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RESEARCH

Monitoring of Adverse Events and Safety in Autoinflammatory Diseases: Real-Life Data from the Eurofever Registry

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Abstract

Objectives The study is aimed to evaluate the impact of safety events in the Eurofever registry for Autoinflammatory diseases.

Methods This was a retrospective and longitudinal observational multicentre study. Data were retrieved from the international registry Eurofever, starting patients' enrolment since 2009. All moderate, severe, or very severe AEs reported by treating physician in Eurofever were analyzed regardless of a possible suspected causal relationship to any therapies and according to the latest release of the Medical Dictionary for Regulatory Activities.

Results Complete information on safety were available in 2464 patients enrolled in the registry. In 1499 of them retrospective data encompassing the period from disease onset to enrolment were available, whereas 965 consecutive patients entered in the longitudinal part of the study. A total of 479 AEs have been reported in 275 patients. Eighty-two AEs were reported as serious and 99 were drug-related according to the physicians. Infections or infestations (94; 19.6%), gastrointestinal disorders (66; 13.8%), nervous system disorders (41; 8.6%) and systemic disorders or administration site reactions (35; 7.3%) were the most frequent reported events. The highest absolute number of drug-related AEs were related to biologic DMARDs (40/99 reports, 40,4%) and colchicine (31/99 reports, 31.3%).

Conclusions Present study shows the importance of a longitudinal and homogeneous registration of the AEs in rare conditions, with a particular focus on the safety profile of the treatments used in these conditions.

Keywords Autoinflammatory diseases · Safety events · Drug-related adverse events

Introduction

Autoinflammatory diseases (AIDs) represent a large and heterogeneous group of monogenic and multifactorial diseases with recurrent or chronic inflammation secondary to an abnormal innate immune system activation, in absence of infection or autoimmune disorders [1–3].

Most AIDs are related to an over-activation of Inflammasomes (Inflammasomopathies), leading to an exaggerated activation of secretion of some pro-inflammatory cytokines, such as interleukin (IL)-1 and IL-18 [3, 4]. Other diseases are associated to an alteration in the regulation of the activation of the NF-KB pathway (Relopathies). The Interferonopathies are characterized by an uncontrolled signaling via the interferon (IFN) pathway [4]. Clinical presentation of the AIDs is heterogeneous: some of them characterized by episodes of flares followed with fever and variety of clinical signs; other conditions are characterized by a more chronic disease course associated with an involvement of different organs and tissues [4].

Non-steroidal anti-inflammatory drugs (NSAIDS) and systemic glucocorticoids are used as first-line non-specific symptomatic treatments [2, 3]. Colchicine is effective in Familial Mediterranean Fever (FMF) [5]. The identification of the precise molecular mechanisms causative for the hyper-inflammatory in most of the AIDs led to the identification of tailored treatment targeting the most relevant pathogenic consequences of the genetic defect, such as anti-cytokine drugs (mainly anti IL-1, TNF and IL-6) or JAK inhibitors [6].

Extended author information available on the last page of the article

The increasing experience with all these drugs has allowed to estimate the associated risk of developing potential complications and safety issues, associated with treatment. Particular attention was given to the safety data reported across pivotal randomized controlled trials (RCTs) and relevant post-marketing surveillance studies [7–10]. The published literature underlines the risk of bacterial infections, mainly in form of respiratory, urinary tract and skin and skin structure infections. However, little is known about the long-term safety of the current therapies.

The aim of this study was to evaluate the impact of adverse events (AEs) in patients enrolled in the Eurofever international registry for AID, with particular interest of severe adverse events (SAs) and AEs related to the different treatment used in AIDs.

Patients and Methods

The Eurofever registry was promoted in 2008 by the working group for autoinflammatory diseases of the Paediatric Rheumatology European Society (PRES) and was initially supported by the Executive Agency for Health and Consumers (EAHC), with the electronic data capture system developed by PRINTO in November 2009. All patients included in the registry with completed clinical and safety information were eligible to this study. Written informed consent/assent was obtained for each patient during primary enrolling and updated with amendments of the study protocols. The study was approved by the Ethical review board of Regione Liguria and from all participating centres according to local regulations.

