11].

For JIA, the burden of comorbidities is largely unknown. Following the introduction of biologic DMARDs in the 2000s, several patient registries were established with the aim of monitoring treatment, disease activity and adverse events (AEs) in CYP with JIA. The long follow-up time of these registries means they can be an important source of real-world evidence on comorbidities. Through collaboration between the various registries, a better understanding of the occurrence of comorbidities in CYP with JIA can be obtained by identifying key comorbidities and their prevalence in this patient population. Detailed information on the occurrence of key comorbidities in JIA may be of use for health-care providers, health-care authorities and health-care insurance companies.

The aim of this project was to carry out a parallel analysis in three of the largest JIA registries to quantify the occurrence of selected comorbidities in CYP with JIA: uveitis, MAS, varicella (and herpes zoster) infection, and tuberculosis (TB). The specific objectives were (1) to compare the methodology of each register in terms of capturing data on comorbidity, (2) to describe the prevalence of the four comorbidities above and (3) to quantify the incidence of these comorbidities that later develop under treatment by final follow-up.

Methods

Comparison of registry methodology

This analysis included three of the largest JIA cohorts; United Kingdom (UK) JIA Biologics Registers, German biologic registers, international Pharmachild registry. Data from each registry were extracted (UK: 6-Jan-2021; Germany: 10-Nov-2019; Pharmachild: 12-Nov-2020) regarding target population of each cohort, patient recruitment, baseline data collection, baseline comorbidities data, follow-up data collection, and serious AE reporting.

Cohort descriptions

UK JIA biologic registers

The UK JIA Biologic Registers consist of two parallel registers: the British Society for Paediatric and Adolescent Rheumatology Etanercept Cohort Study (BSPAR-ETN; established 2004) and the Biologics for Children with Rheumatic Diseases Study (BCRD; established 2010) [12]. These prospective multicentre observational cohort studies run in parallel, aiming to monitor drug safety and assess the effectiveness of therapy in routine care of CYP with JIA in the UK. Patients register when they start either MTX or biologic therapy. Recruitment is encouraged, although not mandatory.

Data are collected via an online web-portal completed by the treating physician or an affiliated clinical research nurse at the start of therapy (registration), at 6 months, at 1 year and then annually. The collected data include patient demographics, disease activity (joint count, physician global assessment and inflammatory parameters), functional ability using the Childhood Heath Assessment Questionnaire (CHAQ) [13], comorbidities, and anti-rheumatic therapies. The rheumatologist or research nurse reports new AEs on each follow-up form.

German biologic registers

BiKeR (biologics in pediatric rheumatology) and JuMBO (Juvenile Arthritis MTX/Biologics Long- Term Observation) are ongoing multicentre, prospective, observational

cohort studies aiming to monitor the drug safety of DMARDs and assess the effectiveness of therapy in routine care of patients with JIA in Germany.

Patients with JIA enrol in BiKeR at the start of biologic therapy (since 2001) or MTX monotherapy (since 2005). JuMBO (established in 2007) is the follow-up register for further observation of patients who have reached 18 years old in BiKeR or who have left paediatric care. The register ensures the long-term follow-up of JIA patients in adult rheumatologic care.

Data are collected via paper questionnaires. Patients are assessed in BiKeR by the paediatric rheumatologist at enrolment, at 3 months, at 6 months, and 6-monthly thereafter. The follow-up visits are scheduled 6-monthly in JuMBO. Both registers collect patient demographics, disease activity (joint count, physician global assessment and inflammatory parameters), functional ability (CHAQ in BiKeR, HAQ in JuMBO), comorbidities, and anti-rheumatic therapies. The rheumatologist reports any new AEs on each follow-up form.

Pharmachild

Pharmacovigilance in JIA (Pharmachild) is an ongoing observational register (established in 2011); the aim of Pharmachild is to monitor drug safety and to assess the effectiveness of therapy in routine care of patients with JIA. Patients are enrolled from 87 member centres around the world that belong to the Paediatric Rheumatology International Trials Organization (PRINTO) [8, 14].

