Anakinra in patients with systemic juvenile idiopathic arthritis: long-term safety from the Pharmachild registry

Gabriella Giancane, MD, PhD^{1, 2}, Riccardo Papa, MD¹, Sebastiaan Vastert, MD³, Francesca Bagnasco, MSc⁴, Joost F Swart, MD⁵, Pierre Quartier, MD⁶, Jordi Anton, MD⁷, Sylvia Kamphuis, MD⁸, Helga Sanner, MD⁹, Mia Glerup, MD¹⁰, Fabrizio De Benedetti, MD¹¹, Elena Tsitsami, MD¹², Agustin Remesal, MD¹³, Estefania Moreno, MD¹⁴, Jaime De Inocencio, MD¹⁵, Charlotte Myrup, MD¹⁶, Chiara Pallotti, MA¹, Isabelle Koné-Paut, MD¹⁷, Karin Franck-Larsson, MD, PhD¹⁸, Håkan Malmström, PhD¹⁸, Susanna Cederholm, MSc Pharm¹⁸, Angela Pistorio, MD⁴, Nico Wulffraat, Prof.⁵, Nicolino Ruperto, MD MPH¹⁹ for the Paediatric Rheumatology International Trials Organisation (PRINTO).

¹ Clinica Pediatrica e Reumatologia, IRCCS Istituto Giannina Gaslini, Genoa, Italy

² Dipartimento di Neuroscienze, Riabilitazione, Oftalmologia, Genetica e Scienze Materno-Infantili (DiNOGMI), Università degli Studi di Genova, Genoa, Italy

³ Department of Pediatric Immunology and Rheumatology, room number KC 03.063, Wilhelmina Kinderziekenhuis, Utrecht, Netherlands.

⁴ Servizio di Epidemiologia e Biostatistica, IRCCS Istituto Giannina Gaslini, Genoa, Italy

⁵ Department of Pediatric Immunology and Rheumatology, Wilhelmina Children's Hospital, Utrecht, The Netherlands

⁶ Université de Paris, Institut IMAGINE, Centre de référence national pour les Rhumatismes inflammatoires et les maladies Auto-Immunes Systémiques rares de l'Enfant (RAISE), Unité d'Immunologie, Hématologie et Rhumatologie Pédiatrique, Hôpital Necker-Enfants Malades, Assistance Publique Hôpitaux de Paris, Paris, France

⁷ Division of Pediatric Rheumatology, Hospital Sant Joan de Déu, Universitat de Barcelona, Esplugues de Llobregat (Barcelona), Spain

⁸ Department of Paediatric Rheumatology/Department of Rheumatology, Sophia Children's Hospital, Erasmus University Medical Centre, Rotterdam, Netherlands

⁹ Dept. of Rheumatology - Norwegian National Advisory Unit on Rheumatic Diseases in Children and Adolescents, Oslo University Hospital, Oslo, Norway

¹⁰ Pediatric rheumatology unit, Aarhus University Hospital, Aarhus, Denmark

¹¹ Division of Rheumatology, IRCCS Ospedale Pediatrico Bambino Gesù, Rome, Italy

¹² First Department of Pediatrics, Aghia Sophia Childrens Hospital, University of Athens Medical School, Athens, Greece

¹³ Rheumatology Unit, University Hospital La Paz, Madrid, Spain

¹⁴ Rheumatology Unit, University Hospital Valle de Hebron, Barcelona, Spain

¹⁵ Department of Pediatric Rheumatology, 12 de Octubre University Hospital, Madrid, Spain

¹⁶ Pediatric rheumatology unit 4272, Rigshospitalet, Copenhagen, Denmark

¹⁷ Department of Pediatric Rheumatology, National Referral Centre of Auto-Inflammatory Diseases and inflammatory amyloidosis, CEREMAIA, CHU de Bicêtre, APHP, University of Paris Sud Saclay, le Kremlin Bicêtre, France

¹⁸ Sobi, Stockholm, Sweden

¹⁹ Clinica Pediatrica e Reumatologia, IRCCS Istituto Giannina Gaslini, PRINTO, Genoa, Italy

Key Indexing Terms:

Systemic Arthritis, Juvenile; Anakinra; Adverse Effects, Long Term.

Funding

Pharmachild was supported by a grant from the European Union (grant 260353) and by funding from the IRCCS G. Gaslini.

This study was supported by Swedish Orphan Biovitrum (Sobi) AB (publ). Analysis and reporting were performed independently by the Paediatric Rheumatology International Trials Organisation (PRINTO, www.printo.it) with final report shared with company and regulatory authorities.

Conflicts of interest

Dr. Giancane has nothing to disclose.

Dr. Papa has nothing to disclose.

Dr. Vastert reports grants from Swedish Orphan Biovitrum, personal fees (consultancy, < 2500 euro) from Swedish Orphan Biovitrum during the conduct of the study.

Dr. Bagnasco has nothing to disclose.

Dr. Swart reports grants from Swedish Orphan Biovitrum during the conduct of the study.

