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Original article

## Safety of biological agents in paediatric rheumatic diseases: A real-life multicenter retrospective study using the JIRcohort database

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### ABSTRACT

**Objective:** To analyse and report the incidence of side effects of biological agents in paediatric patients with inflammatory diseases using of real-life follow-up cohort.

**Methods:** In this international, observational, retrospective, multicentre study of children treated by biological agents and followed in the Juvenile Inflammatory Rheumatism (JIR) cohort (JIRcohort) network, a Kaplan–Meier method was used to estimate the occurrence of adverse events. A Cox model was constructed to identify independent predictors of adverse events.

**Results:** Overall 813 patients totalling 3439 patients–year (PY) of biological agents were included. The main diagnosis was juvenile idiopathic arthritis (84%). A total of 222 patients (27.3%) had 419 adverse events, representing an incidence rate of 12.2 per 100 PY 95% CI [11.0; 13.4]. The overall incidence rate of serious adverse events was 3.9 per 100 PY 95% CI [3.2; 4.6]. Tocilizumab and infliximab were significantly associated with adverse events and canakinumab with serious adverse events. Univariate and multivariable analysis of adverse events and serious adverse events indicated that patients under biological agents with concomitant immunosuppressive drugs (excluding methotrexate) suffered from more of these events.

**Conclusion:** This study suggests an overall an acceptable safety of biologic agents in children with inflammatory rheumatic diseases treated with biological agents. However, the concomitant prescription of immunosuppressive drugs with biological agents represents a substantial risk of adverse events.

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## 1. Introduction

At the start of the century, American (FDA) and European (EMA) agencies were concerned with the accessibility of innovative medicines for children, and new regulations on paediatric clinical trials [1] led to several studies investigating biological agents (BA) in the field of paediatric inflammatory diseases [2–4]. The efficacy of BAs has now been well demonstrated in various subtypes of juvenile idiopathic arthritis (JIA) [5–7], in auto-inflammatory diseases such as cryopyrinopathies [8,9], and to a lesser extent in systemic auto-immune diseases such as systemic lupus erythematosus [10,11]. However, there are only a few observational studies that have been conducted in children with rheumatic diseases [12–17] and among these, those that have compared BAs only consider JIA patients [13,16]. Adequate safety has been suggested in both randomised trials [18,19] and observational studies [16,20]. In spite of several other studies that have explored at the risk of cancer associated with anti-TNFs [21,22], there is a lack of information in relation to the long-term immunological consequences of other BAs [23]. For the investigation of such tolerance issues, the Juvenile Inflammatory Rheumatism cohort (JIRcohort) platform collects prospective and retrospective data, including treatments and their adverse events (AEs), for all patients with juvenile inflammatory rheumatism reflecting daily practice in paediatric rheumatology departments of tertiary care centres. Therefore, the objective of the present study is to provide real-life data on long-term safety of BAs used in inflammatory rheumatism in the paediatric centres participating in the JIRcohort network.

## 2. Methods

### 2.1. Study design

This was an observational, retrospective, multicentre study. Independent ethics committees in each paediatric rheumatology centre approved the study. Parental or guardian consent was required before the inclusion of patients, in accordance with the respective national regulations.

### 2.2. Patients

Patients were selected from the JIRcohort database, which includes all patients with a diagnosis of inflammatory rheumatic (auto-inflammatory or auto-immune) disease starting in childhood. Those who were treated with at least one of either etanercept, adalimumab, infliximab, golimumab, anakinra, canakinumab, rituximab, abatacept, or tocilizumab, regardless of concomitant treatments, up to the 31 August 2014 were included.

The JIRcohort database includes data collected by chart reviews, comprised of the use of disease-modifying anti-rheumatic drugs (DMARD) and the side effects of the prescribed treatments. The presence of auto-immune diseases in a first-degree relative was also recorded. Outpatient clinic and hospitalisation-related consultations were analysed to extract adverse events (AEs). AEs and serious adverse events (SAEs) were coded and defined in accordance with the International Conference on Harmonization guidelines (using MedDRA) [24] version 17.1. According to MedDRA codes, the intensity of AEs was categorised as mild, moderate, severe, or very severe. SAEs included: hospitalisations, incapacity of life functions, life threatening, and death. Reactivation or relapse of disease was not considered as an AE. All AEs during BA treatment were collected, regardless of concomitant medication.

In the present study, the safety of BAs was also described using the medical important infections (MII) and the immune-mediated diseases (IMD) of each BA, as a way to describe long-term tolerance. The infections leading to hospitalisation or intravenous antibiotic

treatment were defined as MIIs; uveitis, intestinal chronic inflammatory disease, psoriasis, lupus-like and haematological disorders including macrophage activation syndrome (MAS), were defined as IMDs.

At the time of the study there were 15 centres participating in the JIRcohort (Switzerland: Basel, Zurich, Aarau, Lucerne, Vaud, and Graubünden; France: Paris – 2 centres, Lyon, Montpellier, Bordeaux, Strasbourg, Clermont-Ferrand; Morocco: Casablanca; Belgium: Leuven).

