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Anakinra in Patients With Systemic Juvenile Idiopathic Arthritis: Long-term Safety From the Pharmachild Registry

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ABSTRACT. *Objective.* To evaluate the long-term safety profile of anakinra in patients with systemic juvenile idiopathic arthritis (sJIA).

Methods. Data from patients with sJIA enrolled in the Pharmachild registry (ClinicalTrials.gov: NCT03932344) prior to September 30, 2018, and treated with anakinra were analyzed. The study endpoints were the occurrence of non-serious adverse events (SAEs) of at least moderate severity and SAEs, including macrophage activation syndrome (MAS), and the duration of anakinra treatment with reasons for discontinuation. All endpoints were analyzed overall by 6-month time windows, and in different treatment sets represented by those patients treated continuously with anakinra for at least 12, 18, and 24 months (set-12, -18, and -24, respectively).

Results. Three hundred six patients were enrolled. Of these patients, 46%, 34%, and 28% had been treated for at least 12, 18, and 24 months, respectively. Two hundred and one AEs, mostly represented by infections, were reported for 509.3 patient-years (PY) with an overall incidence rate (IR) of 39.5 per 100 PY. Among 56 SAEs (IR 11.0/100 PY), 23.2% were infections and 19.6% MAS episodes. The IR of AEs was higher during the first 6 months of anakinra treatment, followed by decreasing IRs in the long-term treatment sets. Treatment discontinuation occurred in 76% of patients, most frequently in the first 6 months, because of inefficacy (43%), remission (31%), or AEs/intolerance (15%). No deaths or malignancies occurred during anakinra treatment.

Conclusion. The results of the present study confirm the long-term safety profile of anakinra in patients with sJIA and demonstrate an overall decreasing incidence of AEs over time. [ClinicalTrials.gov: NCT01399281and NCT03932344]

Key Indexing Terms: anakinra, long-term adverse effects, systemic juvenile idiopathic arthritis

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Systemic juvenile idiopathic arthritis (sJIA) is characterized by high, spiking, intermittent fever, chronic arthritis or arthralgias, maculopapular rash, hepatosplenomegaly, lymphadenopathy, serositis, and marked increase in acute-phase reactants.[1,2,3,4] sJIA may be associated with complications, such as the potentially fatal macrophage activation syndrome (MAS) and the rare AA amyloidosis.[5,6,7,8] Laboratory and clinical observations suggest an inappropriate activation of the innate immunity, with hypersecretion of proinflammatory cytokines, such as interleukin (IL)-1 and IL-6.[3] Anakinra is a recombinant human IL-1 receptor antagonist that blocks the biological activity of both IL-1α and IL-1β by competitively inhibiting its binding to the IL-1 receptor type 1, thereby controlling active inflammation.[9] Anakinra has been studied for several disease states including the European Union–approved indications for rheumatoid arthritis (RA), Still disease, sJIA, different forms of cryopyrin-associated periodic syndrome, as well as familial Mediterranean fever, and its safety profile is now well established.[9,10]

Although there have been consolidated data on the efficacy of anakinra in treating glucocorticoid (GC)-dependent patients with sJIA[11,12] and data on anakinra as first-line monotherapy in patients with new-onset sJIA,[13,14,15] little evidence has been collected on long-term safety in large cohorts of patients with sJIA treated with anakinra.[14,15,16,17,18,19] Events of MAS have been described in patients treated with anakinra for sJIA; however, a causal relationship between anakinra and MAS has not been established.[9,18] On the contrary, anakinra has been reported to be an effective treatment for MAS.[20,21,22] Phase III clinical trials of canakinumab[23] and tocilizumab in sJIA[24,25,26] clearly demonstrate that these treatments do not provide protection against MAS and suggest that IL-1 and IL-6 may not be the only cytokines with a central role in the pathogenesis of this syndrome. As well, scarce literature exists on the role of anakinra in influencing MAS occurrence in patients with sJIA, especially in the long term.[27]

The present study was designed with the objective of evaluating and characterizing the long-term safety profile of anakinra when used in standard clinical practice to treat patients with sJIA, including the occurrence of MAS, the most severe complication of the disease.

METHODS

Study design. The study was a noninterventional, postauthorization safety study (PASS), and the protocol was developed in accordance with the European Medicines Agency guidance for the format and content of the protocol of a noninterventional PASS.[28] The study was conducted by the Paediatric Rheumatology International Trials Organisation (PRINTO) using the European Network of Centres for Pharmacoepidemology and Pharmacovigilance–certified pharmacovigilance registry named Pharmachild (ClinicalTrials.gov: NCT03932344). In brief, one of the aims of the Pharmachild registry, set up in December 2011, is to evaluate the long-term safety of synthetic (s-) and biologic (b-) disease-modifying antirheumatic drugs (DMARDs). More details on the Pharmachild registry and data collection and validation are reported elsewhere.[29,30]

For the present study, data from patients with sJIA, as per the International League of Associations for Rheumatology classification criteria,[31,32] who were enrolled in the Pharmachild registry before September 30, 2018, and treated with anakinra at any point in time after sJIA diagnosis were included in the analysis.