Dr. Quartier reports personal fees, consultancies and participation to symposium/meetings and support for the participation of team members to congresses from Swedish Orphan Biovitrum, Novartis; personal fees, consultancies and participation to symposium/meetings and for my participation to congresses from BMS, Ely Lilly, ABBVIE, Novimmune; personal fees for participation to 2 data safety monitoring boards SANOFI.

Dr. Antón reports grants, personal fees and non-financial support from Swedish Orphan Biovitrum, grants, personal fees and non-financial support from Novartis, grants, personal fees and non-financial support from Roche, grants from Sanofi, grants from Lilly.

Dr. Kamphuis has nothing to disclose.

Dr. Sanner has nothing to disclose.

Dr. Glerup has nothing to disclose.

Dr. De Benedetti reports grants from Swedish Orphan Biovitrum, Novartis, Sanofi, Roche, Novimmune.

Dr. Tsitsami reports personal fees from Novartis and Abbvie.

Dr. Remesal has nothing to disclose.

Dr. Moreno has nothing to disclose.

Dr. De Inocencio has nothing to disclose.

Dr. Myrup has nothing to disclose.

Dr. Pallotti has nothing to disclose.

Dr. Kone Paut reports personal fees from Novartis, Abbvie, Swedish Orphan Biovitrum, Chugai, Novimmune, Pfizer.

Dr. Franck-Larsson was at the time of the study employed by Swedish Orphan Biovitrum, and has nothing further to disclose.

Long-term safety of anakinra

Dr. Malmström is employed by Swedish Orphan Biovitrum.

Dr. Cederholm is employed by Swedish Orphan Biovitrum and holder of Swedish Orphan Biovitrum shares.

Dr. Pistorio has nothing to disclose.

Dr. Wulffraat reports grants from Swedish Orphan Biovitrum during the conduct of the study.

Dr. Ruperto reports personal fees from AstraZeneca - Medimmune, Ablynx, Biogen, Boehringer, Takeda, EMD Serono, Merck, R-Pharma, Sanofi, Servier, Sinergie, Aurinia, Centrical Global, Domain Therapeutics, Idorsia; grants and personal fees from Hoffman-La Roche, Pfizer, Novartis, Eli-Lilly, GSK, Janssen, Swedish Orphan Biovitrum, Bristol Myers and Squibb outside the submitted work

Clinicaltrials.gov: NCT01399281; NCT03932344

Corresponding Author:

Gabriella Giancane, MD, PhD

IRCCS Istituto Giannina Gaslini

Clinica Pediatrica e Reumatologia, Università degli Studi di Genova

Via G. Gaslini 5, 16147 Genoa, Italy

Telephone: +39-010-5636 2843

Fax: +39-010-4211018

Email: gabriellagiancane@gaslini.org

www.printo.it

Word count: 3499

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 (NCT03932344) before 30 September 2018 and treated with anakinra were analyzed. The study endpoints were the occurrence of non-serious adverse events (AEs) of at least moderate severity and serious AEs (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 continuously treated with anakinra for at least 12, 18 and 24 months (set-12, -18, -24, respectively).

Results. 306 patients were enrolled. 46%, 34% and 28% of them had been treated for at least 12, 18 and 24 months, respectively. 201 AEs, mostly represented by infections, were reported for 509.3 patient-years (py) with an overall incidence rate (IR) of 39.5/100 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, followed by decreasing IR in the long-term treatment sets. Treatment discontinuation occurred in 76% of patients, most in the first 6 months, due to 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 SJIA patients and show a decreasing overall incidence of AEs over time.

Introduction

Systemic juvenile idiopathic arthritis (SJIA) is characterized by high spiking intermittent fever, chronic arthritis/arthralgias, maculopapular rash, hepatosplenomegaly, lymphadenopathy, serositis, and marked increase in acute-phase reactants.(1-4) SJIA may be associated with complications, such as the potentially fatal macrophage activation syndrome (MAS) and the rare AA amyloidosis.(5-8) Laboratory and clinical observations suggest an inappropriate activation of the innate immunity, with hypersecretion of proinflammatory cytokines, such as interleukin-1 (IL-1) and 6 (IL-6).(3) Anakinra is a recombinant human IL-1 receptor antagonist that blocks the biological activity of both IL-1 α and IL-1 β 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 EU approved indications Rheumatoid Arthritis, Still's disease, SJIA and different forms of Cryopyrin-Associated Periodic Syndrome as well as Familial Mediterranean Fever, and its safety profile is now well established.(9, 10)

Beside consolidated data on the efficacy of anakinra in treating glucocorticoid-dependent patients with SJIA(11, 12) and data on anakinra as first-line monotherapy in new-onset SJIA patients,(13-15) little evidence has been collected in the last years on long-term safety in large cohorts of SJIA patients treated with anakinra.(14-19) 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.(20-22) Phase III clinical trials of canakinumab (23) and tocilizumab in SJIA (24-26) clearly demonstrated that these treatments do not provide protection against MAS and suggest that IL-1 and IL-6 might 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 SJIA patients, especially in the long-term.(27)