### 2.3. Statistical analysis

Demographic and baseline disease characteristics were summarised with the use of descriptive statistics. Distribution of paediatric inflammatory rheumatic diseases was described. Rheumatic diseases were grouped as follows: JIA and non-JIA (auto-inflammatory diseases, idiopathic uveitis, inflammatory bowel diseases (IBD) related arthritis, vasculitis, connective tissue diseases, chronic recurrent multifocal osteomyelitis, Behçet disease, unclassified auto-inflammatory disease, Blau syndrome, synovitis acne pustulosis hyperostosis and osteitis [SAPHO] syndrome, immune dysregulation polyendocrinopathy enteropathy X-linked [IPEX] syndrome and Castleman disease). JIA was further subdivided according to ILAR classification [25]. The occurrence of MAS and uveitis in JIA in relation to positivity of antinuclear antibodies (ANAs) prior to initiation of BA treatment were also recorded.

To analyse safety, the population was divided according to BA into 9 groups: etanercept, adalimumab, infliximab, golimumab, tocilizumab, rituximab, canakinumab, anakinra and abatacept. In the present study, corticosteroids (CTCs), MTX, and other DMARDs were analysed. We described the AEs (mild, moderate, severe, and very severe) and SAEs of the whole population and then according to the diagnostic group (JIA and non-JIA). To avoid a double analysis of side effects in the survival analysis, mild and moderate AEs were considered together, and severe and very severe AEs were grouped along with the SAEs for the regression model. The Kaplan-Meier estimator was used to estimate the occurrence of AE and SAE; follow-up time and time-to-event outcomes were calculated from the time of initiation of BAs. Curves were compared using the Logrank test, with significance set at  $P < 0.05$ . To identify independent predictors of AE and SAE a multivariable mixed effects Cox proportional hazards model was constructed using a stepwise approach selecting variables at  $P < 0.20$  in univariate analysis. The parameters considered were: sex, MTX, CTCs, other immunosuppressive drugs (azathioprine, cyclosporine, hydroxychloroquine, leflunomide and sulfasalazine), total number of BA and type of disease (JIA vs. non-JIA). Significance was set at  $P < 0.05$ .

We also described the incidence rate of the side effects considering medical important infections (MII) and immune-mediated diseases (IMD) according to each BA, regardless of the intensity or seriousness. The duration of exposure to BA is heterogeneous and therefore all safety analyses were evaluated using incidence rates, reported as the number of events per 100 patient-years (PY). Statistical analyses were performed using R software version 3.4.4 (R Development Core Team 2017. R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL <http://www.R-project.org>).

### 2.4. Role of the funding source

This study received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

**Table 1**  
Demographic and clinical data of patients.

	Sex	Age at diagnosis (years)			Follow-up (years)
	n (M/F)	Mean ± SD	Min	Max	Mean ± SD
All patients	813 (295/518)	9.4 ± 3.6	0.3	18.4	4.7 ± 3.1
Juvenile idiopathic arthritis	681 (238/443)	7.5 ± 4.7	1.0	18.4	6.8 ± 4.4
RF negative polyarthritis	147 (36/111)	6.7 ± 4.1	1.0	17.2	7.0 ± 4.5
Enthesitis-related arthritis	140 (90/50)	11.2 ± 3.5	0.7	18.4	4.6 ± 3.0
Systemic arthritis	117 (48/69)	6.3 ± 4.8	0.3	17.8	6.2 ± 4.7
Extended oligoarthritis	109 (19/90)	4.3 ± 2.0	1.1	18.4	7.8 ± 4.5
Persistent oligoarthritis	89 (21/68)	5.3 ± 3.7	1.0	16.2	5.9 ± 4.1
Psoriatic arthritis	33 (14/19)	10.7 ± 4.1	1.8	16.5	4.5 ± 2.9
RF positive polyarthritis	30 (3/27)	11.3 ± 2.7	5.2	15.6	4.5 ± 4.1
Unclassified arthritis	16 (7/9)	11.0 ± 5.2	1.9	17.4	4.3 ± 4.1
Non-JIA	132 (57/75)	8.3 ± 4.3	0.3	16.6	4.8 ± 3.4
Auto-inflammatory diseases	52 (25/27)	6.3 ± 4.9	0.3	14.6	5.5 ± 2.5
Cryopyrinopathies	35 (20/15)	5.4 ± 4.8	0.3	14.6	5.7 ± 4.4
TRAPS	6 (2/4)	9.0 ± 4.1	3.9	12.8	5.7 ± 2.0
HIDS	7 (2/5)	4.8 ± 4.1	0.4	9.9	3.2 ± 3.0
FMF	4 (1/3)	6.2 ± 2.7	3.2	9.7	6.5 ± 1.0
Idiopathic uveitis	28 (10/18)	8.7 ± 3.0	4.7	14.8	4.0 ± 2.6
IBD-related arthritis	9 (4/5)	11.0 ± 4.7	4.3	16.6	4.5 ± 2.9
Vasculitis	8 (4/4)	9.6 ± 3.7	5.5	15.9	3.1 ± 2.4
AAV	4 (1/3)	11.7 ± 3.4	7.5	15.9	2.9 ± 1.4
Kawasaki disease	2 (2/0)	5.6 ± 0.1	5.5	5.6	2.5 ± 0.6
Takayasu arteritis	1 (0/1)	6.0	–	–	0.3
Unclassified vasculitis	1 (1/0)	13.5	–	–	8.2
Connective tissue disease	8 (0/8)	12.1 ± 3.1	7.2	16.1	4.5 ± 4.3
Paediatric LES	4 (0/4)	13.7 ± 2.0	11.6	16.1	3.6 ± 2.9
Juvenile dermatomyositis and MCTD	4 (0/4)	12.1 ± 4.3	7.2	15.4	6.1 ± 6
Chronic recurrent multifocal osteomyelitis	8 (5/3)	8.7 ± 4.9	1.5	13.9	6.8 ± 3.5
Behçet disease	8 (4/4)	9.8 ± 5.2	1.7	15.0	3.6 ± 1.6
Unclassified auto-inflammatory diseases <sup>a</sup>	3 (1/2)	6.6 ± 5.3	0.7	11.2	1.3 ± 1.1
Blau syndrome	3 (1/2)	6.9 ± 2.3	4.9	9.4	7.2 ± 2.7
SAPHO syndrome	3 (2/1)	14.5 ± 0.8	13.6	15.1	2.5 ± 2.9
IPEX syndrome	1 (0/1)	25.8	–	–	0.4
Castleman disease	1 (1/0)	6.0	–	–	1.7