Data are collected either retrospectively from enrolment or both retrospectively and prospectively every 6 months. Data are collected via a web-based registration system completed by the treating physician, and patient-reported outcomes are entered by the patients or their parents directly into the system. The data collected includes patient demographics, disease activity (joint count, physician global assessment and inflammatory parameters), a juvenile arthritis multidimensional assessment report (JAMAR) [15], comorbidities, and anti-rheumatic therapies. The rheumatologist reports any new AEs on each follow-up form.

All registries—adverse events and ethics

Patients in the UK JIA Biologics Registers and Pharmachild continue (yearly) follow-up into adulthood (>18 years old). All registries report the history of comorbidities from a tick-box list of pre-defined conditions at registration. Reported AEs are coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding system. AEs may include comorbidities and adverse drug reactions. All registries and centres obtained ethics committee approval according to national requirements, and all patients or their parents provided written informed consent/assent as appropriate in accordance with the Declaration of Helsinki. For the UK, BSPAR-ETN was approved by the West Midlands Research Ethics Committee and BCRD was approved by the North West 7 REC Greater Manchester Central Ethics Committee. For Germany, BiKeR was approved by the ethics committee of the Medical Council of North Rhine – Westphalia, Duesseldorf, Germany, and JuMBO was approved by the ethics committee of Charité University Medicine Berlin. All participating centres in Pharmachild provided institutional ethics committee approval. No additional ethical approval was required for this analysis.

Data analysis

Four key comorbidities/diseases were compared between the cohorts: uveitis, MAS, varicella (varicella and herpes zoster infection), and TB. These were chosen since they are considered important in relation to JIA and its treatment.

All patients were included from the UK registries. Only patients successfully transferred to JuMBO were included in the German registers to analyse the occurrence of comorbidities in childhood, adolescence and adulthood in the same cohort, although patient characteristics were described at registration into BiKeR. For Pharmachild, patients with at least one prospective visit after registration were included. For all registries, baseline data were presented at the point of registration, including the history of comorbidities at baseline. The proportions of patients with comorbidities (ever uveitis, MAS, TB, and varicella) at the most recent study follow-up were also presented, including comorbidities reported at registration, and thus it refers to the time from JIA diagnosis until the most recent study follow-up.

Subsequently, the incidence rates of the four comorbidities of interest on MTX or biologic therapy within the studies were investigated. Patients were included from first registration, and exposure censored at the event of interest, or the patient's last follow-up, whichever came first. An event on MTX was defined as an event on MTX therapy only; patients were censored 3 months following MTX cessation, at the start date of the biologic, or at the last follow-up, whichever came first. An event on a biologic was defined as an event on a biologic or within 3 months of the last dose (if stopped, regardless of other therapies). Patients could contribute to both analyses if they switched between treatments, providing they met the inclusion criteria for each of the comorbidity analyses (see below). The information about MAS prior to BiKeR enrolment is available since 2004. Incidence rates for the German registers were presented separately, so the paediatric cohort rates (BiKeR) could be compared with the other registers, and the adult cohort (JuMBO) could demonstrate the rates in an adult JIA population .

The analyses were limited to first event of uveitis, MAS, varicella, or TB reported within each register. Patients with an existing history of uveitis, MAS, or TB at registration into the registers were excluded for their respective incidence analyses. For varicella, separate incidence rates were reported for (a) varicella infection only, (b) herpes zoster infection only and (c) either varicella or herpes zoster infection. All patients were included in these analyses, regardless of varicella vaccination (VZV) history or a well-noted history of varicella

infection, with the exception of those with missing data at baseline, who were excluded. The percentage of varicella/herpes zoster infections resulting in hospitalization were analysed to compare the seriousness of the patients' infection on therapy. For MAS, the incidence rates on therapy were reported for systemic-JIA patients only.

The MedDRA-preferred term used to identify MAS was 'Histiocytosis haematophagic'. BiKeR/JuMBO and Pharmachild identified TB cases from the MedDRA-preferred terms 'tuberculosis', 'latent tuberculosis', 'pulmonary tuberculosis' and 'disseminated tuberculosis'. Infection coding in the UK register (to site rather than organism) meant all events including the causative organism '*Mycobacterium tuberculosis*' were included. All registers identified uveitis from the MedDRA-preferred terms 'uveitis', 'iridocyclitis', 'autoimmune uveitis' and 'iritis'. All registries used the MedDRA-preferred terms 'varicella' for varicella infection and 'herpes zoster' for herpes zoster infection.