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

Materials and Methods

Study design

The study was a non-interventional, post-authorization safety study (PASS) and the protocol was developed in accordance with the EMA guidance for the format and content of the protocol of a non-interventional PASS.(28) The study was conducted by the Paediatric Rheumatology International Trials Organisation (PRINTO) using the ENCePP certified pharmacovigilance registry named Pharmachild (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 conventional and biologic disease modifying anti-rheumatic drugs (sDMARDs and bDMARDs). 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 ILAR classification criteria,(31, 32) enrolled in the Pharmachild registry before 30 September 2018 and treated with anakinra at any point in time after SJIA diagnosis were included in the analysis.

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

Study endpoints

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

Data collection in Pharmachild

Both retrospective safety and drug exposure data since disease onset collected prior to the enrollment in the registry, and subsequent prospective data were used in this study. All AEs of moderate/severe/very severe intensity and serious AEs are reported in Pharmachild; mild intensity is reported only for those AEs which do not resolve and require a follow-up report. In the present study, mild intensity was also reported for AEs of such intensity determining a reason for discontinuation. AEs are reported in Pharmachild irrespective 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 five-level structure depending on the specificity required (from the most specific Lowest Level Term (LLT) and Preferred Term (PT) to the least, System Organ Class (SOC)). According to this terminology, the PT Haemophagocytic lymphohistiocytosis (HLH) was used in this study as synonymous interchangeably of MAS.

Statistical methods

Data were analyzed overall, including all patients with SJIA and treated at any point in time with anakinra in the registry, and by three defined populations, the long-term treatment set -12, -18, -24, including patients with 12-18-24 months or more of continuous anakinra treatment. Continuous treatment was defined as ongoing treatment when no more than 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, standard deviation (SD), median, minimum and maximum, 1st and 3rd quartiles. The IR per 100 patient-years was calculated by taking the number of the specific incident event and dividing by the sum of patient years under risk, i.e., exposed to anakinra, multiplied by 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% Confidence Interval (CI) was estimated using the Poisson estimator with a cluster-robust estimate of variance to control for both overdispersion and intra-cluster correlation. AE specific IRs were calculated overall for the complete study period and by 6-month calendar time windows (1-6 months, 7-12 months, 13-18 months, 19-24 months and >24 months). 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 two days, which accounted for approximately five 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, i.e before, and when anakinra treatment was paused or stopped were not counted.

In addition, the IR of MAS was analyzed with respect to 1st occurrence and recurrence, respectively. 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, i.e., no imputation of missing data was performed. Statistical analyses were performed using SAS software Version 9.3 or later (SAS Institute Inc, Cary, North Carolina, United States).

Analysis and reporting were done independently by PRINTO with final report shared with the marketing authorization holder (MAH) and regulatory authorities.

Results

Population

Out of 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 them, 141 (46.1%), 104 (34.0%), and 86 (28.1%) patients were continuously

treated with anakinra for at least 12, 18, and 24 months, respectively. (Figure 1 and Table 1)

Prospective data were collected for 174 (56.9%) patients. Of the 32 countries participating in the Pharmachild JIA registry, 38 centres from 15 countries (37.5%) reported data on anakinra treatment for SJIA: 97.7% of the patients were from Europe, 2.3% from Asia. Caucasian ethnicity was most prevalent (70.6%). (Table 1) Anakinra had been given as monotherapy or in combination with other glucocorticoids/DMARDs, as per the local standard of care. (Supplementary table S1)

Both genders 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)

Out of 306 patients, 94 (30.7%) received anakinra as first-line treatment and among the remaining 212 patients, 78 (36.8%) were treated with various combinations of DMARDs and glucocorticoids before starting anakinra and continued with those treatments concomitantly with the IL-1 inhibitor. 134 (63.2%) patients stopped other treatments before starting anakinra. At start of anakinra treatment, 193 (63.1%) patients received at least 1 concomitant SJIA related medication other than NSAIDs, mostly glucocorticoids (161 patients, 52.6%). (Supplementary table S1)

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 (9.1 years). In 92/306 (30.1%) of the patients anakinra treatment was ongoing at the last report in the registry.

Adverse events

A total of 201 AEs was 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 and supplementary table S2) The group of AEs that was the most frequently reported was “Infections and Infestations” (52 AEs, IR=10.2 per 100 py), followed by

“Skin and subcutaneous tissue disorders” (25 AEs, IR=4.9 per100 py), “General disorders and administration site conditions” (23 AEs, IR=4.5 per 100 py), and “Gastrointestinal disorders” (18 AEs, IR=3.5 per 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 (ISR) were the most common PTs both among “General disorders and administration site conditions” (16 occurrences) and “Injury, poisoning, and procedural complications” (10 occurrences). Among “Gastrointestinal disorders”, constipation (6 occurrences) and abdominal pain (4 occurrences) were the most frequently reported.