AAV: anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis; FMF: familial mediterranean fever; HIDS: hyperimmunoglobulinemia D syndrome; IBD: inflammatory bowel diseases; JIA: juvenile idiopathic arthritis; IPEX: immune dysregulation polyendocrinopathy enteropathy X-linked; MCTD: mixed connective tissue disease; RF: rheumatoid factor; SAPHO: synovitis acne pustulosis hyperostosis and osteitis; SD: standard deviation; SLE: systemic lupus erythematosus; TRAPS: tumor necrosis factor receptor associated periodic syndrome; M: male; F: female.

<sup>a</sup> Idiopathic pericarditis and unclassified auto-inflammatory fever.

### 3. Results

#### 3.1. Baseline characteristics of the patients

A total of 813 patients were included in the study. The mean ± standard deviation (SD) age at disease onset was 9.4 ± 3.6 years (range: 0.3 to 18.4 years). The mean ± SD follow-up was 4.7 ± 3.1 years. The majority of patients had JIA ( $n = 681$ , 84% of the population; Table 1), followed by auto-inflammatory diseases ( $n = 52$ , 6% of the total population), mainly cryopyrinopathies ( $n = 35$ ; Table 1).

Uveitis was found in all subtypes of JIA, except in the polyarthritis-rheumatoid factor positive JIA subtype, and occurred in 123 patients (sex ratio 2.1:1). MAS occurred in 33 patients; one episode each and 29 belonging to systemic JIA subtype. History of auto-immune disease in a first-degree relative was found in 16% of patients ( $n = 129/813$ ).

#### 3.2. Biological agents and immunosuppressive drug exposure

In the database, the first BA was prescribed in June 1999. There was a total of 1179 BA prescriptions for 813 patients. The TNF $\alpha$  antagonists represented 75% ( $n = 885/1179$ ) of all BA prescribed, and etanercept was the most frequently used (42%,  $n = 492/1179$ ) followed by adalimumab (20%,  $n = 236/1179$ ), irrespective of the type of rheumatic disease. The total duration of exposure to BAs was 3439 PY (the median exposure of an individual patient was 56.4 months). MTX was frequently associated with etanercept,

adalimumab, infliximab, tocilizumab, abatacept, and golimumab. Among the group of anti-IL1 agents, 47% of patients treated by anakinra and 25% of those treated by canakinumab were also prescribed MTX. Corticosteroids were associated with rituximab perfusion in 53% of the cases; for other BAs, CTC co-prescription varied from 22 to 43% [Appendix A, Tables S1–S2; see the supplementary material associated with this article online].

#### 3.3. Safety of biological agents

A total of 222 patients had 419 AEs (without exclusion of SAEs), representing an incidence rate of 12.2 per 100 PY (95% confidence interval, CI [11.0; 13.4]). Seventy-four patients (9.1%) had at least 1 SAE ( $n = 134$  SAE), the overall incidence rate of SAE was 3.9 per 100 PY [95% CI: 3.2; 4.6]. No AE was reported with rituximab.

AEs were most frequently mild (46%, 193/419), followed by moderate AEs (39%, 165/419), and severe and very severe AEs represented 15% (61/419). The incidence of AEs was greater among JIA patients (335/419; incidence rate of 9.7 per 100 PY, 95% CI [8.2; 11.3]) than among non-JIA patients (84/419; 2.4 per 100 PY, 95% CI [1.7; 3.2]), and this was the case for all BAs except for canakinumab (Tables 2 and 3).