Data collection in the Eurofever Registry: from a Retrospective Registry to a Longitudinal Observational Study

The structure of the registry initially included 2 type of retrospective information—one for demographic data and genotype and the other for the collection of the clinical manifestations and the treatments administered from disease onset to the last follow-up. In 2015, the Eurofever registry was amended and transformed in a longitudinal observational study, including a standardised data collection for safety events. For all patients enrolled before 2015, the Investigators had the possibility to update the complete information on safety, retrospectively. For all patients enrolled after 2015 or with follow-up visits after that date, the AE were recorded longitudinally.

After enrolment, centres were invited to collect longitudinal data at least yearly. Electronic data capturing system was used to collect data including clinical, laboratory and other procedural information.

The registry collects information on previous and ongoing treatments used in AIDs. In brief treatment were classified as conventional synthetic disease-modifying antirheumatic drugs (cs-DMARS, 10 compounds) and biologic DMARDs (b-DMARDs, 30 compounds), small molecules (4 compounds), NSAIDs, systemic and intraarticular steroids; bisphosphonates, plasma products, anticoagulants, anti-hypertensive drugs and hematopoetic stem cell transplantation. Additional medications could be included, if required. Drug exposure along with dates of start and discontinuation of the drug, dosages, route of administration, reasons for discontinuation, and possible correlation with the AEs were also collecetd.

All moderate, severe, or very severe AEs reported were analyzed. AEs are reported by treating physician regardless of a possible causal relationship to any therapies and analysed according to the latest release of the Medical Dictionary for Regulatory Activities (MedDRA, Version 23.1). MedDRA classifies 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]). All the AEs of at least moderate/severe/very severe intensity and serious.

AEs, using the MedDRA dictionary, were reported; mild intensity was reported only for those AEs which did not resolve and require a follow-up report.

Some AE were re-classified by consensus by the Eurofever Steering Committee as events of special interest (ESI) that are medical conditions or findings requiring specific medical intervention or monitoring. Among them: serious infections, tuberculosis; gastrointestinal complications (ulcer, perforation, inflammatory bowel disease); hematological manifestations (aplastic anemia, neutropenia, pancytopenia); infusion and injection-related reactions; autoimmune diseases; macrophage activation syndrome; malignancies (lymphomas, leukaemias, haematopoetic neoplasms and other tumors); demyelination and multiple sclerosis; optic neuritis; pregnancy.

The endpoints of the present study were the following: i) to evaluate the impact of AEs in the patients enrolled in Eurofever in which complete standardized information on AEs were available), ii) to compare the accuracy of AEs reporting between patients enrolled in the retrospective part of the registry (retrospective study group) and those enrolled in the observational longitudinal study (longitudinal study group); iii) to analyse the impact of SEA and AE of special interest in different AIDs; iv) to perform a preliminary evaluation of the incidence rate of drug-related AE in the patients enrolled in the longitudinal study.

Statistical Analysis

This study follows the EULAR recommendations for safety data reporting in rheumatology. Categorical data were reported in terms of absolute frequencies and percentages. Continuous data were described in terms median, 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. A patient could contribute with multiple events over the different time periods. 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).

Results

From November 2009 to August 2022 a total of 4552 patients with AIDs were enrolled in the registry, 2464 of them (54%) reported complete safety information according to the latest release of the Medical Dictionary for Regulatory Activities. In 1499 of them only retrospective data (from disease onset to the enrolment in the registry) were available (Table 1). In 965 consecutive patients both retrospective and longitudinal data were available (Fig. 1). The information on patients with complete safety profiles was collected from 36 centres across 12 countries: Austria, Ecuador, Egypt, France, Germany, Greece, Italy, the

Table 1 Demography and epidemiology of patients with completed safety information