By single PTs, MAS, in SOC “Immune system disorders”, was the most frequent event with 12 occurrences and an IR of 2.4 per 100 py (Table 2) followed by injection-related reactions (2.0/100py), ISR (1.6/100py), rash (1.6/100py), and constipation (1.2/100py). The IRs for the remaining AEs were below 1 per 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 ISR occurred early after start of anakinra. Three infusion related reactions were connected to tocilizumab, which was administered in close connection to anakinra treatment.

Serious adverse events

56 of the 201 AEs were serious. (Table 3 and supplementary table S3) Overall, the IR of the SAEs was of 11.0 per 100 py (95% CI 7.9-15.2), with events within SOC “Infections and Infestations” being the most reported (a total of 13 SAEs, IR=2.6 per 100 py), followed by “Immune system disorders” (a total of 11 SAEs, IR=2.2 per 100 py, all describing MAS). “Injury, poisoning and

procedural complications” covered 9 events, with an IR of 1.8 per 100 py. The remaining SAEs had an IR below 1.0 per 100 py.

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

By single PTs, MAS was the most frequently reported serious adverse event (n=11, IR=2.2 per 100 py) (Table 3), primarily reported in the first 6 months of anakinra (IR=6.0/100 py), followed by injection-related reactions (n=6, IR=1.2 per 100 py). All remaining events had an IR below 1 event per 100 py. Among these, one patient reported an event of interstitial lung disease after receiving treatment with anakinra for more than 24 months (supplementary table S2). No 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 glucocorticoids and in one case combined with sDMARDs. Death reasons were sepsis, multi-organ failure and sudden death, respectively.

Analysis of AE and SAE 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, 13.5 per 100 py for AEs, of which the IR of SAEs were 5.1, 3.8, 2.9 per 100 py. In the 86 patients treated continuously for more than 24 months, the IR for AEs per 100 py in the first 6 months of treatment was 21.1 and after 24 months the IR was 13.1 per 100 py. Among AEs, the SOC “Infections and infestations” was the most frequent in the different treatment sets. (Please refer to complete report (33))

In the SAE subset, the SOC “Infections and infestations” and “Injury, poisoning and procedural complications” were equally represented with an IR of 1.2 per 100 py in the long-term treatment set-12, while the SOC “Immune system disorders”, where MAS is included, and “Injury, poisoning and procedural complications” were equally represented with an incidence of 0.8 per 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 non-serious AE) of MAS during anakinra treatment. (Table 4) In one patient MAS was considered non-serious by the reporting physician; there was an increase in ferritin levels (67390 mg/ml), and clinical and lab 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 per 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 (95% CI) = 2.1 per 100 py (1.1-3.9)) compared to those with MAS before anakinra start (IR (95% CI) = 5.6 per 100 py (0.7-42.9)). (Table 4) The average time from start of anakinra to first MAS occurrence was 9 months. 36.4% of MAS events 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 S6)

After stopping anakinra, MAS was reported in 8 patients. The earliest recurrence was in the time window 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 S7)

Reasons for anakinra treatment discontinuation

233 out of 306 patients (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 due to events of moderate intensity, mild in the remaining cases. Intolerance was given as the reason for discontinuation in 5.0% of the cases. Discontinuations due to 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 coming from different countries, provides a safety real-world overview, which could be generalized to the wider general population of patients with SJIA treated with anakinra.

It has been suggested that already after a few months of anakinra treatment in new onset SJIA patients, it is possible to achieve excellent responses and after 1 year of therapy 39-76% of the patients achieve clinical remission on therapy, with a glucocorticoid sparing effect.(38) Patients with persistently active SJIA may need continuous treatment with anakinra for one year or more. 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 at least 1 year, and 28% for more than 2 years.

Our results showed that the safety of anakinra after long-term administration is in line with the well-established profile of the drug.(12) as also showed by previous reports. Moreover, data from

the prospective, observational BiKeR registry demonstrated fewer AEs with anakinra compared to other biologic treatments.(39)

Additionally, in this study we showed 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 rheumatoid arthritis treated with TNF inhibitors (40, 41), and could possibly be explained by immune system dysregulation when adapting to the new immunomodulatory drug. Furthermore, higher doses of glucocorticoids, often given at start of SJIA treatment, may contribute to more AEs reported early in the patient history. In addition, ISR 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 ISR, confirming data from previous publications.(14, 15) ISR are a common adverse reaction to anakinra; however, it was not the most commonly reported AE in this study, maybe due to the fact that mild AEs are not reported in Pharmachild. Among the SAEs, infections and MAS were most frequently reported. In the last decade, rare lung disorders, i.e. pulmonary arterial hypertension, interstitial lung disease, and alveolar proteinosis, have been reported in children with Still's disease,(42-45) often associated with MAS, sometimes with fatal outcome. It has been discussed whether immunosuppressive therapy including IL-1 inhibitors can contribute to the development of these disorders. However, in our study, only one patient presented with a pulmonary SAE, an unspecified interstitial lung disease that occurred after more than 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 due to sepsis, multi-organ 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 due to 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 main 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 due to 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 adverse events. In addition, most of the patients received at least 1 concomitant SJIA-related medication at start of anakinra treatment, and half of the patients were treated with concomitant glucocorticoids, 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 SJIA patients and show that the overall incidence of AEs and SAEs declines over time. The study also highlights that there is no evidence that long-term treatment with anakinra increases the risk for MAS.