In regard to very severe AEs, in the JIA group, there were two MAS episodes during tocilizumab treatment (incidence rate 0.8 per 100 PY, 95% CI [0.0; 1.9]) and two events with etanercept treatment in patients with polyarthritis-rheumatoid factor positive JIA subtype: one Hodgkin's lymphoma (nodular sclerosis) in stage IV with bone and lung involvement (incidence rate 0.1 per 100 PY,

**Table 2**  
Incidence of adverse events and serious adverse events in patients treated by anti-TNFs.

	Etanercept	Adalimumab	Infliximab	Golimumab
Total of exposure, PY	1543	627	472	31
Total number of prescriptions	492	236	142	15
Co-prescription MTX (%) <sup>a</sup>	399 (81)	191 (81)	123 (87)	14 (93)
Co-prescription CTC (%) <sup>a</sup>	113 (23)	74 (31)	31 (22)	6 (40)
<i>n</i> , incidence rate per 100 PY [95% CI]				
AEs <sup>b</sup>	119, 7.7 [6.3; 9.1]	58, 9.3 [6.9; 11.6]	78, 16.5 [12.6; 20.2]	2, 6.5 [0.0; 15.4]
Mild and moderate AEs	106, 6.9 [5.6; 8.2]	52, 8.3 [6.0; 10.5]	59, 12.5 [9.1; 15.7]	2, 6.5 [0.0; 15.4]
Severe and very severe AEs	13, 0.8 [0.4; 1.3]	6, 1.0 [1.7; 60.2]	19, 4.0 [2.1; 5.8]	–
SAE <sup>c</sup>	43, 2.8 [2.0; 3.6]	20, 3.2 [1.8; 4.6]	25, 5.3 [3.1; 7.4]	–
JIA				
Mild and moderate AEs	100, 6.5 [5.2; 7.8]	43, 6.9 [4.8; 8.9]	50, 10.6 [7.5; 13.5]	2, 6.5 [0.0; 15.4]
Severe AEs	11, 0.7 [0.3; 1.1]	5, 0.8 [0.1; 1.5]	16, 3.4 [1.6; 5.1]	–
Very severe AEs <sup>f</sup>	2, 0.1 [0.0; 0.3]	–	1, 0.2 [0.0; 0.6]	–
Hospitalisation	11, 0.7 [0.3; 0.0]	3, 0.5 [0.0; 1.0]	4, 0.8 [0.0; 1.7]	–
Non-JIA				
Mild and moderate AEs	6, 0.4 [0.1; 0.7]	9, 1.4 [0.5; 2.4]	9, 1.9 [0.6; 3.2]	–
Severe AEs	–	1, 0.2 [0.0; 0.5]	1, 0.2 [0.0; 0.6]	–
Very severe AEs <sup>g</sup>	–	–	1, 0.2 [0.0; 0.6]	–
Hospitalisation	1, 0.1 [0.0; 0.2]	–	3, 0.6 [0.0; 1.4]	–
All infections	43, 2.8 [2.0; 3.6]	17, 2.7 [1.4; 4.0]	23, 6.1 [3.8; 8.4]	2, 6.5 [0.0; 15.4]
Bacteria	5, 0.3 [0.0; 0.6]	5, 0.8 [0.1; 1.5]	6, 1.7 [0.4; 2.9]	1, 3.2 [0.0; 9.5]
Virus	16, 1.0 [0.5; 1.5]	7, 1.1 [0.3; 1.9]	7, 0.8 [0.0; 1.7]	1, 3.2 [0.0; 9.5]
EBV infection	–	–	–	–
VZV infection	7, 0.4 [0.1; 0.7]	3, 0.5 [0.0; 1.0]	2, 0.4 [0.0; 1.0]	–
Another virus <sup>h</sup>	9, 0.1 [0.0; 0.2]	–	1, 0.2 [0.0; 0.6]	–
Other infections	22, 1.4 [0.8; 2.0]	5, 0.8 [0.1; 1.5]	10, 2.1 [0.7; 3.4]	–
All MII <sup>d</sup>	4, 0.3 [0.0; 0.5]	1, 0.2 [0.0; 0.5]	5, 1.1 [0.1; 2.0]	–
Sepsis	–	–	1, 0.2 [0.0; 0.6]	–
VZV infection	2, 0.1 [0.0; 0.3]	1, 0.2 [0.0; 0.5]	2, 0.4 [0.0; 1.0]	–
Others MII	1, 0.1 [0.0; 0.2]	–	2, 0.6 [0.0; 1.4]	–
Incidence of IMD				
Incident uveitis	5, 0.3 [0.0; 0.6]	–	–	–
Incident IBD	1, 0.1 [0.0; 0.2]	–	–	–
Psoriasisiform lesions	1, 0.1 [0.0; 0.2]	6, 1.0 [0.2; 1.7]	2, 0.4 [0.0; 1.0]	–
Lupus <sup>e</sup>	1, 0.1 [0.0; 0.2]	2, 0.3 [0.0; 0.8]	3, 0.6 [0.0; 1.4]	–
All blood disorders	7, 0.5 [0.1; 0.8]	4, 0.6 [0.0; 1.2]	2, 0.4 [0.0; 1.0]	–
Leukopenia	1, 0.1 [0.0; 0.2]	3, 0.5 [0.0; 1.0]	2, 0.2 [0.0; 0.6]	–
Thrombocytopenia	–	–	–	–
Pancytopenia	1, 0.1 [0.0; 0.2]	–	–	–
MAS	1, 0.1 [0.0; 0.2]	–	–	–
Other hospitalisations <sup>i</sup>	3, 0.2 [0.0; 0.4]	–	2, 0.2 [0.0; 0.6]	–

AEs: adverse events; CI: confidence interval; EBV: Epstein–Barr virus; HPV: human papillomavirus; IMD: immune-mediated disease; MAS: macrophage activation syndrome; VZV: varicella-zoster virus.