Statistical analysis

All registers reported data in predefined tables providing descriptive statistics of the baseline demographic and clinical data. For Pharmachild, the clinical data assessed within 31 days after registration were reported. The median and interquartile range (IQR) were reported for numerical data, and frequencies and percentages were reported for categorical data. All registers reported the incidence rates of comorbidities as the number of new events per 100 person years with 95% CIs. No formal statistical comparisons were undertaken.

Results

Comparison of the three cohorts

The cohorts are presented in Supplementary Table S1 (available at *Rheumatology* online), including populations, and data collection. All of the registers include JIA patients (per ILAR criteria) on MTX and biologic therapy. While the UK and German registers are national and include patients starting these therapies, safety data are collected in Pharmachild, an international study, from disease onset either retrospectively or prospectively after registration. The moment of inclusion is therefore not necessarily at the start of therapy. Furthermore, Pharmachild uses a more limited comorbidity tick-box list, although additional comorbidities are captured through the registrations full safety and event history form.

All studies collect patient demographics and most core outcome variables, including the ability to measure JADAS-71. While Pharmachild collects moderate, severe or serious AEs, the German and UK registers also collect mild AEs. The four comorbidities of interest in this manuscript—uveitis, MAS, varicella and TB—were all captured in a similar format at baseline across all cohorts. VZV information is collected from all cohorts, although the UK only have vaccination data from July 2016 onwards.

Patient characteristics

A total of 8066 CYP with JIA from the three registers were included in this analysis: 2963 from the UK, 1541 from Germany, and 3562 in the prospective cohort of Pharmachild. Table 1 shows the characteristics of the patients registered into these studies. Overall, 68–70% of patients were female, and age at registration varied from 11 years (UK/Pharmachild) to 14 years (Germany). In addition, the UK had a lower disease duration at registration (1 year) *vs* Germany/Pharmachild (3 years).

The prevalence of most comorbidities at registration were similar across the studies: 13–19% had a history of uveitis, and 0–1.5% had ever had TB. However, VZV coverage was higher in Germany (56% *vs* 13–16%) resulting in a lower varicella infection at registration (11% *vs* 32–49%). VZV coverage per country for Pharmachild is provided in Supplementary Table S2 (available at *Rheumatology* online).

At final follow-up, the prevalence of ever uveitis (15–19%) and ever TB (0.1–1.8%) was similar across all registers. Differences in varicella infection was again observed at final follow-up: 15% in Germany, 37% in UK, and 50% in Pharmachild.

Incidence rates of comorbidities on therapy

The incidences of comorbidities were investigated for CYP within the registers on MTX and biologic therapy (Tables 2 and 3). The rate of uveitis varied between cohorts for patients on MTX therapy from 2.1 (in the UK) to 0.22 (in Pharmachild) per 100 person years, while Germany reported no patients. The rates of uveitis on biologic therapy remained higher in the UK (0.75) *vs* Pharmachild (0.20) and BiKeR (0.14) per 100 person years. The German adult JIA (JuMBO) register reported a higher incidence of uveitis compared with the paediatric cohort (0.33 *vs* 0.14 per 100 person years). The rates of varicella and herpes zoster infection were also higher for the UK on MTX and biologic therapy: varicella infection on biologic therapy 1.7 (UK) *vs* 0.32 (Pharmachild) and 0.07 (BiKeR) per 100 person years. The percentage of varicella or herpes zoster infections that resulted in hospitalization was higher in the UK register compared with in the German registers and Pharmachild. No obvious differences in hospitalizations for varicella or herpes zoster infections were observed between events on MTX and biologic therapy within any of the registers.