	Total number ($n=2464$)	Retrospective study group ($n=1499$)	Longitudinal study group ($n=965$)
Male	1268 (51.5)	757 (50.5)	511 (53)
Age groups, yrs:			
Infant (< 2)	17 (0.7)	11 (0.7)	6 (0.6)
Child (2 to < 12)	1024 (41.6)	614 (41.0)	410 (42.5)
Adolescent (12 to < 18)	654 (26.5)	397 (26.5)	257 (26.6)
Adult (≥ 18)	769 (31.2)	477 (31.8)	292 (30.3)
Time since diagnosis, yrs, median (IQR)	6.98 (5.24 – 12.22)	6.74 (4.51 – 11.25)	5.98 (7.22 – 13.19)
Time from disease onset to first visit, yrs, median (IQR)	9.62 (7.93 – 17.55)	9.6 (6.86 – 16.45)	9.82 (9.44 – 19.25)
Longitudinal follow-up, yrs, median (IQR)	NA	N/A	1.9 (0.6 – 2.55)
Origin:			
Caucasian (European)	2038 (82.7)	1188 (79.2)	850 (88.1)
Caucasian (Middle East)	230 (9.3)	175 (11.7)	55 (5.7)
Other	196 (8.0)	136 (9.1)	60 (6.2)
Diseases			
FMF	882 (35.8)	447 (29.8)	435 (45.1)
TRAPS	98 (4.0)	59 (4.0)	39 (4.0)
NLRP3—AID	91 (3.7)	43 (2.8)	48 (5.0)
MKD	85 (3.4)	52 (3.5)	33 (3.4)
PAPA	48 (1.9)	36 (2.4)	12 (1.2)
DADA2	40 (1.6)	25 (1.7)	15 (1.5)
Schnitzler syndrome	14 (0.5)	8 (0.5)	6 (0.6)
PFAPA	274 (11.1)	232 (15.5)	42 (4.3)
Behcet disease	250 (10.1)	151 (10.1)	99 (10.2)
CRMO	226 (9.2)	101 (6.7)	125 (12.9)
Undefined AID	203 (8.2)	197 (13.1)	6 (0.6)
SURF	197 (8.0)	105 (7.0)	92 (9.5)
Medications used:			
Colchicine	1028 (41.7)	433 (28.9)	595 (61.6)
b-DMARDs	697 (28.3)	310 (20.7)	387 (40.1)
cs-DMARDs	425 (17.2)	273 (18.2)	152 (15.7)
Systemic glucocorticoids	711 (28.8)	404 (26.9)	307 (31.8)

Data are presented as median (1st-3rd quartile) or N (%).

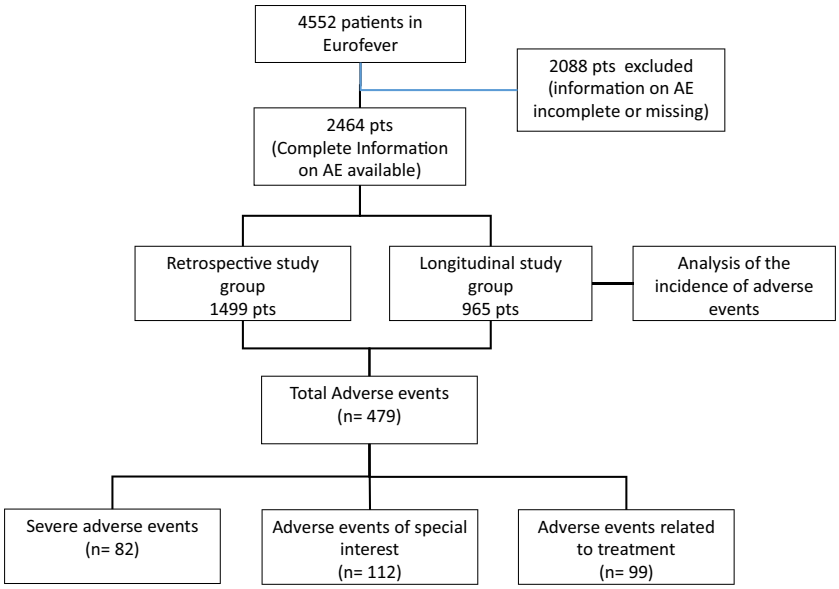

Fig. 1 Study flow on the impact of adverse events in the Eurofever registry

Netherlands, Norway, Slovakia, Spain, and Turkey. This distribution was representative of the overall distribution of centres enrolling patients in Eurofever, which encompassed 50 centres across 19 countries, including Armenia, Austria, Canada, Croatia, the Czech Republic, Ecuador, France, Germany, Greece, Israel, Italy, the Netherlands, Norway, Romania, Russia, Slovakia, Spain, Turkey, and the United Kingdom.