<sup>a</sup> Relative to each biological agent.

<sup>b</sup> All AEs: mild, moderate, severe and very severe AE.

<sup>c</sup> SAE: life threatening, hospitalization, incapacity life functions, cancer, death.

<sup>d</sup> MII: infections that led to hospitalization and/or required intravenous antibiotic treatment.

<sup>e</sup> Lupus-like or positivity of the antinuclear antibodies.

<sup>f</sup> 2 under etanercept (1 Hodgkin's disease, 1 anaphylactic shock) and 1 under infliximab (1 anaphylactic shock).

<sup>g</sup> 1 under infliximab (severe sepsis to *S. epidermidis*).

<sup>h</sup> Measles under adalimumab; enterovirus meningitis under infliximab.

<sup>i</sup> 3 under etanercept (1 poor wound healing, 1 suspected of acute abdomen, 1 anaphylactic shock) and 2 under infliximab (1 syncope episode, 1 paradoxical reaction).

95% CI [0.0; 0.2]) and one JIA associated with familial pulmonary fibrosis died from aggravation of fibrosis and a pulmonary infection. In the non-JIA group, one severe sepsis due to *Staphylococcus epidermidis* that needed two days in an intensive care unit occurred during infliximab perfusion (incidence rate 0.2 per 100 PY, 95% CI [0.0; 0.6]; Table 2) and one demyelinating lesion appeared concomitantly with canakinumab (incidence rate 0.4 per 100 PY, 95% CI 0.4 [0.0; 1.2]; Table 3).

The incidence of hospitalisation during BA treatment in the JIA group were ranged from 0.5 per 100 PY (95% CI [0.0; 1.0]) for adalimumab (Table 2) to 4.5 per 100 PY (95% CI [1.7; 8.1]) for tocilizumab (Table 3).

MII were described for all BAs. The varicella-zoster virus was the main infection reported among the MII events. Two episodes of sepsis were encountered, one with infliximab (Table 2) and

another severe sepsis due to *S. epidermidis* during canakinumab treatment (Table 3). No MII was found during abatacept or golimumab treatment. No case of tuberculosis was encountered during BA treatment.

Among the IMDs with BAs, the appearance of lupus-like syndrome and/or a positivity of antinuclear antibodies was found only under anti-TNF $\alpha$  treatments (one for etanercept, two for adalimumab, and three for infliximab; Table 2). Psoriatic lesions had an incidence rate of 0.5 per 100 PY (95% CI [0.0; 1.4]) with anakinra (Table 3) and with the anti-TNF $\alpha$  treatments, the incidence rate ranged from 0.1 per 100 PY (95% CI [0.0; 0.2]) for etanercept to 1.0 per 100 PY (95% CI [0.2; 1.7]) for adalimumab. Uveitis was encountered only in patients treated with etanercept, among whom the incidence rate was 0.3 per 100 PY (95% CI [0.0; 0.6]; Table 2).

**Table 3**  
Incidence of adverse events and serious adverse events in patients treated by another biological agent than anti-TNFs.