All centers obtained ethics committee approval according to national requirements and parents/patients provided consent/assent as appropriate.

Study endpoints. The study endpoints were (1) the occurrence of non-serious adverse events (SAEs) of at least moderate severity and SAEs, including MAS as an event of special interest; and (2) the duration of the anakinra treatment, with reasons for discontinuation.

Data collection in Pharmachild. Both retrospective safety and drug exposure data from disease onset (collected prior to the enrollment in the registry) and subsequent prospective data were used in this study. All AEs of moderate, severe, or very severe intensity and SAEs are reported in Pharmachild; mild intensity is reported only for those AEs that do not resolve and require a follow-up report. In the present study, mild intensity was also reported for any AE of an intensity that resulted in discontinuation. AEs are reported in Pharmachild regardless of a possible suspected causal relationship to anakinra or other therapies and according to the latest release of the Medical Dictionary for Regulatory Activities (MedDRA, Version 21.1), which classifies them on a 5-level structure depending on the specificity required (from the most specific, Lowest Level Term and Preferred Term [PT] to the least, System Organ Class [SOC]). According to this terminology, the PT *hemophagocytic lymphohistiocytosis* (*HLH*) was used in this study as interchangeable with MAS.

Statistical methods. Data were analyzed (1) overall, inclucing all patients with sJIA and treated at any point in time with anakinra in the registry; and (2) by 3 defined populations of patients treated continuously with anakinra for 12, 18, or > 24 months: the long-term treatment set-12, -18, and -24, respectively. Continuous treatment was defined as ongoing treatment

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when ≤ 30 consecutive days of unexposed duration occurred in between treatment periods. Neither AEs nor patient-time were counted during the unexposed period.

Categorical data were reported in terms of absolute frequencies and percentages. Continuous data were described in terms of mean, SD, median, minimum and maximum, and 1st and 3rd quartiles (IQR). The incidence rate (IR) per 100 patient-years (PY) was calculated by taking the number of the specific incident events and dividing by the sum of PY under risk (ie, exposed to anakinra × 100). A patient could contribute with multiple events of the same AE and to different treatment sets. The IR was derived by a Poisson regression model (with only intercept) and the 95% CI was estimated using the Poisson estimator with a cluster-robust estimate of variance to control for both overdispersion and intracluster correlation. AE-specific IRs were calculated overall for the complete study period and by 6-month calendar time windows (1–6 mos, 7–12 mos, 13–18 mos, 19–24 mos, and > 24 mos). Each period of anakinra treatment exposure was calculated as the period between the start date of anakinra until (and including) the stop date of anakinra plus 2 days, which accounted for approximately 5 half-lives of the drug. Where applicable, the stop date was substituted with the end of the time window, date of discontinuation of the anakinra treatment exposure, last visit, or death. AEs occurring outside anakinra treatment exposure (ie, before and when anakinra treatment was paused or stopped) were not counted.

In addition, the IR of MAS was analyzed with respect to first occurrence and recurrence. The rationale for this was to account for a biological distinction in altered risk following a first event.

Analysis and presentation were based on available data (ie, no imputation of missing data was performed). Statistical analyses were performed using SAS software Version 9.3 or later (SAS Institute). Analysis and reporting were done independently by PRINTO, with the final report shared with the marketing authorization holder and regulatory authorities.

RESULTS

Population. Of the 944 patients with sJIA included in the Pharmachild registry, 306 (32.4%) had been treated with anakinra (Figure 1; first documented anakinra treatment in 2004) and were included in the analysis. Among these, 141 (46.1%), 104 (34.0%), and 86 (28.1%) patients were treated continuously with anakinra for at least 12, 18, and 24 months, respectively (Figure 1 and Table 1). Prospective data were collected for 174/306 (56.9%) patients. Of the 32 countries participating in the Pharmachild JIA registry, 38 centers from 15/32 countries (46.9%) reported data on anakinra treatment for sJIA; 97.7% of the patients were from Europe and 2.3% from Asia. White race was most prevalent (70.6%; Table 1). Anakinra had been given as monotherapy or in combination with other GCs or DMARDs, as per the local standard of care (Supplementary Table 1, available with the online version of this article). Both sexes were equally represented, with a median age at first anakinra treatment of 8.0 years, and a median time between disease diagnosis and anakinra start of 0.3 years (Table 1).