The demographic features of patients with completed clinical information presented in Table 1.

Adverse Events and Severe Adverse Events

A total of 479 AEs have been reported in 275 patients (Fig. 1 and 2A). AEs were reported in 74 out 1499 patients of the retrospective group data in 201 in the longitudinal group. Eighty-two out 479 AEs were classified as SEA and reported in a total 64 patients (Fig. 1 and 2A). The percentage of patients reporting AEs and SEAs were significantly higher in the longitudinal group (Fig. 2B).

AEs most frequently reported were infections/infestations (19.6%), gastrointestinal disorders (13.8%), nervous system disorders (8.6%), general and administration site drug reactions (7.3%), skin and subcutaneous disorders (Supplementary Table 1).

SAEs were collected among the reported AEs and classified according to MedRA classification with the most common infections/infestations (4 reported in retrospective and 15 in longitudinal groups), followed by nervous system disorders (1 from the retrospective and 10 from the longitudinal), surgical and medical procedures (1 in retrospective and 9 in longitudinal).

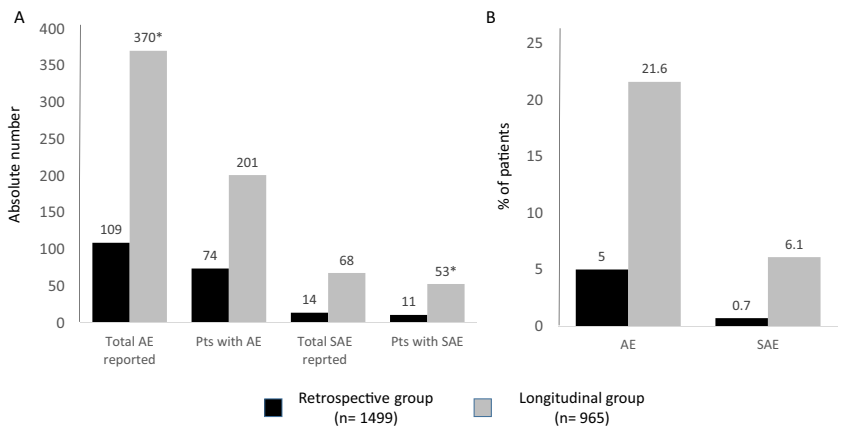

Fig. 2 **A** Number of the AEs, SAEs reported in in patients from both retrospective and longitudinal groups. **B** Percentage of the patients with reported AEs, SAEs in a retrospective and longitudinal group

Adverse Events of Special Interest

Among all AEs reported, 112 were judged as events of a special interest. 21 AEs were reported in the retrospective study group, with 6 of them reported as SAEs and 91 in the longitudinal study group with 27 of them reported as SAE.

The major part of AEs of a special interest came from SOC "infections and infestations" (76/112). Latent tuberculosis was reported in 5 patients with AIDs according to routine QuantiFERON testing with the next administration of the specific preventive medications. 4/5 patients did not receive any treatment when latent tuberculosis was discovered: 2 patients with TRAPS (diagnosed in the adulthood), 1 with FMF and Undefined AID. In 1 patient with NLRP3-AID latent tuberculosis was diagnosed soon after anakinra therapy initiation, but not considered as drug-related.