	Tocilizumab	Canakinumab	Anakinra	Abatacept
Total of exposure, PY	245	243	207	54
Total number of prescriptions	80	75	85	37
Co-prescription MTX (%) <sup>a</sup>	63 (79)	19 (25)	40 (47)	34 (92)
Co-prescription CTC (%) <sup>a</sup>	34 (43)	17 (23)	20 (24)	11 (30)
	<i>n</i> , incidence rate per 100 PY [95% CI]			
AEs <sup>b</sup>	63, 25.7 [19.4; 32.1]	57, 23.5 [17.4; 29.5]	33, 15.9 [10.5; 21.4]	9, 16.7 [5.8; 27.6]
Mild and moderate AEs	54, 22.0 [16.2; 27.9]	50, 20.6 [14.9; 26.3]	26, 12.6 [7.7; 17.4]	9, 16.7 [5.8; 27.6]
Severe and very severe AEs	9, 3.7 [1.3; 6.1]	7, 2.9 [0.7; 5.0]	7, 3.4 [0.9; 5.9]	–
SAE <sup>c</sup>	20, 8.2 [4.6; 11.7]	12, 4.9 [2.1; 7.7]	10, 4.8 [1.8; 7.8]	4, 7.4 [0.1; 14.7]
JIA				
Mild and moderate AEs	48, 19.6 [14.0; 25.1]	15, 6.2 [3.0; 9.3]	19, 9.2 [5.1; 13.3]	7, 13.0 [3.4; 22.6]
Severe AEs	5, 2.0 [0.0; 3.8]	2, 0.8 [0.0; 2.0]	6, 2.9 [0.6; 5.2]	–
Very severe AEs <sup>f</sup>	3, 1.2 [0.0; 2.6]	–	–	–
Hospitalisation	11, 4.5 [1.8; 7.1]	3, 1.2 [0.0; 2.6]	6, 2.9 [0.6; 5.2]	1, 1.9 [0.0; 5.5]
Non-JIA				
Mild and moderate AEs	6, 2.4 [0.5; 4.4]	35, 14.4 [9.6; 19.2]	7, 3.4 [0.9; 5.9]	2, 3.7 [0.0; 8.8]
Severe AEs	–	4, 1.6 [0.0; 3.3]	1, 0.5 [0.0; 1.4]	–
Very severe AEs <sup>g</sup>	1, 0.4 [0.0; 1.2]	1, 0.4 [0.0; 1.2]	–	–
Hospitalisation	–	2, 0.8 [0.0; 2.0]	–	–
All infections	20, 8.2 [4.3; 11.7]	28, 11.5 [7.3; 15.8]	11, 5.3 [2.2; 8.5]	3, 5.6 [0.0; 11.8]
Bacteria	6, 2.4 [0.5; 4.4]	5, 2.1 [0.3; 3.9]	4, 1.9 [0.0; 3.8]	–
Virus	5, 2.0 [0.3; 3.8]	12, 4.9 [2.1; 7.7]	4, 1.9 [0.0; 3.8]	–
EBV infection	1, 0.4 [0.0; 1.2]	–	1, 0.5 [0.0–1.4]	–
VZV infection	1, 0.4 [0.0; 1.2]	1, 0.4 [0.0; 1.2]	–	–
Another virus <sup>h</sup>	3, 0.4 [0.0; 1.2]	10, 4.1 [1.6; 6.7]	3, 1.4 [0.0; 3.1]	–
Other infections	9, 3.7 [1.3; 6.1]	11, 4.5 [1.9; 7.2]	3, 1.4 [0.0; 3.1]	3, 5.6 [0.0; 11.8]
All MII <sup>d</sup>	3, 1.6 [0.0; 3.2]	3, 1.2 [0.0; 2.6]	5, 2.4 [0.3; 4.5]	–
Sepsis	–	1, 0.4 [0.0; 1.2]	–	–
VZV infection	1, 0.4 [0.0; 1.2]	1, 0.4 [0.0; 1.2]	–	–
Others MII	2, 1.2 [0.0; 2.6]	1, 0.4 [0.0; 1.2]	5, 2.4 [0.3; 4.5]	–
Incidence of IMD				
Incident uveitis	–	–	–	–
Incident IBD	–	–	–	–
Psoriasiform lesions	–	–	1, 0.5 [0.0; 1.4]	–
Lupus <sup>e</sup>	–	–	–	–
All Blood disorders	17, 6.9 [3.6; 10.2]	2, 0.8 [0.0; 2.0]	4, 1.9 [0.0; 3.8]	1, 1.9 [0.0; 5.5]
Leukopenia	10, 4.1 [1.6; 6.6]	–	2, 1.0 [0.0; 2.3]	1, 1.9 [0.0; 5.5]
Thrombocytopenia	1, 0.4 [0.0; 1.2]	–	–	–
Pancytopenia	–	–	–	–
MAS	4, 1.6 [0.0; 3.2]	–	1, 0.5 [0.0; 1.4]	–
Other hospitalisations <sup>i</sup>	2, 0.8 [0.0; 1.9]	2, 0.8 [0.0; 2.0]	–	–

Rituximab does not appear in this table because no side effects have been registered under this BAs.

AEs: adverse events; CI: confidence interval; EBV: Epstein–Barr virus; HPV: human papillomavirus; IMD: immune-mediated disease; MAS: macrophage activation syndrome; VZV: varicella-zoster virus.

<sup>a</sup> Relative to each biological agent.

<sup>b</sup> All AEs: mild, moderate, severe and very severe AE.

<sup>c</sup> SAE: life threatening, hospitalization, incapacity life functions, cancer, death.

<sup>d</sup> MII: infections that led to hospitalization and/or required intravenous antibiotic treatment.

<sup>e</sup> Lupus-like or positivity of the antinuclear antibodies.

<sup>f</sup> 3 under tocilizumab (2 MAS, 1 prescription error).

<sup>g</sup> 1 under tocilizumab (MAS) and 1 under canakinumab (demyelinating lesion).

<sup>h</sup> 2 under tocilizumab (1 digestive disorders with hepatic cytolysis, 1 thrombosis of the superior vena cava and subclavian vein).

<sup>i</sup> 2 under canakinumab (1 digestive disorders, 1 demyelinating lesion).

The highest incidence rate of blood disorders was found with tocilizumab (6.9 per 100 PY, 95% CI [3.6; 10.2]); for this drug, the most frequently reported were leukopenia, followed by MAS (Table 3). Mostly MAS occurred in patients with JIA disease (29 in systemic JIA subtype, one in a polyarthritis-rheumatoid factor negative JIA subtype, one in an extended oligoarticular JIA subtype), five had a probable infectious trigger. One episode of central nervous system demyelinating lesion was described during canakinumab treatment. No IMD was found during golimumab treatment, the number of prescriptions of golimumab treatment was 15 (1% of all prescriptions).