Acknowledgments

We thank all participating sites who contributed to the collection of data and for Hospital Necker in Paris: Ms Ngoc-Bao Duong, Dr Brigitte Bader-Meunier, Dr Florence Aeschlimann, Dr Isabelle Melki, Dr Carine Wouters, Dr Chantal Job-Deslandre and Dr Caroline Freychet.

References

1. Martini A, Ravelli A, Di Fuccia G, Rosti V, Cazzola M, Barosi G. Intravenous iron therapy for severe anaemia in systemic-onset juvenile chronic arthritis. *Lancet*. 1994; 344: 1052-4.
2. Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet*. 2007; 369: 767-78.
3. Prakken B, Albani S, Martini A. Juvenile idiopathic arthritis. *Lancet*. 2011; 377: 2138-49.
4. Nirmala N, Brachat A, Feist E, Blank N, Specker C, Witt M, et al. Gene-expression analysis of adult-onset still's disease and systemic juvenile idiopathic arthritis is consistent with a continuum of a single disease entity. *Pediatr Rheumatol Online J*. 2015; 13: 50,015-0047-3.
5. De Benedetti F, Alonzi T, Moretta A, Lazzaro D, Costa P, Poli V, et al. Interleukin 6 causes growth impairment in transgenic mice through a decrease in insulin-like growth factor-I. A model for stunted growth in children with chronic inflammation. *J Clin Invest*. 1997; 99: 643-50.
6. Packham JC, Hall MA, Pimm TJ. Long-term follow-up of 246 adults with juvenile idiopathic arthritis: Predictive factors for mood and pain. *Rheumatology (Oxford)*. 2002; 41: 1444-9.
7. Ravelli A, Magni-Manzoni S, Pistorio A, Besana C, Foti T, Ruperto N, et al. Preliminary diagnostic guidelines for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis. *J Pediatr*. 2005; 146: 598-604.
8. Ravelli A, Minoia F, Davi S, Horne A, Bovis F, Pistorio A, et al. 2016 classification criteria for macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: A european league against rheumatism/american college of rheumatology/paediatric rheumatology international trials organisation collaborative initiative. *Ann Rheum Dis*. 2016; 75: 481-9.

9. Kineret. summary of product characteristics [homepage on the Internet]. . January 2021. Available from: https://www.ema.europa.eu/en/documents/product-information/kineret-epar-product-information_en.pdf.
10. Cavalli G, Colafrancesco S, Emmi G, Imazio M, Lopalco G, Maggio MC, et al. Interleukin 1alpha: A comprehensive review on the role of IL-1alpha in the pathogenesis and targeted treatment of autoimmune and inflammatory diseases. *Autoimmun Rev*. 2021: 102763.
11. Ilowite N, Porras O, Reiff A, Rudge S, Punaro M, Martin A, et al. Anakinra in the treatment of polyarticular-course juvenile rheumatoid arthritis: Safety and preliminary efficacy results of a randomized multicenter study. *Clin Rheumatol*. 2009; 28: 129-37.
12. Quartier P, Allantaz F, Cimaz R, Pillet P, Messiaen C, Bardin C, et al. A multicentre, randomised, double-blind, placebo-controlled trial with the interleukin-1 receptor antagonist anakinra in patients with systemic-onset juvenile idiopathic arthritis (ANAJIS trial). *Ann Rheum Dis*. 2011; 70: 747-54.
13. Nigrovic PA, Mannion M, Prince FH, Zeft A, Rabinovich CE, van Rossum MA, et al. Anakinra as first-line disease-modifying therapy in systemic juvenile idiopathic arthritis: Report of forty-six patients from an international multicenter series. *Arthritis Rheum*. 2011; 63: 545-55.
14. Vastert SJ, de Jager W, Noordman BJ, Holzinger D, Kuis W, Prakken BJ, et al. Effectiveness of first-line treatment with recombinant interleukin-1 receptor antagonist in steroid-naive patients with new-onset systemic juvenile idiopathic arthritis: Results of a prospective cohort study. *Arthritis Rheumatol*. 2014; 66: 1034-43.
15. Ter Haar NM, van Dijkhuizen EHP, Swart JF, van Royen-Kerkhof A, El Idrissi A, Leek AP, et al. Treatment to target using recombinant interleukin-1 receptor antagonist as first-line monotherapy in new-onset systemic juvenile idiopathic arthritis: Results from a five-year follow-up study. *Arthritis Rheumatol*. 2019; 71: 1163-73.