Discussion

This analysis is the first and largest to investigate the occurrence of a selection of routinely collected comorbidities in 8066 CYP with JIA from three of the largest JIA registries. At registration into the cohorts, the proportions of patients with a history of uveitis (13–19%) and TB (0–1.5%) were similar. However, there were

Table 1 Characteristics of patients included from the three registers

	UK JIA Biologics Registers: registered by 6 January 2021	BiKeR/JuMBO: registered by 10 November 2019	Pharmachild prospective cohort: registered by 12 November 2020
Number of patients, *n*	2963	1541	3562
Female, *n* (%)	2014 (68%)	1046 (68%)	2476 (70%)
ILAR category, *n* (%)			
Oligoarticular	880 (30%)	415 (27%)	1426 (40%)
Oligoarticular (persistent)	359 (12%)	137 (9%)	903 (25%)
Oligoarticular (extended)	521 (18%)	278 (18%)	523 (15%)
Polyarticular RF−	962 (32%)	414 (27%)	913 (26%)
Polyarticular RF+	242 (8%)	129 (8%)	148 (4%)
Systemic	259 (9%)	82 (5%)	370 (10%)
Psoriatic	189 (6%)	131 (8%)	120 (3%)
Enthesitis-related	253 (9%)	315 (20%)	333 (9%)
Undifferentiated	94 (3%)	54 (5%)	252 (7%)
Unknown	84 (3%)	1 (<1%)	–
At registration			
Age (years), median (IQR)	11 (6, 14)	14 (12, 16)	11 (7–14)
Disease duration (years) from diagnosis, median (IQR)	1 (0, 4), *N* = 2894	3 (1, 7), *N* = 1531	3 (1–6)
Disease activity, median (IQR)			
Active joint count (71-joint)	4 (1, 8), *N* = 2724	4 (2, 8), *N* = 1537	1 (0, 4), *N* = 906
Limited joint count (71-joint)	3 (1, 6), *N* = 2658	4 (2, 9), *N* = 1537	1 (0, 4), *N* = 906
Physician global assessment (10 cm)	3 (2, 5), *N* = 1909	5 (3, 7), *N* = 1513	2 (0, 4), *N* = 906
Parent (patient) assessment of well-being (10 cm)	4 (1, 6), *N* = 1978	5 (3, 7), *N* = 1384	2 (0, 5), *N* = 668
Functional ability	CHAQ (range 0–3) 0.9 (0.3, 1.5), *N* = 1871	CHAQ (range 0–3) 0.5 (0.125, 1.00), *N* = 1395	JAMAR 2 (0, 6), *N* = 560
Pain VAS (10 cm)	4 (1, 7), *N* = 1899	4 (2, 7), *N* = 1228	2 (0, 5), *N* = 619
ESR (mm/h)	13 (5, 30), *N* = 2444	16 (7, 35), *N* = 1451	12 (6, 28), *N* = 710
CRP (mg/l)	5 (4, 15), *N* = 2497	5.5 (2.1, 24) *N* = 947	3 (1, 11) *N* = 728
JADAS-71	13 (7, 20), *N* = 1337	15 (10, 20), *N* = 1370	8 (2, 16), *N* = 510
Varicella vaccination, *n* (%)	95 (16%), *N* = 609	136 (56%), *N* = 241	376 (13%) *N* = 2934
History of comorbidities, *n* (%)			
Ever uveitis	444 (16%), *N* = 2738	204 (13%)	664 (19%), *N* = 3484
Ever MAS (systemic JIA only)	32 (24%), *N* = 136	2 (3.9%), *N* = 56	53 (14%), *N* = 366
Had varicella infection	750 (32%)[b], *N* = 2351	98 (11%), *N* = 871	1120 (49%), *N* = 2279
Ever tuberculosis	12 (0.6%), *N* = 1900	0 (0.0%)	46 (1.5%)[a], *N* = 3005
Drugs, *n* (%)			
MTX (monotherapy)	1092 (37%)	544 (35%)	1084 (30%)
Etanercept	1105 (37%)	885 (57%)	738 (20.7%)
Adalimumab	430 (15%)	86 (6%)	397 (11.1%)
Infliximab	123 (4%)	0 (0%)	47 (1.3%)
Anakinra	37 (1%)	1 (<1%)	65 (1.8%)
Rituximab	9 (<1%)	0 (0%)	1 (<1%)
Tocilizumab	138 (5%)	18 (2%)	117 (3%)
Abatacept	25 (1%)	3 (<1%)	104 (3%)
Golimumab	1 (<1%)	1 (<1%)	6 (<1%)
Baricitinib	1 (<1%)	0	0 (0%)
Secukinumab	3 (<1%)	0	0 (0%)
Canakinumab	0 (0%)	3 (<1%)	34 (1%)
At most recent follow-up			
Follow-up from JIA diagnosis (years, not necessarily in the study), median (IQR)	5 (3, 9) *N* = 2926	14 (7, 18) *N* = 1514	6 (3–9)