Of the 306 patients, 94 (30.7%) received anakinra as first-line treatment. Among the remaining 212 patients, 78 (36.8%) were treated with various combinations of DMARDs and GCs before starting anakinra and continued with those treatments concomitantly with the IL-1 inhibitor. One hundred thirty-four (63.2%) patients stopped other treatments before starting anakinra. At the beginning of anakinra treatment, 193 (63.1%) patients received ≥ 1 concomitant sJIA-related

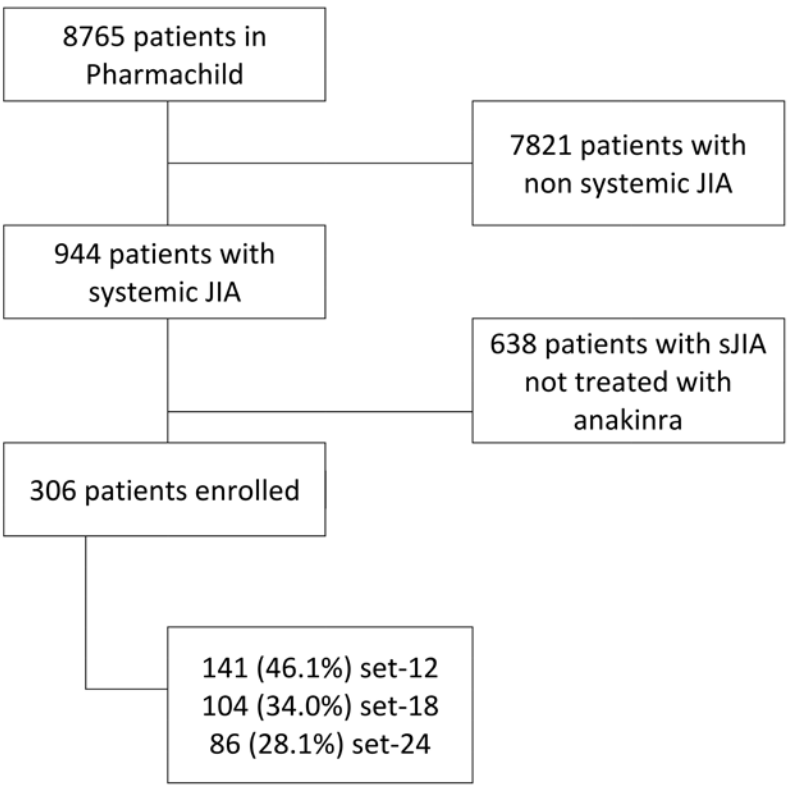

Figure 1. Flow chart of the study population selected. Patients can belong to different treatment sets. Set-12, -18, or -24: patients treated continuously for at least 12, 18, or 24 months with anakinra; sJIA: systemic juvenile idiopathic arthritis.

Table 1. Demographics and baseline characteristics.

	Complete Set	Long-term Treatment		
		Set-12	Set-18	Set-24
n (%)	306 (100.0)	141 (46.1)	104 (34.0)	86 (28.1)
Male	152 (49.7)	81 (57.4)	59 (56.7)	49 (57.0)
Age, yrs (IQR)[a]	8.0 (4.0–11.8)	8.5 (4.6–11.9)	8.5 (4.9–11.4)	8.5 (4.9–11.1)
Age groups, yrs				
Infant (< 2)	22 (7.2)	7 (5.0)	2 (1.9)	1 (1.2)
Child (2 to < 12)	210 (68.6)	100 (70.9)	81 (77.9)	68 (79.1)
Adolescent (12 to < 18)	69 (22.6)	31 (22.0)	19 (18.3)	16 (18.6)
Adult (≥ 18)	5 (1.6)	3 (2.1)	2 (1.9)	1 (1.2)
Time since sJIA onset, yrs, median (IQR)	0.6 (0.2–2.2)	1.1 (0.4–3.4)	1.5 (0.6–4.3)	1.5 (0.6–4.3)
Time since sJIA diagnosis, yrs, median (IQR)	0.3 (0.0–1.9)	0.8 (0.1–3.0)	1.1 (0.2–3.8)	1.3 (0.2–4.0)
Time from sJIA onset to first visit[b], yrs, median (IQR)	0.2 (0.0–0.8)	0.2 (0.1–0.8)	0.2 (0.1–0.9)	0.2 (0.1–0.8)
History of MAS	10 (3.3)	6 (4.2)	5 (4.8)	4 (4.6)
Origin				
Europe	299 (97.7)	138 (97.9)	101 (97.1)	83 (96.5)
Asia	7 (2.3)	3 (2.1)	3 (2.9)	3 (3.5)
Ethnicity				
White	216 (70.6)	97 (68.8)	75 (72.1)	60 (69.8)
Other	90 (29.4)	44 (31.2)	29 (27.9)	26 (30.2)

Data presented as n (%) unless otherwise indicated. [a] Age at baseline for the complete set; age at baseline or at index date for the long-term treatment set-12, -18, and -24. [b] First visit in the clinical center. MAS: macrophage activation syndrome; sJIA: systemic juvenile idiopathic arthritis.

medication other than nonsteroidal antiinflammatory drugs, primarily GCs (161 patients, 52.6%; Supplementary Table 1, available with the online version of this article).