From the SOC group "neoplasms benign, malignant and unspecified (including cysts and polyps)" 7 reports had been described. 63-year-old patients with NLRP3-AID (W414L p.(Trp414Leu) presented 2 neoplasms: recurrent basal cell carcinoma and well differentiated squamous cell carcinoma. Patient received late diagnosis at the age of 61.5 y.o. Recurrent basal carcinoma was diagnosed in 3 years before the diagnose of AID, differentiated squamous cell carcinoma – in 7 years after. Patient did not undergo any therapy. Prostatic cancer was reported in a 71-year-old NLRP3-AID patient with a late diagnosis at the age of 68 years. Another NLRP3-AID patient (p.Ala439Val variant) was diagnosed with carcinoma in situ of cervix at the age of 22. Her final diagnosis was done at the age of 50. Neoplasms were also reported in 2 FMF patients: one 27-year-old patients with a breast cancer, who received anakinra therapy for 2 years before the event, and was forced to interrupt it to start chemotherapy. 20 years-old FMF patient displayed the benign Warthin`s tumour. In one patient with Blau syndrome, lipoma was diagnosed at the age of 7, 4 years before his/her definitive diagnosis.

Macrophage activation syndrome (MAS was reported in 6 patients with a total of 7 events (6 SAEs and 1 non-SAE). One patient with MKD, compound heterozygous for p.Ile268Thr/p.Thr237Ser MVK mutations, display a lethal MAS episode at the age of 6 months. A MAS episode was reported in one FMF patient one year after his/her diagnosis and during colchicine treatment. One patient displayed 2 subsequent episodes of MAS with an interval of 3 months apart, at the age of 2 and 5 months old. The patient was classified as undifferentiated recurrent fever, even if the genetic analysis performed at the moment of the enrolment was restricted to few genes. One single MAS episode was reported in 2 patients included in the registry as at the age of 15 and 16, respectively. In one case a possible relation with methotrexate therapy was reported with consequent discontinuation.

In one patient with undefined AID, MAS episode was not considered as serious AE by physician, due to the identification of isolated elevation of ferritin and GPT/GOT without other clinical and laboratory findings. The patients were successfully treated with high dose of steroids.

Incidence of AEs and Drug Related AEs in the Longitudinal Study Group

The availability of longitudinal data allowed to calculate the incidence of AEs according to the different conditions. We evaluated the total exposure to the drug, from the initiation of the drug until the most recent reported follow-up.

The incidence was expressed as rate of AE per 100 patient-years, and was higher for FMF [IR 47.5 (33—68)], followed by CRMO [IR 42.6 (29—63)], SURF [IR 34.4 (22—53)] and NLRP3-SAID [IR 31.1 (20—49)] (Fig. 3).

Overall, adult patients were 30% of the entire cohort. AE were observed in 223/275 (81%) children and in 52/275 (19.0%) adults.

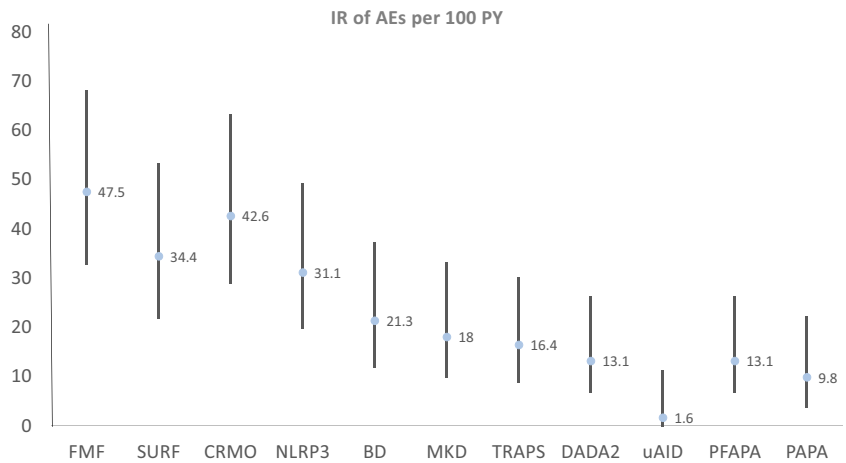

Fig. 3 Incidence of the reported AEs per 100 patient-years among the different AIDs

AEs Related to Treatment

Ninety-nine drug-related AEs were reported and described by treating physicians at the context of their severity, relation with event onset, and action taken toward the medication (supplementary Table 2). 6 of them were reported as SAEs by the treating physician. 33 drug-related AEs were reported in the retrospective group and 66 in the longitudinal group.