(continued)

TABLE 1 Continued

	UK JIA Biologics Registers: registered by 6 January 2021	BiKeR/JuMBO: registered by 10 November 2019	Pharmachild prospective cohort: registered by 12 November 2020
Mean (S.D.)	6.5 (4.6)	13.2 (6.1)	6.5 (4.5)
Age (years), median (IQR)	14 (10–17)	22 (19–25)	13 (9–17)
Comorbidities, *n* (%)			
Ever uveitis	556 (19%)	238 (15%)	676 (19%) $N = 3484$
Ever MAS (systemic JIA only)	37 (15%) $N = 250$	5 (6%) $N = 82$	62 (17%) $N = 366$
Ever varicella infection	822 (37%)[b] $N = 2238$	127 (15%) $N = 871$	1166 (50%) $N = 2312$
Ever tuberculosis	17 (0.6%)	2 (0.1%) $N = 1541$	54 (1.8%)[a] $N = 3006$

[a]Including latent tuberculosis. [b]Identified at baseline as either ticked varicella infection, or were chicken pox immune (providing they had not had the vaccination).

differences in the proportion of systemic-JIA patients with a history of MAS (4–24%). This study also identified differences in the general health systems reporting into these registries, such as the common use of VZV in Germany (56%), but not in the UK (16%) or Pharmachild countries (13%), which could result in an apparent difference in the occurrence of related comorbidities. As a result, the proportion of patients in Germany who had a history of varicella infection was much lower (11% *vs* 32–49%).

The difference in disease activity parameters at registration between Pharmachild and the UK/Germany can be explained by the moment of inclusion into the registries. Patients in the UK and German registers are included following initiation of biologic or MTX therapy, which might indicate a worsening of the disease. The moment of inclusion into Pharmachild is at random and not necessarily after starting a particular therapy.

The increased prevalence of TB at registration and the incidence rates within Pharmachild as compared with the other registers is likely due to the countries involved. The countries known to have relatively high rates of TB that contribute patients to Pharmachild include Russia, South Africa and Brazil [9]. The observed rate of TB on biologic therapy in the UK register was higher than the overall rate of TB in children <15 years old reported by Public Health England in 2018 [16]. JIA patients under biologic therapy are thus at an increased risk for developing TB and other serious infectious diseases [17]. Given the potential severity of TB infection, it is recommended that CYP with immune-mediated diseases such as JIA should be screened for latent-TB infection before commencing immunosuppressive drugs [18–20], although this would not prevent symptomatic *de novo* infection.

The prevalence rates of uveitis at the most recent follow-up in this study (15–19%) were in concordance with rates reported in the existing literature [6]. The UK had higher incidence rates of uveitis compared with BiKeR/JuMBO and Pharmachild, most likely due to the shorter disease duration at registration (1 *vs* 3 years). In addition, within the UK and Pharmachild, CYP on MTX had higher incidence rates of uveitis compared with those on biologics. It is known that uveitis is more likely to happen within the first 2 years following JIA diagnosis [21], and therefore it is more common among CYP on MTX therapy (first-choice therapy). In contrast, Germany observed higher rates of uveitis on biologic *vs* MTX therapy, perhaps explained because uveitis occurs most frequently in oligoarthritis patients, and those on MTX were not enrolled in BiKeR [21].