Anakinra treatment. The mean (SD) duration of anakinra treatment for the total study population was 17.0 (21.1) months and the median (IQR) was of 8.9 (3.1–23.5) months. The shortest treatment course was 0.2 months and the longest was 109.9 months (or 9.1 yrs). In 92 of 306 (30.1%) patients, anakinra treatment was ongoing at the last report in the registry.

AEs. A total of 201 AEs were identified, with an overall IR of 39.5/100 PY (95% CI 30.8–50.6; Table 2). The overall incidence of AEs decreased over time, with the highest IRs during the first 6 months of anakinra treatment (Table 2; Supplementary Table 2, available with the online version of this article). The group of AEs that was the most frequently reported was infections and infestations (52 AEs, IR 10.2/100 PY), followed by skin and subcutaneous tissue disorders (25 AEs, IR 4.9/100 PY), general disorders and administration site conditions (23 AEs, IR 4.5/100 PY), and gastrointestinal (GI) disorders (18 AEs, IR 3.5/100 PY).

Among infections and infestations, respiratory tract infections accounted for 53.8% (28/52). In the group of infections, 3 cases of varicella, and 1 case of herpes zoster were also identified. Among skin and subcutaneous tissue disorders, rash (8 occurrences) and urticaria and eczema (3 occurrences each) were the most frequently reported events. Injection-site reactions (ISRs) were the most common PTs both among "general disorders and administration site conditions" (16 occurrences) and "injury, poisoning, and procedural complications" (10 occurrences). Among GI disorders, constipation (6 occurrences) and abdominal pain (4 occurrences) were the most frequently reported.

By single PTs, MAS (HLH), in the SOC "immune system disorders," was the most frequent event, with 12 occurrences and an IR of 2.4/100 PY (Table 2) followed by injection-related reactions (2.0/100 PY), ISRs (1.6/100 PY), rash (1.6/100 PY), and constipation (1.2/100 PY). The IRs for the remaining AEs were < 1/100 PY. This included known adverse reactions of anakinra, such as neutropenia and hepatitis, which accounted for few events among the total (6 AEs of increased liver enzymes and 4 AEs of neutropenia). The majority of the ISRs occurred early after initiation of anakinra. Three infusion-related reactions were connected to tocilizumab, which was administered in close connection to anakinra treatment.

SAEs. Fifty-six of the 201 AEs were serious (Table 3; Supplementary Tables 3–5, available with the online version of this article). Overall, the IR of the SAEs was 11.0/100 PY (95% CI 7.9–15.2), with events within the SOC infections and infestations being the most reported (a total of 13 SAEs, IR 2.6/100 PY), followed by immune system disorders (a total of 11 SAEs, IR 2.2/100 PY, all describing MAS). Injury, poisoning, and procedural complications covered 9 events, with an IR of 1.8/100 PY. The remaining SAEs had an IR < 1.0/100 PY.

Similarly, as for all AEs, the subset of SAEs also occurred primarily during the first 6 months of treatment (IR 28.1/100 PY during the 1- to 6-month time window).

By single PTs, MAS (HLH) was the most frequently reported SAE (n = 11, IR 2.2/100 PY; Table 3), primarily reported in the first 6 months of anakinra treatment (IR 6.0/100 PY), followed by injection-related reactions (n = 6, IR 1.2/100 PY). All remaining events had an IR < 1/100 PY. Among these, 1 patient reported an event of interstitial lung disease (ILD) after receiving treatment with anakinra for > 24 months (Supplementary Table 2, available with the online version of this article). No

Table 2. Number of AEs and incidence rates in the complete set, overall, and by different time windows.[a]