The calculation of IR of the drug-related safety events (Table 2) was performed in patients from both retrospective and longitudinal groups, where at least two subsequent visits were reported.

The detailed description of drug–induced AEs according to the SOCs and PTs reported in Table 3.

The highest number of drug-related AEs were related to colchicine (31/99 reports, 31.3 %) and were reported from 15 FMF, 3 SURF, 2 MKD, 1 PFAPA and 1 Behcet disease patients. Colchicine discontinuation or temporary interruption due to drug-related AE was reported in 6/31 and 9/31 patients, respectively.

Forty (40%) drug-related AE were associated to b-DMARDSs. Twenty-one AEs coming from 19 patients were associated to anakinra (6 NLRP3-SAID, 5 SURF, 2 FMF, 2 CRMO and 1 TRAPS, 1 DADA2, 1 PAPA, 1 Behcet disease) and 7 to canakinumab reported from 6 patients (3 TRAPS, 3 NLRP3-AID patients).

Ten drug-related AEs were associated to anti-TNF treatment: 5 to etanercept (2 SURF, 2 CRMO and Behcet`s disease). In two other cases the therapy was temporarily interrupted as result of an infection: pneumonia or herpes zoster. Three AEs were related to adalimumab. In one Blau patient leukopenia prompted to drug discontinuation, while one CRMO and one DADA2 discontinued the drug for an episode of pneumonia. Two patients received infliximab displayed an episode of herpes zoster and skin rash, respectively, leading to drug interruption.

Two patients treated with tocilizumab developed infusion related reaction and allergy to medication, that resulted into permanent drug discontinuation.

Among synthetic DMARDs, the highest number of the AEs were reported for methotrexate in patients with CRMO, undefined AID and Behcet`s disease, followed by azathioprine (3 patients), thalidomide (one patient with Behcet disease). Cyclosporine was the cause of a posterior reversible encephalopathy in one patient with undefined AID. One CRMO patient on sulfasalazine therapy, interrupted the treatment due to nausea.

Seven AEs related to the use of systemic glucocorticoids were reported in five patients. Three of them required dose reduction due to signs of the hyperadrenocorticism. One patient developed osteonecrosis leading to treatment discontinuation.

Overall, drug-related AEs prompted the discontinuation of the medication in 29 cases with the highest rate among colchicine (7/29), methotrexate (6/29) and anakinra (6/29) (Table 3).

Discussion

Our study report data from the larger series of patients with AIDs in which safety data were homogeneously recorded and classified according to Medical Dictionary for Regulatory Activities (MedDRA), in a period of more 14 years.

In its initial version (2009-2015), the Eurofever registry primarily aimed to gather historical data on patients with AIDs. The retrospective study design enabled the collection of valuable insights into patients' medical histories, spanning

Table 2 Drug-related AE reported in the longitudinal study group

Name of the drug/group	Duration of the follow-up, Median (q1 – q3), yrs	Number of patients on therapy	Exposure of the therapy, Median (q1 – q3), yrs	Number of drug-related AE reported	Incidence Rate (95% CI)*
Colchicine	2.82 (1.12 – 6.01)	261	1.24 (0.55 – 1.97)	31	2.7 (1.9 – 3.8)
Systemic glucocorticoids	2.79 (1.01 – 5.97)	368	0.22 (0.03 – 1.10)	7	1.7 (0.8 – 3.6)
cs-DMARds					
Methotrexate	3.74 (1.99 – 7.30)	88	0.78 (0.31 – 1.93)	14	11.3 (6.7 – 19.1)
Azathioprine	3.64 (1.78 – 7.75)	51	1.25 (0.49 – 3.19)	4	3.6 (1.3 – 9.5)
b-DMARds					
Anakinra	3.04 (1.47 – 6.63)	144	1.08 (0.33 – 2.03)	21	7.6 (4.9 – 11.7)
Canakinumab	2.82 (1.65 – 6.20)	90	1.35 (0.54 – 3.04)	7	3.5 (1.7 – 7.3)
Etanercept	3.79 (1.72 – 6.68)	46	0.72 (0.26 – 2.23)	5	5.4 (2.2 – 12.9)
Adalimumab	3.75 (1.80 – 6.49)	59	1.24 (0.55 – 1.97)	3	2.8 (0.9 – 8.6)
Infliximab	4.87 (2.18 – 6.71)	30	0.52 (0.17 – 1.61)	2	8.0 (2.6 – 12.3)