In Germany, VZV has been part of the routine childhood vaccination programme, in the first 2 years of life, since 2004 [22]. The proportion of the population covered by VZV vaccination in 2010, the most appropriate comparison for the age of this cohort, was roughly 50%, consistent with the 56% of the patients vaccinated in the German registers. In contrast, the UK does not offer VZV as part of their routine childhood vaccination programme, resulting in minimal national coverage. However, UK patients with JIA without varicella immunity are considered for vaccination [23]. While 16% of patients were vaccinated, due to the late introduction of this question into the registers (with data available since 2016), this percentage could be as low as 3% (assuming patients with missing data were unvaccinated). In addition, Pharmachild covers 31 countries, the majority of which do not routinely vaccinate against varicella [24]. These differences in vaccination coverage between register are likely to explain the lower rate of varicella and herpes zoster infection in Germany. In addition, the higher incidence rate of varicella in the UK compared with Pharmachild could be explained by the younger average age of patients in the UK register. This could also explain why more patients in Pharmachild had had varicella at registration *vs* those in the UK register. As to be expected, higher rates of herpes zoster were observed in the adult JuMBO cohort compared with the juvenile BiKeR cohort, while the opposite was true for varicella on biologic therapy [25]. Although little is known about this subject, a meta-analysis showed that the most frequent serious infections on biologics in JIA were varicella and bronchopulmonary infections [26]. Taking into account the potential seriousness of this diagnosis in immunocompromised children, the results of our analysis provide rationale for routine VZV in JIA. It must be noted that, although VZV in JIA appears to be safe, it does not always protect against varicella infection [27]. Nevertheless, the

Table 2 Incidence of comorbidities on MTX monotherapy in the three registers

	UK JIA Biologics Registers		BiKeR		JuMBO		Pharmachild	
Total number of patients	1065		544				2462[a]	
ILAR								
Oligoarthritis	372 (35%)		179 (33%)				988 (40%)	
(Persistent)	**194 (18%)**		**100 (18%)**				**623 (25%)**	
(Extended)	**178 (17%)**		**79 (15%)**				**365 (15%)**	
Polyarticular RF−	341 (32%)		140 (26%)				692 (28%)	
Polyarticular RF+	84 (8%)		30 (6%)				116 (5%)	
Systemic	46 (4%)		15 (3%)				202 (8%)	
Psoriatic	83 (8%)		57 (10%)				84 (3%)	
Esthesitis	71 (7%)		104 (19%)				218 (9%)	
Undiff.	35 (3%)		19 (3%)				162 (7%)	
Unknown	33 (3%)		0 (0%)				0 (0%)	
Total exposure, years	2499		2226		642		1659	
	Frequency, *N*	Rate per 100 person years (95% CI)	Frequency, *N*	Rate per 100 person years (95% CI)	Frequency, *N*	Rate per 100 person years (95% CI)	Frequency, *N*	Rate per 100 person years (95% CI)
Uveitis	41 patients, *N* = 952	2.2 (1.6, 3.0)	No patients, *N* = 544	–	No patients, *N* = 544	–	3 patients, *N* = 1967	0.22 (0.05, 0.64)
MAS (systemic JIA only)	1 patient, *N* = 42	1.2 (0.2, 8.3)	No patients, *N* = 82	–	No patients, *N* = 82	–	1 patient, *N* = 177	1.57 (0.04, 8.74)
Varicella	50 patients, *N* = 1065	2.4 (1.8, 3.1)	No patients, *N* = 544	–	No patients, *N* = 544	–	9 patients, *N* = 2462	0.55 (0.25, 1.04)
Herpes zoster	12 patients, *N* = 1065	0.5 (0.3, 1.0)	1 patient, *N* = 544	0.04 (0.001, 0.24)	2 patients, *N* = 544	0.3 (0.03, 1.1)	2 patients, *N* = 2462	0.12 (0.01, 0.44)
Varicella + herpes zoster	61 patients, 25 (41%) hospitalized, *N* = 1065	2.9 (2.3, 3.8)	1 patient, 0 (0%) hospitalized, *N* = 544	0.04 (0.001, 0.24)	2 patients, 0 (0%) hospitalized *N* = 544	0.3 (0.03, 1.1)	11 patients, 1 (9%) hospitalized, *N* = 2462	0.67 (0.33, 1.20)
TB	No patients, *N* = 1062	–	No patients, *N* = 544	–	1 patient, *N* = 544	0.15 (0.02, 1.11)	3 patients, *N* = 2430	0.18 (0.04, 0.53)

[a]Number of Pharmachild patients ever treated with MTX monotherapy is greater than the number reported on MTX monotherapy at registration (Table 1).