	Time Window[b]	1–6 Months		7–12 Months		13–18 Months		19–24 Months		> 24 Months		Overall	
	N	306		194		144		106		104		306	
	PY[c]	117.3		80.2		58.1		47.0		206.7		509.3	
SOC	PT	n[d]	Rate (95% CI)[e]	n[d]	Rate (95% CI)[e]	n[d]	Rate (95% CI)[e]	n[d]	Rate (95% CI)[e]	n[d]	Rate (95% CI)[e]	n[d]	Rate (95% CI)[e]
All	All	116	98.9 (75.8–129.0)	26	32.4 (19.6–53.5)	16	27.5 (14.5–52.2)	7	14.9 (6.0–37.1)	36	17.4 (11.1–27.4)	201	39.5 (30.8–50.6)
Infections and infestations	All	23	19.6 (12.4–31.0)	12	15.0 (6.8–32.9)	5	8.6 (3.6–20.7)	–	–	12	5.8 (2.4–14.1)	52	10.2 (6.7–15.6)
	Pneumonia	2	1.7 (0.4–6.8)	1	1.2 (0.2–8.8)	1	1.7 (0.2–12.2)	–	–	–	–	4	0.8 (0.3–2.1)
	Respiratory tract infection	2	1.7 (0.4–6.8)	–	–	2	3.4 (0.9–13.7)	–	–	–	–	4	0.8 (0.3–2.1)
Skin and subcutaneous tissue disorders	All	18	15.3 (9.5–24.7)	3	3.7 (1.2–11.5)	1	1.7 (0.2–12.2)	–	–	3	1.5 (0.5–4.4)	25	4.9 (3.2–7.5)
	Rash	6	5.1 (2.0–12.8)	1	1.2 (0.2–8.8)	–	–	–	–	1	0.5 (0.1–3.5)	8	1.6 (0.7–3.4)
General disorders and administration site conditions	All	16	13.6 (8.2–22.7)	3	3.7 (1.2–11.5)	1	1.7 (0.2–12.2)	1	2.1 (0.3–15.1)	2	1.0 (0.2–3.8)	23	4.5 (2.9–7.0)
	Injection-site reaction	7	6.0 (2.9–12.4)	–	–	–	–	–	–	1	0.5 (0.1–3.3)	8	1.6 (0.8–3.1)
Gastrointestinal disorders	All	13	11.1 (6.0–20.4)	1	1.2 (0.2–8.8)	–	–	1	2.1 (0.3–14.9)	3	1.5 (0.5–4.3)	18	3.5 (2.1–5.9)
	Constipation	5	4.3 (1.8–10.2)	–	–	–	–	–	–	1	0.5 (0.1–3.5)	6	1.2 (0.5–2.7)
	Abdominal pain	3	2.6 (0.8–7.9)	1	1.2 (0.2–8.8)	–	–	–	–	–	–	4	0.8 (0.3–2.1)
Injury, poisoning and procedural complications	All	10	8.5 (4.6–15.8)	1	1.2 (0.2–8.8)	2	3.4 (0.9–13.6)	1	2.1 (0.3–15.1)	2	1.0 (0.3–3.7)	16	3.1 (1.9–5.2)
	Injection-related reaction	6	5.1 (2.3–11.4)	1	1.2 (0.2–8.8)	2	3.4 (0.9–13.6)	–	–	1	0.5 (0.1–3.3)	10	2.0 (1.1–3.7)
Immune system disorders	All	7	6.0 (2.8–12.5)	1	1.2 (0.2–8.8)	2	3.4 (0.9–13.6)	–	–	3	1.5 (0.5–4.4)	13	2.6 (1.4–4.6)
	HLH	7	6.0 (2.8–12.5)	1	1.2 (0.2–8.8)	1	1.7 (0.2–12.2)	–	–	3	1.5 (0.5–4.4)	12	2.4 (1.3–4.3)

[a] Events with a frequency of > 10 by overall SOC and > 3 by overall PT are presented in this table. For the complete table, please refer to the Supplementary Material (available with the online version of this article). [b] In relation to baseline (beginning of anakinra treatment). [c] PY: patient-year; only time while anakinra treatment was ongoing and 2 days after discontinuation were counted. [d] No. of events. Only AEs occurring during anakinra exposed periods and 2 days after discontinuation were counted. [e] Incidence rate per 100 PY. AE: adverse event; HLH: hemophagocytic lymphohistiocytosis; MedDRA: Medical Dictionary for Regulatory Activities; N: no. of patients ever treated with anakinra during the time window irrespectively of the length of any unexposed periods; PT: preferred term, MedDRA version 21.1; SOC: system organ class.

Table 3. Number of SAEs and incidence rates in the complete set, overall, and by different time windows.[a]