### 3.4. Factors associated with adverse events

In univariate analyses, patients receiving any concomitant treatment suffered from more frequent AE or SAE. This applied to association with azathioprine, cyclosporine, hydroxychloroquine, leflunomide and sulfasalazine for both AE and SAE and CTCs only for AE. Methotrexate was not significantly associated with AE and SAE. Among BAs, tocilizumab and infliximab contributed more than etanercept to the incidence rate of mild and moderate AEs (Appendix A, Table S3). Infliximab and canakinumab also contributed more than etanercept to the incidence rate of severe AEs,

**Table 4**  
Univariate and multivariable analysis of serious adverse events.

	Univariate analysis		Multivariable analysis	
	HR [95% CI]	P	HR [95% CI]	P
Male sex	0.89 [0.47; 1.70]	NS	–	–
Age at diagnosis	0.99 [0.93; 1.06]	NS	–	–
Corticosteroids	1.02 [0.27; 3.81]	NS	–	–
Methotrexate (MTX)	0.99 [0.51; 1.94]	NS	–	–
Other immunosuppressive drugs <sup>a</sup>	3.50 [1.76; 6.94]	<0.001	3.45 [1.62; 7.35]	<0.05
Total number of biological agents <sup>b</sup>	1.20 [0.88; 1.62]	NS	–	–
JIA vs. non-JIA	0.72 [0.31; 1.67]	NS	–	–
Biological agents				
Etanercept	1	–	1	–
Adalimumab	1.37 [0.49; 3.71]	NS	1.44 [0.53; 3.92]	NS
Tocilizumab	1.70 [0.55; 5.38]	NS	1.55 [0.47; 5.10]	NS
Infliximab	3.27 [1.42; 7.52]	<0.05	2.73 [0.89; 5.84]	NS
Anakinra	2.77 [0.85; 9.97]	NS	2.93 [0.90; 9.55]	NS
Canakinumab	3.04 [1.05; 8.84]	<0.05	3.85 [1.36; 10.90]	<0.05
Abatacept <sup>c</sup>	NA	–	NA	–
Golimumab <sup>c</sup>	NA	–	NA	–
Rituximab <sup>c</sup>	NA	–	NA	–

Only variables with  $P < 0.2$  in the univariate analysis were used as candidate in the multivariate model.

CI: confidence interval; HR: hazard ratio, JIA: juvenile inflammatory arthritis; NA: not available because convergence failure; NS: non-significant.

<sup>a</sup> Other immunosuppressive drugs include: azathioprine, cyclosporine, hydroxychloroquine, leflunomide and sulfasalazine.

<sup>b</sup> Total number of biological agents prescribed during the retrospective period of study. Note that, they are not the previous biological agents to the adverse event.

<sup>c</sup> Lack of convergence in rituximab, golimumab and abatacept.

very severe AEs and SAE (Appendix A, Fig. S1). Sex, age at diagnosis, number of BAs and type of disease (JIA or non-JIA) were not significantly associated with the incidence rate of AE or SAE (Table 4 and Appendix A, Table S3). The multivariable analyses also supported the association between other immunosuppressive drugs with AE (Appendix A, Table S3) and SAE (Table 4). Corticosteroids has been associated only with mild and moderate AEs (Appendix A, Table S3). In the group of anti-IL1, canakinumab was associated with a significant incidence rate of SAE in multivariable analysis (Table 4). Notably, no AE or SAE occurred with rituximab, abatacept, and golimumab, leading to lack of convergence in the statistical regression model of SAEs and AEs.

#### 4. Discussion

The present study found an overall favourable outcome for children with paediatric inflammatory rheumatic diseases treated in real-life with all BAs in terms of severity and intensity of reported side effects, irrespective of the rheumatic disease. Despite the 4% rate for SAE, no sequelae were reported after BA discontinuation.

The incidence of SAE herein was lower for each BA when compared to that reported in the Finnish study which is the only retrospective observational investigation that also compared all BAs [13]. This difference may be in relation to the methodology employed because the Finnish study used at least three sources of information (medical records, as well as notes by nurses and other health professionals) to collect data, which increased the frequency of data collection and consequently multiplied the opportunities to detect an SAE. Conversely, in this study, only the medical records held by the rheumatologist were used. However, owing to the serious nature of these events they are more likely to be notified. Another plausible explanation may come from the difference in coding; the authors of the Finnish study note that the Common Terminology Criteria for AEs (CTCAE) system that they used codes neutropenia and ALT elevation as SAEs, which is not the case for the MedDRA classification used herein. These hypotheses are substantiated by the observation that SAE incidence rates for etanercept and adalimumab found in the present study were comparable to that previously reported in other registers/cohort studies [26–30] that also used a single source of data (for tolerance) and MedDRA.