16. Ruperto N, Martini A. Current and future perspectives in the management of juvenile idiopathic arthritis. *Lancet Child Adolesc Health*. 2018; 2: 360-70.
17. Vitale A, Cavalli G, Colafrancesco S, Priori R, Valesini G, Argolini LM, et al. Long-term retention rate of anakinra in adult onset still's disease and predictive factors for treatment response. *Front Pharmacol*. 2019; 10: 296.
18. Vastert SJ, Jamilloux Y, Quartier P, Ohlman S, Osterling Koskinen L, Kullenberg T, et al. Anakinra in children and adults with still's disease. *Rheumatology (Oxford)*. 2019; 58: vi9-vi22.
19. Consolaro A, Giancane G, Alongi A, van Dijkhuizen EHP, Aggarwal A, Al-Mayouf SM, et al. Phenotypic variability and disparities in treatment and outcomes of childhood arthritis throughout the world: An observational cohort study. *Lancet Child Adolesc Health*. 2019; 3: 255-63.
20. Kelly A, Ramanan AV. A case of macrophage activation syndrome successfully treated with anakinra. *Nat Clin Pract Rheumatol*. 2008; 4: 615-20.
21. Miettunen PM, Narendran A, Jayanthan A, Behrens EM, Cron RQ. Successful treatment of severe paediatric rheumatic disease-associated macrophage activation syndrome with interleukin-1 inhibition following conventional immunosuppressive therapy: Case series with 12 patients. *Rheumatology (Oxford)*. 2011; 50: 417-9.
22. Schulert GS, Minoia F, Bohnsack J, Cron RQ, Hashad S, KonE-Paut I, et al. Effect of biologic therapy on clinical and laboratory features of macrophage activation syndrome associated with systemic juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)*. 2018; 70: 409-19.
23. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat NM, Horneff G, et al. Canakinumab in patients with systemic juvenile idiopathic arthritis and active systemic features: Results from the 5-year long-term extension of the phase III pivotal trials. *Ann Rheum Dis*. 2018; 77: 1710-9.

24. Shimizu M, Nakagishi Y, Kasai K, Yamasaki Y, Miyoshi M, Takei S, et al. Tocilizumab masks the clinical symptoms of systemic juvenile idiopathic arthritis-associated macrophage activation syndrome: The diagnostic significance of interleukin-18 and interleukin-6. *Cytokine*. 2012; 58: 287-94.
25. Ravelli A, Schneider R, Weitzman S, Devlin C, Daimaru K, Yokota S, et al. Macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis treated with tocilizumab. *Arthritis and Rheumatology*, Special Issue: Abstracts from the 2014 Pediatric Rheumatology Symposium. 2014;66(S3):S83-4.
26. Yokota S, Itoh Y, Morio T, Sumitomo N, Daimaru K, Minota S. Macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis under treatment with tocilizumab. *J Rheumatol*. 2015; 42: 712-22.
27. Minoia F, Davi S, Horne A, Demirkaya E, Bovis F, Li C, et al. Clinical features, treatment, and outcome of macrophage activation syndrome complicating systemic juvenile idiopathic arthritis: A multinational, multicenter study of 362 patients. *Arthritis Rheumatol*. 2014; 66: 3160-9.
28. Guidance for the Format and Content of the Protocol of Non-Interventional Post-Authorisation Safety Studies, current Version Dated 26 September 2012. , (2012).
29. Swart J, Giancane G, Horneff G, Magnusson B, Hofer M, Alexeeva capital IE,Cyrillic, et al. Pharmacovigilance in juvenile idiopathic arthritis patients treated with biologic or synthetic drugs: Combined data of more than 15,000 patients from pharmachild and national registries. *Arthritis Res Ther*. 2018; 20: 285,018-1780-z.
30. Giancane G, Swart JF, Castagnola E, Groll AH, Horneff G, Huppertz HI, et al. Opportunistic infections in immunosuppressed patients with juvenile idiopathic arthritis: Analysis by the pharmachild safety adjudication committee. *Arthritis Res Ther*. 2020; 22: 71,020-02167-2.

31. Petty RE, Southwood TR, Baum J, Bhattay E, Glass DN, Manners P, et al. Revision of the proposed classification criteria for juvenile idiopathic arthritis: Durban, 1997. *J Rheumatol.* 1998; 25: 1991-4.

32. Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, et al. International league of associations for rheumatology classification of juvenile idiopathic arthritis: Second revision, edmonton, 2001. *J Rheumatol.* 2004; 31: 390-2.

33. A non-interventional, post-authorization safety study (PASS) to evaluate long-term safety of anakinra (kineret®) in patients with systemic juvenile idiopathic arthritis.[homepage on the Internet]. . 2019.

Available from:

<http://www.encepp.eu/encepp/openAttachment/studyResult/33061;jsessionid=TNKRRG19iduYjR8qtoVOYmIs9LvZ70dvLAccunMWOXvQVvpBEMru!-1919965229>.