	Time Window[b]	1–6 Months		7–12 Months		13–18 Months		19–24 Months		> 24 Months		Overall	
	n	306		194		144		106		104		306	
	PY[c]	117.3		80.2		58.1		47.0		206.7		509.3	
SOC	PT	n[d]	Rate (95% CI)[e]	n[d]	Rate (95% CI)[e]	n[d]	Rate (95% CI)[e]	n[d]	Rate (95% CI)[e]	n[d]	Rate (95% CI)[e]	n[d]	Rate (95% CI)[e]
All	All	33	28.1 (19.1–41.5)	4	5.0 (1.9–13.2)	8	13.8 (5.9–31.9)	2	4.3 (1.1–16.9)	9	4.3 (2.2–8.8)	56	11.0 (7.9–15.2)
Infections and infestations	All	7	6.0 (2.9–12.4)	1	1.2 (0.2–8.8)	2	3.4 (0.9–13.8)	–	–	3	1.5 (0.3–6.3)	13	2.6 (1.4–4.8)
	Pneumonia	2	1.7 (0.4–6.8)	1	1.2 (0.2–8.8)	1	1.7 (0.2–12.2)	–	–	–	–	4	0.8 (0.3–2.1)
Immune system disorders	All	7	6.0 (2.8–12.5)	1	1.2 (0.2–8.8)	1	1.7 (0.2–12.2)	–	–	2	1.0 (0.2–3.8)	11	2.2 (1.1–4.1)
	HLH	7	6.0 (2.8–12.5)	1	1.2 (0.2–8.8)	1	1.7 (0.2–12.2)	–	–	2	1.0 (0.2–3.8)	11	2.2 (1.1–4.1)
Injury, poisoning, and procedural complications	All	5	4.3 (1.8–10.2)	–	–	2	3.4 (0.9–13.6)	1	2.1 (0.3–15.1)	1	0.5 (0.1–3.3)	9	1.8 (0.9–3.4)
	Infusion-related reaction	1	0.9 (0.1–6.0)	–	–	–	–	1	2.1 (0.3–15.1)	–	–	2	0.4 (0.1–1.6)
	Injection-related reaction	4	3.4 (1.3–9.1)	–	–	2	3.4 (0.9–13.6)	–	–	–	–	6	1.2 (0.5–2.6)
Metabolism and nutrition disorders	All	3	2.6 (0.8–7.9)	–	–	1	1.7 (0.2–12.1)	–	–	–	–	4	0.8 (0.3–2.1)
Skin and subcutaneous tissue disorders	All	3	2.6 (0.8–7.9)	1	1.2 (0.2–8.8)	–	–	–	–	–	–	4	0.8 (0.3–2.1)
Blood and lymphatic system disorders	All	1	0.9 (0.1–6.1)	–	–	–	–	–	–	1	0.5 (0.1–3.4)	2	0.4 (0.1–1.6)
General disorders and administration site conditions	All	1	0.9 (0.1–6.1)	1	1.2 (0.2–8.8)	–	–	–	–	–	–	2	0.4 (0.1–1.6)
Investigations	All	2	1.7 (0.4–6.8)	–	–	–	–	–	–	–	–	2	0.4 (0.1–1.6)
Nervous system disorders	All	1	0.9 (0.1–6.0)	–	–	–	–	1	2.1 (0.3–14.9)	–	–	2	0.4 (0.1–1.6)
Surgical and medical procedures	All	1	0.9 (0.1–6.0)	–	–	–	–	–	–	1	0.5 (0.1–3.3)	2	0.4 (0.1–1.5)

[a] Events with a frequency of > 1 by overall SOC and > 1 by overall PT are presented in this table. For the complete table, please refer to the supplementary material (available with the online version of this article). [b] In relation to baseline (start of anakinra treatment). [c] PY: patient-year; only time while anakinra treatment was ongoing and 2 days after discontinuation were counted. [d] No. of events. Only SAEs occurring during anakinra exposed periods and 2 days after discontinuation were counted. [e] Incidence rate per 100 PY. HLH: hemophagocytic lymphohistiocytosis; MedDRA: Medical Dictionary for Regulatory Activities; N: no. of patients ever treated with anakinra during the time window irrespectively of the length of any unexposed periods; PT: preferred term, MedDRA version 21.1; SAE: serious adverse event; SOC: system organ class.

malignancies or SAEs leading to death occurred during anakinra exposure. Outside of anakinra exposure, 3 patients died 0.5, 3, and 5 years after anakinra discontinuation, while receiving GCs, and in 1 case, combined with sDMARDs. Reasons for death were sepsis, multiorgan failure, and sudden death, respectively.

Analysis of AEs and SAEs by long-term treatment set. The analysis of the total group of AEs with respect to the long-term treatment sets 12, 18, and 24 showed an overall IR of 20.9, 14.3, and 13.5 per 100 PY for AEs, respectively, of which the IR of SAEs were 5.1, 3.8, and 2.9 per 100 PY, respectively. In the 86 patients treated continuously for > 24 months, the IR for AEs in the first 6 months of treatment was 21.1/100 PY and after 24 months the IR was 13.1/100 PY. Among AEs, the SOC "infections and infestations" was the most frequent in the different treatment sets (see complete report[33]).

In the SAE subset, the SOCs "infections and infestations" and "injury, poisoning, and procedural complications" were equally represented with an IR of 1.2/100 PY in the long-term treatment set-12, whereas the SOC "immune system disorders," where MAS is included, and "injury, poisoning, and procedural complications" were equally represented with an incidence of 0.8/100 PY in the long-term treatment set-18. Finally, for the long-term treatment set-24, MAS was the most frequent SAE with only 3 events for an IR of 0.9/100 PY.[33]

MAS as an event of special interest. In total, 11 patients experienced 12 events (11 SAEs and 1 nonSAE) of MAS during anakinra treatment (Table 4). In 1 patient MAS was considered nonserious by the reporting physician; there was an increase in ferritin levels (67,390 mg/mL), and clinical and laboratory tests were consistent with MAS. However, the event was considered severe by the reporting physician and anakinra was continued.

The IR of the first occurrence was 2.2/100 PY (Table 4). Ten patients (3.3%) had a previous history of MAS at baseline; 9 of these did not experience any new MAS episode while on anakinra and 1 patient had 2 additional episodes of MAS during anakinra treatment.