In the regression model, a significant difference was found in the incidence of AE/SAE between the BAs investigated, irrespective of concomitant drug. Canakinumab in one hand and infliximab and tocilizumab in another hand were associated with an increased frequency of SAE and AE, respectively. Although the latter finding is not in agreement with a network meta-analysis performed in adult rheumatoid arthritis (RA) patients (the indirect comparisons made between the BAs were negative for the BAs analysed in this study), it is of note that there was a significant increase of withdrawal due to AEs in patients receiving infliximab in comparison to the control group [31]. The difference found herein for infliximab not could be explained by its indication as the second-line BA in patients with JIA in regards of our results. Other studies are needed to confirm our finding. Furthermore, the higher incidence of SAEs related to canakinumab treatment could be because these drugs are mainly used in auto-inflammatory diseases in paediatric patients, in particular, for systemic JIA subtype (one of the more severe diseases). Because of possible residual confounding bias (including MAS related to relapse of systemic JIA), these results must be interpreted with caution and should be viewed as exploratory.

In the present study, the combination of BAs and non-MTX immunosuppressive drugs was significantly associated with the incidence rate of AE and SAE. Corticosteroids were only associated with the occurrence of AE. Numerous studies reporting the occurrence of AE related to CTC exposure [32]. However, our study pointed the relation between non-MTX immunosuppressive drugs using a sparing in the burden of the disease. Contrarily to previous study in adults [33], the number of BAs prescribed as a risk factor for AEs or SAEs in juvenile inflammatory diseases was not associated with the occurrence AE. Beyond their efficacy to achieve remission [34,35], the present results question the weight of the non-MTX immunosuppressive drugs in the burden of paediatric rheumatologic diseases. This data suggests that other immunosuppressive drugs are more often associated with AEs and SAEs, irrespective of BAs in paediatric rheumatic disease. This may be because analyses of SAE are often performed in relation to an immunosuppressive drug without consideration of possible combinations [13,14,20]. Furthermore, in a Portuguese cohort of JIA patients [36], concomitant therapy with systemic CTCs was significantly associated with withdrawal of anti-TNF $\alpha$  treatments and was negative after adjusting on clinical covariates. Taken together, the results suggest that

monotherapy with BAs may be preferred when possible as well as de-escalation of immunosuppression after early aggressive therapy in JIA diseases [37–39]. Considering the risk of anti-drug antibody development, mainly in the anti-TNF $\alpha$  group the risk and benefit of a combination therapy should be balanced. A rate of 4% of occurrence of SAE is still unsatisfactory, therefore further investigations by prospective series and randomized trials are needed to help the clinician decide when a combination therapy is useful for the patient.

Additionally we described MII and IMD occurring during BA treatment, regardless of their severity, since they may better reflect long-term tolerance [23]. Focusing on infections, the higher rate of MII found with tocilizumab and anakinra may be explained by the severity of the underlying disease (systemic and polyarticular JIA subtypes and auto-inflammatory diseases), and as we discussed above by the co-prescription [40]. It is interesting to note that we found infections preventable by vaccines (chicken-pox and measles). We also provide evidence that the IMDs are present mainly with anti-TNF $\alpha$  treatments; the most frequent IMD in this study with anti-TNF $\alpha$  treatments was clinical and/or biological manifestation of lupus. This would be consistent with a French retrospective series of patients with rheumatoid arthritis, that retrieved 22 patients with lupus-like syndrome induced by anti-TNF $\alpha$ , and who were all positive for antinuclear antibodies [41]. The positivity of antinuclear antibodies with anti-TNF $\alpha$  is also described in the paediatric population treated with infliximab [42] and etanercept [43]; this was also found herein for infliximab, etanercept, and adalimumab. To the best of our knowledge, there is no description of a paediatric series that analyses the incidence of this IMD, probably because it is more infrequent than in the adult population. Therefore, it is the clinical sense of the rheumatologist that directs the search for antinuclear antibodies in patients with paediatric rheumatic diseases treated with some anti-TNF $\alpha$ .

The strength of the study is to report the evaluation of BA safety observed in real life by paediatric rheumatologists from various centres (reference and competence centre) in 4 different countries. Thus, we have shown the safety profile of children treated by all available BAs, including off-label use, for all disease severity levels. We have also to acknowledge several limitations; first the retrospective design might be responsible for potential missing data that may lead to overestimation of the safety profile of BAs. In this sense to ensure the accuracy and consistency of results and to minimise errors, we decided to describe and analyse only severe and very severe AEs and SAEs, because these were most likely the events registered in the medical record. Second, because of the non-randomized design of the present study, we could not draw firm conclusions for the causal relation between AEs or SAEs and drug exposures. Third, the small number of children receiving rituximab, golimumab, and abatacept precludes firm conclusions to be made regarding safety issues. Four, it is noteworthy that, compared to the usual epidemiological data of JIA disease, the oligoarticular subtype was underrepresented in this study. In fact, this subtype is associated with less polyarticular involvement and is known to have a better prognosis and the use of BA was very infrequent in this setting [44]. To improve the quality of data collection, long-term follow-up of children treated with BAs may be undertaken, through national and/or international cohorts, as a way to identify of possible factors predisposing for the occurrence of AEs and SAEs related to BAs exposure in this population.

## Disclosure of interest

The following authors: N.C., A.D., D.K., A.C., E.C., F.A., B.K., A.K., A.M., S.R., C.J., S.M., L.H., G.B., V.H., I.K.-P., and A.B. declare that they have no competing interest, J.-C. L. reports personal fees from Roche, during the conduct of the study. A.W. reports grants from

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## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at <https://doi.org/10.1016/j.jbspin.2018.08.003>.

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