34. Pardeo M, Pires Marafon D, Insalaco A, Bracaglia C, Nicolai R, Messia V, et al. Anakinra in systemic juvenile idiopathic arthritis: A single-center experience. *J Rheumatol.* 2015; 42: 1523-7.

35. Saccomanno B, Tibaldi J, Minoia F, Bagnasco F, Pistorio A, Guariento A, et al. Predictors of effectiveness of anakinra in systemic juvenile idiopathic arthritis. *J Rheumatol.* 2019; 46: 416-21.

36. Tibaldi J, Saccomanno B, Caorsi R, Ravelli A. Dr. tibaldi, et al reply. *J Rheumatol.* 2019; 46: 1424.

37. Pardeo M, Rossi MN, Pires Marafon D, Sacco E, Bracaglia C, Passarelli C, et al. Early treatment and il1rn snps affect response to anakinra in systemic juvenile idiopathic arthritis. *Arthritis & Rheumatology.* 2020; n/a.

38. Kearsley-Fleet L, Beresford MW, Davies R, De Cock D, Baildam E, Foster HE, et al. Short-term outcomes in patients with systemic juvenile idiopathic arthritis treated with either tocilizumab or anakinra. *Rheumatology (Oxford).* 2019; 58: 94-102.

39. Horneff G, Schulz AC, Klotsche J, Hospach A, Minden K, Foeldvari I, et al. Experience with etanercept, tocilizumab and interleukin-1 inhibitors in systemic onset juvenile idiopathic arthritis patients from the BIKER registry. *Arthritis Res Ther*. 2017; 19: 256,017-1462-2.
40. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Watson KD, Lunt M, et al. The risk of serious infections in patients receiving anakinra for rheumatoid arthritis: Results from the british society for rheumatology biologics register. *Rheumatology (Oxford)*. 2011; 50: 1341-2.
41. Galloway JB, Hyrich KL, Mercer LK, Dixon WG, Ustianowski AP, Helbert M, et al. Risk of septic arthritis in patients with rheumatoid arthritis and the effect of anti-TNF therapy: Results from the british society for rheumatology biologics register. *Ann Rheum Dis*. 2011; 70: 1810-4.
42. Kimura Y, Weiss JE, Haroldson KL, Lee T, Punaro M, Oliveira S, et al. Pulmonary hypertension and other potentially fatal pulmonary complications in systemic juvenile idiopathic arthritis. *Arthritis Care Res (Hoboken)*. 2013; 65: 745-52.
43. Saper VE, Chen G, Deutsch GH, Guillerman RP, Birgmeier J, Jagadeesh K, et al. Emergent high fatality lung disease in systemic juvenile arthritis. *Ann Rheum Dis*. 2019.
44. Schulert GS, Fall N, Harley JB, Shen N, Lovell DJ, Thornton S, et al. Monocyte MicroRNA expression in active systemic juvenile idiopathic arthritis implicates MicroRNA-125a-5p in polarized monocyte phenotypes. *Arthritis Rheumatol*. 2016; 68: 2300-13.
45. Nigrovic PA. Storm warning: Lung disease in systemic juvenile idiopathic arthritis. *Arthritis Rheumatol*. 2019; 71: 1773-5.
46. Ruperto N, Brunner HI, Quartier P, Constantin T, Wulffraat N, Horneff G, et al. Two randomized trials of canakinumab in systemic juvenile idiopathic arthritis. *N Engl J Med*. 2012; 367: 2396-406.

47. Grom AA, Ilowite NT, Pascual V, Brunner HI, Martini A, Lovell D, et al. Rate and clinical presentation of macrophage activation syndrome in patients with systemic juvenile idiopathic arthritis treated with canakinumab. *Arthritis Rheumatol.* 2016; 68: 218-28.
48. Sawhney S, Woo P, Murray KJ. Macrophage activation syndrome: A potentially fatal complication of rheumatic disorders. *Arch Dis Child.* 2001; 85: 421-6.
49. Brachat AH, Grom AA, Wulffraat N, Brunner HI, Quartier P, Brik R, et al. Early changes in gene expression and inflammatory proteins in systemic juvenile idiopathic arthritis patients on canakinumab therapy. *Arthritis Res Ther.* 2017; 19: 13,016-1212-x.

FIGURE LEGEND

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

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

338x254mm (72 x 72 DPI)

Table 1. Demographics and baseline characteristics.

	Complete set	Long-term treatment set-12	Long-term treatment set-18	Long-term treatment 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, n (%)				
Infant (< 2 yrs)	22 (7.2)	7 (5.0)	2 (1.9)	1 (1.2)
Child (2 yrs - <12 yrs)	210 (68.6)	100 (70.9)	81 (77.9)	68 (79.1)
Adolescent (12 yrs - <18 yrs)	69 (22.6)	31 (22.0)	19 (18.3)	16 (18.6)
Adult (≥ 18 yrs)	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 (yrs) ^b , 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)
Patients with History of MAS, n (%)	10 (3.3)	6 (4.2)	5 (4.8)	4 (4.6)
Origin, n (%)				
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, n (%)				
Caucasian	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)

Abbreviations: yrs, years; n, number of patients;; IQR, inter quartile range.