Table 3 Incidence of comorbidities on biologic therapy in the three registers

	UK JIA Biologics Registers		BiKeR		JuMBO		Pharmachild	
Total number of patients	2185		1256				2475[b]	
ILAR								
Oligoarthritis	579 (26%)		298 (24%)				834 (34%)	
(Persistent)	**181 (8%)**		**47 (4%)**				**430 (17%)**	
(Extended)	**398 (18%)**		**251 (20%)**				**404 (16%)**	
Polyarticular RF−	715 (33%)		345 (27%)				699 (28%)	
Polyarticular RF+	189 (9%)		125 (10%)				106 (4%)	
Systemic	226 (10%)		84 (7%)				291 (12%)	
Psoriatic	133 (6%)		93 (7%)				95 (4%)	
Enthesitis	212 (10%)		266 (21)				266 (11%)	
Undiff.	64 (3%)		45 (4%)				184 (7%)	
Unknown	67 (3%)		0 (0%)				0 (0%)	
Total biologic exposure, years	6078		5180		1920		4778	
Individual biologic exposure[a], years								
TNF-α inhibitors								
Adalimumab	1176		570		521		1332	
Certolizumab	–		4		94		7	
Etanercept	3193		4222		571		2260	
Golimumab	6		20		110		50	
Infliximab	686		56		154		125	
IL-1 inhibitors								
Anakinra	132		66		25		112	
Canakinumab	5		21		13		139	
Other								
Abatacept	167		95		62		348	
Baricitinib	3		1		10		<1	
Rituximab	94		4		41		4	
Secukinumab	–		2		13		–	
Tocilizumab	794		120		306		400	
Ustekinumab	4		–		–		–	
	Frequency, *N*	Rate per 100 person years (95% CI)	Frequency, *N*	Rate per 100 person years (95% CI)	Frequency, *N*	Rate per 100 person years (95% CI)	Frequency, *N*	Rate per 100 person years (95% CI)
Uveitis	34 patients, *N* = 1781	0.7 (0.5, 1.0)	10 patients, *N* = 1256	0.14 (0.07, 0.26)	11 patients, *N* = 1256	0.33 (0.17, 0.60)	7 patients, *N* = 1930	0.20 (0.08, 0.40)
		0.5 (0.2, 1.4)	1 patient *N* = 82	0.15 (0.02, 1.13)	1 patient *N* = 82	0.48 (0.07, 3.39)		1.73 (0.75, 3.40)

(continued)

TABLE 3 Continued

	UK JIA Biologics Registers		BiKeR		JuMBO		Pharmachild	
MAS (systemic JIA only)	4 patients $N = 196$						8 patients, $N = 246$	
Varicella	96 patients, $N = 2185$	1.7 (1.4, 2.0)	5 patients, $N = 1256$	0.07 (0.02, 0.16)	1 patient, $N = 1256$	0.03 (0.001, 0.17)	15 patients, $N = 2475$	0.32 (0.18, 0.53)
Herpes zoster	46 patients, $N = 2185$	0.8 (0.6, 1.1)	10 patients, $N = 1256$	0.14 (0.07, 0.26)	6 patients, $N = 1256$	0.18 (0.07, 0.40)	18 patients, $N = 2475$	0.38 (0.23, 0.61)
Varicella + herpes zoster	139 patients, 55 (40%) hospitalized, $N = 2185$	2.5 (2.1, 2.9)	15 patients, 2 (13%) hospitalized, $N = 1256$	0.21 (0.12, 0.35)	7 patients, 1 (14%) hospitalized, $N = 1256$	0.21 (0.08, 0.44)	33 patients, 3 (9%) hospitalized, $N = 2475$	0.70 (0.48, 0.99)
TB	3 patients, $N = 2185$	0.05 (0.02, 0.15)	No patients, $N = 1256$	–	1 patient, $N = 1256$	0.03 (0.004, 0.22)	5 patients, $N = 2436$	0.11 (0.03, 0.25)

[a]The sum of individual biologic exposures is greater than overall total exposure as it includes the 90 days added exposure window. [b]The number of Pharmachild patients ever treated with biologic therapy is greater than the number reported on biologic therapy at registration (Table 1).

most recent EULAR recommendations for vaccination in adult patients with rheumatic diseases already indicate that VZV may be considered in high-risk patients [28].