The IR for the first occurrence of MAS while on anakinra was lower in patients without a history of MAS (IR 2.1/100 PY, 95% CI 1.1–3.9) compared to those with MAS before anakinra initiation (IR 5.6/100 PY, 95% CI 0.7–42.9; Table 4). The average time from initiation of anakinra to first MAS occurrence was 9 months. Of MAS events, 36.4% occurred during the first 30 days of anakinra treatment and 36.3% occurred ≥ 6 months after the first injection. The shortest time from baseline to a MAS event was 4 days. The frequency of MAS did not increase during continued treatment (Supplementary Table 6, available with the online version of this article).

After stopping anakinra, MAS was reported in 8 patients. The earliest recurrence was in the time window of 90–180 days, with no indication of an increase in MAS incidence immediately after stopping anakinra.

Triggers for the MAS events were recorded as disease flares (4 events, 33.3%), changes of treatments (3 events, 25.0%), infections (2 events, 16.7%), and unknown (3 events, 25.0%; Supplementary Table 7, available with the online version of this article).

Reasons for anakinra treatment discontinuation. Out of 306 patients, 233 (76.1%) discontinued anakinra at least once (Table 5). In total, there were 268 discontinuations with 281 reasons recorded. The most frequent reason for anakinra discontinuation was inefficacy (43.1%), followed by remission (30.6%). AEs caused 10.0% of discontinuations: in 8.2% of the cases because of events of moderate intensity, and mild in the remaining cases. Intolerance was given as the reason for discontinuation in 5.0% of the cases. Discontinuations as a result of AEs and intolerance were more frequently reported during the first 6 months of therapy.

DISCUSSION

We analyzed the long-term safety profile of anakinra used in standard clinical practice to treat patients with sJIA from the international cohort of the Pharmachild registry.[29] The evidence collected in this study, with patients from different countries, provides a real-world safety overview that could be generalized to the wider general population of patients with sJIA treated with anakinra.

It has been suggested that after a few months of anakinra treatment in patients with new-onset sJIA, it is possible to achieve

Table 4. Number of first occurrence and recurrence of MAS events and incidence rates, overall and by history of MAS in the complete set of patients treated with anakinra.

	Occurrence	MAS Events[a], n	PY[b]	Rate (95% CI)[c]
History of MAS at baseline (N = 10)[d]	First occurrence[e]	1	18.0	5.6 (0.7–42.9)
	Second occurrence	1	1.0	100
No history of MAS recorded at baseline (N = 296)[d]	First occurrence[e]	10	479.5	2.1 (1.1–3.9)
	Second occurrence	0	5.2	0
Complete study population (N = 306)[d]	First occurrence[e]	11	497.5	2.2 (1.2–4.1)
	Second occurrence	1	6.2	16.1 (2.6–97.7)

[a] Only MAS occurring during anakinra treatment (including 2 days after discontinuation) were included. [b] PY: patient-year; only time during periods with anakinra treatment (including 2 days after discontinuation) were included. [c] Incidence rate per 100 PY. [d] N = number of patients starting anakinra treatment. [e] The first occurrence of MAS is defined to occur at or after baseline regardless of whether or not the patient had a history of MAS. MAS: macrophage activation syndrome.

Table 5. Reasons for discontinuation of anakinra treatment.

Time Window[a]	Overall	1–6 Months	7–12 Months	13–18 Months	19–24 Months	> 24 Months
Total no. of patients (N)	306	306	194	144	106	104
Total no. of reasons for discontinuations	281	109	53	34	13	72
Reasons	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
AEs at least of moderate intensity	23 (8.2)	17 (15.6)	2 (3.8)	3 (8.8)	0 (0.0)	1 (1.4)
Intolerance	14 (5.0)	8 (7.3)	3 (5.7)	1 (2.9)	0 (0.0)	2 (2.8)
Dose change	2 (0.7)	1 (0.9)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Inefficacy	121 (43.1)	51 (46.8)	20 (37.7)	8 (23.5)	6 (46.2)	36 (50.0)
Remission	86 (30.6)	20 (18.3)	21 (39.6)	19 (55.9)	4 (30.8)	22 (30.6)
Surgery	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Other reason	23 (8.2)	7 (6.4)	5 (9.4)	3 (8.8)	2 (15.4)	6 (8.3)
Mild AEs[b]	5 (1.8)	4 (3.7)	1 (1.9)	0 (0.0)	0 (0.0)	0 (0.0)
Change therapy	11 (3.9)	2 (1.8)	2 (3.8)	2 (5.9)	1 (7.7)	4 (5.6)
No compliance	4 (1.4)	0 (0.0)	2 (3.8)	0 (0.0)	1 (7.7)	1 (1.4)
Other	3 (1.1)	1 (0.9)	0 (0.0)	1 (2.9)	0 (0.0)	1 (1.4)
Unknown	12 (4.3)	5 (4.6)	1 (1.9)	0 (0.0)	1 (7.7)	5 (6.9)
No. of patients who discontinued[c]	233 (76.1)	102 (33.3)	50 (25.8)	33 (22.9)	13 (12.3)	61 (58.7)
No. of discontinuations[c]	268 (87.6)	103 (33.7)	50 (25.8)	33 (22.9)	13 (12.3)	69 (66.3)