^aAge at baseline for the complete set; age at baseline or at index date for the long-term treatment set 12,18 and 24. ^bFirst visit in the clinical center.

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

	Time window ^a		1-6 months		7-12 months		13-18 months		19-24 months		>24 months		Overall
	N		306		194		144		106		104		306
	Patient-time		117.3		80.2		58.1		47.0		206.7		509.3
	(years) ^b												
SOC	PT	n ^c	Rate (95% CI) ^d	n ^c	Rate (95% CI) ^d	n ^c	Rate (95% CI) ^d	n ^c	Rate (95% CI) ^d	n ^c	Rate (95% CI) ^d	n ^c	Rate (95% CI) ^d
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)

Events with a frequency >10 by overall SOC and >3 by overall PT are presented in this table. For the complete table, please refer to the supplementary material.

Abbreviations: AEs, adverse events; SOC, system organ class; PT, preferred term, MedDRA version 21.1; N, number of patients ever treated with anakinra during the time window irrespective of the length of any unexposed periods; 95% CI, 95% Confidence Interval; HLH, haemophagocytic lymphohistiocytosis.

^a in relation to baseline (start of anakinra treatment)

^b only time (py) while anakinra treatment was ongoing + 2 days after discontinuation was counted

^c number of events. Only AEs occurring during anakinra exposed periods + 2 days after discontinuation were counted

^d incidence rate per 100 patient years; number of events/ Σ patient time

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

	Time window ^a	1-6 months		7-12 months		13-18 months		19-24 months		>24 months		Overall	
	N	306		194		144		106		104		306	
	Patient-time (years) ^b	117.3		80.2		58.1		47.0		206.7		509.3	
SOC	PT	n ^c	Rate (95% CI) ^d	n ^c	Rate (95% CI) ^d	n ^c	Rate (95% CI) ^d	n ^c	Rate (95% CI) ^d	n ^c	Rate (95% CI) ^d	n ^c	Rate (95% CI) ^d
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)

Events with a frequency >1 by overall SOC and >1 by overall PT are presented in this table. For the complete table, please refer to the supplementary material.

Abbreviations: SAE, serious adverse event; SOC, system organ class; PT, preferred term, MedDRA version 21.1; N, number of patients ever treated with anakinra during the time window irrespective of the length of any unexposed periods; 95% CI, 95% Confidence Interval; HLH, haemophagocytic lymphohistiocytosis

^a in relation to baseline (start of anakinra treatment).

^b only time while anakinra treatment was ongoing + 2 days after discontinuation was counted

^c number of events. Only SAEs occurring during anakinra exposed periods + 2 days after discontinuation were counted

^d incidence rate per 100 patient years; number of events/ Σ patient time.

Accepted Article

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

History of MAS at baseline	Patients (N)		10	
	MAS event	n ^a	Patient-time (years) ^b	Rate (95% CI) ^c
	1 st occurrence ^d	1	18.0	5.6 (0.7-42.9)
	2 nd occurrence	1	1.0	100
No History of MAS recorded at baseline	Patients (N)		296	
	MAS event	n ^a	Patient-time (years) ^b	Rate (95% CI) ^c
	1 st occurrence ^d	10	479.5	2.1 (1.1-3.9)
	2 nd occurrence	0	5.2	0
Complete study population	Patients (N)		306	
	MAS event	n ^a	Patient-time (years) ^b	Rate (95% CI) ^c
	1 st occurrence ^d	11	497.5	2.2 (1.2-4.1)
	2 nd occurrence	1	6.2	16.1 (2.6-97.7)

Abbreviations: MAS, macrophage activation syndrome; N, number of patients starting anakinra treatment; 95% CI, 95% Confidence Interval.

^anumber of MAS events. Only MAS occurring during anakinra treatment (including 2 days after discontinuation)

^bonly time during periods with anakinra treatment (including 2 days after discontinuation)

^cincidence rate per 100 patient years; number of events/ Σ patient time;

^dthe 1st occurrence of MAS is defined to occur at or after baseline regardless of whether the patient had a history of MAS or not

Accepted Article

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
N-total number of patients	306	306	194	144	106	104
Total number of reasons for discontinuations	281	109	53	34	13	72
Reasons	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Adverse events 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 adverse events ^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)
Number of patients who discontinued ^c	233 (76.1)	102 (33.3)	50 (25.8)	33 (22.9)	13 (12.3)	61 (58.7)
Number of discontinuations ^d	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 more than 30 days, and multiple reasons for one single discontinuation.

^aIn relation to baseline (start of anakinra treatment).

^bMild adverse events are not reported elsewhere because excluded from the Pharmachild registry

^{c,d}The denominator is the total number of patients (N)