There was no difference in the proportion of varicella or herpes zoster infections that resulted in hospitalization between events on MTX and biologic therapy within the registers, although the UK reported much higher proportions than Pharmachild and BiKeR/JuMBO. These proportions were also much higher than previously reported numbers of complications per varicella case in Europe, which ranged from 0% to 6% [29, 30]. Possible reasons for the discrepancy in the proportions between the UK and other registers are socio-demographic differences, such as reduced access to health care in low- and middle-income countries that contribute to Pharmachild, and cultural/treatment protocol differences in hospitalizing patients on immunosuppressive therapy who experience varicella/herpes zoster [31]. For example, if a varicella infection in an immunocompromised patient is generally assessed as life-threatening, it might be decided to administer i.v. acyclovir or another antiviral therapy (which is likely to be more effective but requires hospitalization) [32], rather than oral therapy.

The proportions of systemic-JIA patients who had experienced MAS at the most-recent follow-up in this study were in line with figures reported in the existing literature [2, 7]. MAS was less common in systemic-JIA patients in the BiKeR/JuMBO registers (6%), compared with those in the UK and Pharmachild registers (15–17%) at most recent follow-up. The lower proportion of MAS in systemic-JIA patients in BiKeR/JuMBO may be explained by the enrolment of patients at the start of treatment with etanercept, most notably in the early years of BiKeR. We hypothesize that those patients had less severe systemic features, and the joint involvement was the primary reason for treatment start with etanercept. Pharmachild and the UK observed a higher rate of MAS in systemic-JIA patients on MTX therapy compared with those on biologic therapy. This might be explained by existing evidence suggesting that the commonly prescribed IL-1–inhibiting agent anakinra is effective in the treatment of MAS in systemic-JIA [33–35].

These analyses are not without limitations. All of these registries are observational cohort studies and rely on data input from clinicians and research nurses. It is possible that events are not reported to the clinic team, and thus the research studies, and therefore these rates may be underestimated. Nevertheless, the similar results reported across the registers increase the reliability of the event rates and low the risk that they have been underestimated. There may also be variations in reporting between countries. However, the analysed events are considered important in paediatric rheumatology internationally, and therefore the impact of this is likely minimal. It is also possible that drug (MTX/biologic) start and stop dates are missing, although most data should be up to date, because patients were censored at their final follow-up date. This analysis did not

report the comorbidities for the entire BiKeR cohort, only the subpopulation that reached 18 years by the cut-off date and were followed into adulthood. These patients tended to be more severely affected by JIA than those not observed in JuMBO. However, the combined BiKeR/JuMBO cohort provided data for the onset of comorbidities in CYP and young adulthood. Considering the variations across the populations, analysis with pooled data might be preferable. Differences in patients within each register may account for variations in the results observed: oligoarthritis patients receiving MTX were not enrolled in BiKeR, and patients enrolled into the UK register were younger with a shorter disease duration, thus influencing rates of uveitis and varicella. It is also important not to directly compare the rates of comorbidities between MTX- and biologic-treated patients, because there may be some confounding by indication. Therefore, no formal statistical testing was performed in order to compare the comorbidity rates between the three cohorts, or between the MTX- and biologic-treated patients.

In conclusion, this study looked at a selection of key comorbidities and the roles of anti-rheumatic drugs in over 8000 CYP with JIA across three large registers. It highlights the relatively similar rates of comorbidities, as well as the impact of VZV in populations on the comparability of varicella infections. This study shows the ability for JIA registers to work together, running synchronized analyses, and is a first step towards more harmonized collaborations.

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Data availability statement

The data underlying this article cannot be shared publicly to maintain the privacy of the individuals who participated in the study. The data will be shared on reasonable request to the corresponding author .

Supplementary data

Supplementary data are available at *Rheumatology* online.

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