A patient can contribute with multiple discontinuations, if starting a new treatment period after a temporary stop of > 30 days, and multiple reasons for a single discontinuation. [a] In relation to baseline (start of anakinra treatment). [b] Mild adverse events are not reported elsewhere because they are excluded from the Pharmachild registry. [c] The denominator is the total number of patients (N). AE: adverse event.

excellent responses and after 1 year of therapy, 39–76% of the patients achieve clinical remission on therapy, with a GC-sparing effect.[34,35,36,37,38] Patients with persistently active sJIA may need continuous treatment with anakinra for ≥ 1 year. This study aimed to investigate the long-term safety of anakinra in these patients. In our population, 46% of patients were on continuous anakinra treatment for ≥ 1 year and 28% for > 2 years.

Our results show that the safety of anakinra after long-term administration is in line with the well-established profile of the drug, as shown in previous reports.[12] Moreover, data from the prospective, observational BIKER registry demonstrated fewer AEs with anakinra compared to other biologic treatments.[39]

Additionally, in this study we show that the rate of reported AEs, including SAEs, was higher in the first 6 months of treatment and then decreased over time. This trend has also been reported in adult patients with RA treated with tumor necrosis factor inhibitors,[40,41] and could possibly be explained by immune system dysregulation when adapting to the new immunomodulatory drug. Further, higher doses of GCs, often given at the start of sJIA treatment, may contribute to more AEs reported early in the patient history. In addition, ISRs typically appear early during treatment with anakinra, usually within 2 weeks of therapy initiation, and disappear within 4–6 weeks during continued anakinra treatment.[9] The most frequently reported AEs were related to infections, skin manifestations, and ISRs, confirming data from previous publications.[14,15] ISRs are a common adverse reaction to anakinra; however, it was not the most commonly reported AE in this study, which may be because mild AEs are not reported in Pharmachild. Among the SAEs, infections and MAS were most frequently reported. In the last decade, rare lung disorders, (ie, pulmonary arterial hypertension, ILD, and alveolar proteinosis) have been reported in children with Still disease,[42,43,44,45] often associated with MAS, sometimes with fatal outcomes. It has been discussed whether immunosuppressive therapy including IL-1 inhibitors can contribute to the development of these disorders. However, in our study, only 1 patient presented with a pulmonary SAE, an unspecified ILD that occurred after > 24 months of treatment, and it is unclear whether this was specifically related to anakinra.

No deaths were reported during anakinra treatment, although 3 patients died after discontinuation of the biologic as a result of sepsis, multiorgan failure, and sudden death. These events were not reported by the treating physician as being related to anakinra, which had been discontinued 0.5, 5, and 3 years earlier, respectively. Moreover, the events occurred while patients were receiving other immunosuppressive medications, so a clear correlation with the previous therapies could not be established.

A specific focus in our study was given to the most severe complication of sJIA, MAS. The frequency of MAS in our cohort was in line with what is expected from the literature.[46,47] One-third of the MAS events occurred during the first 30 days of treatment. A possible explanation for this could be that anakinra was started when symptoms of MAS were already present, the clinical conditions were rapidly deteriorating as a result of a severe sJIA flare onset, or the anakinra dose was not sufficient to counter the hyperinflammatory state. Events of MAS have previously been described in patients treated with anakinra for

sJIA, although a causal relationship between anakinra and MAS has never been established. It should be noted that anakinra has also been reported as an effective treatment for MAS.[13,21] In our study, no increased risk of MAS during or directly after anakinra treatment was identified, and more importantly, there was no evidence that the frequency of MAS events increased during continued treatment with anakinra or during the first 90 days after stopping therapy. The demographic and clinical features of the different populations described in the literature and especially the prior and concomitant treatments should also be considered, as they might influence the frequency of MAS by a long-term or concomitant effect. This may explain the wide range of variability in reporting MAS in the literature.[48,49]

The primary reason for anakinra discontinuation, in our study, was inefficacy, followed by disease remission. In line with the most recent literature, relatively few patients discontinued anakinra as a result of AEs or intolerance, and most of these events occurred during the first 6 months of treatment.[15,17]

The study design carries some general limitations, such as the lack of a control group or of a correlation between the dosage of anakinra and AEs. In addition, most of the patients received ≥ 1 concomitant sJIA-related medication at start of anakinra treatment, and half the patients were treated with concomitant GCs, which may have affected the incidence of AEs. The Pharmachild registry included both prospective and retrospective data. The retrospective part consisted of a medical chart review, and as reported previously by Swart et al,[29] no significant differences were evident in the prospective and retrospective counterparts of the Pharmachild population.

In conclusion, the results of the present study confirm the long-term safety profile of anakinra in patients with sJIA and show that the overall incidence of AEs and SAEs declines over time. The study also highlights there is no evidence that long-term treatment with anakinra increases the risk for MAS.

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ONLINE SUPPLEMENT

Supplementary material accompanies the online version of this article.

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