*Rate per 100 patient-years (PY) was calculated overall for the follow-up period

Table 3 Distribution of the AEs in relation to the therapy according to SOCs and PTs

Colchicine ($n=31$)

Gastrointestinal disorders Abdominal pain: 7 Diarrhoea: 8 Vomiting: 3	Infections and infestations Pneumonia: 3 Pharyngitis: 2 Herpes zoster: 1	Hepatobiliary disorders Hypertransaminasemia: 2	Ear and labyrinth disorders Vertigo: 2	Skin and subcutaneous tissue disorders Skin rash: 1	General disorders and administration site conditions Fatigue: 1	Nervous system disorders Headache: 1

Anakinra ($n=21$)

Infections and infestations Pneumonia: 2 Herpes zoster: 2 Gastroenteritis: 2 Epstein-Barr virus infection: 1	General disorders and administration site conditions Injection site reactions: 1 Injection site rash: 5	Injury, poisoning and procedural complications Injection related reactions: 6	Skin and subcutaneous tissue disorders Urticaria: 1	Blood and lymphatic system disorders Lymphadenitis: 1

Methotrexate ($n=14$)

Gastrointestinal disorders Nausea: 3 Vomiting: 1	Infections and infestations Pneumonia: 1 Herpes zoster: 1	Hepatobiliary disorders Hypertransaminasemia: 4	Nervous system disorders Headache: 1	Skin and subcutaneous tissue disorders Skin rash: 1	Ear and labyrinth disorders Vertigo: 1	Immune system disorders Macrophage activation syndrome: 1

Canakinumab (n = 7)

Infections and infestations Upper respiratory tract infections: 2 Herpes zoster:1 Otitis: 1	Skin and subcutaneous tissue disorders Erythema: 1	Nervous system disorders Headache: 1	Hepatobiliary disorders Hypertransaminasemia: 1	

Etanercept (n = 5)

Infections and infestations Pneumonia: 1 Herpes zoster: 1	Immune system disorders Allergy: 1 Drug hypersensitivity: 1		Skin and subcutaneous tissue disorders Skin rash: 1

Azathioprine ($n=4$)

Blood and lymphatic system disorders Neutropenia: 2	Hepatobiliary disorders Hypertransaminasemia: 1	Skin and subcutaneous tissue disorders Skin rash: 1

Adalimumab ($n=3$)

Infections and infestations Pneumonia: 2	Blood and lymphatic system disorders Neutropenia: 1

Infliximab ($n=2$)

Infections and infestations Herpes zoster: 1	Skin and subcutaneous tissue disorders Urticaria: 1

Tocilizumab ($n=2$)

Injury, poisoning and procedural complications Infusion related reaction: 1	Immune system disorders Allergy: 1 Drug hypersensitivity: 1

Thalidomide ($n=1$)

Nervous system disorders Paraesthesia: 1

Sulfasalazine ($n=1$)

Gastrointestinal disorders Nausea: 1

Cyclosporine ($n=1$)

Nervous system disorders Posterior reversible encephalopathy: 1

Systemic glucocorticoids ($n=7$)

Endocrine disorders Hyperadrenocorticism: 3	Hepatobiliary disorders Hypertransaminasemia: 1	Infections and infestations Lower respiratory tract infection: 1	Musculoskeletal and connective tissue disorders Osteonecrosis: 1	Renal and urinary disorders Haemorrhagic cystitis: 1

from disease onset to their enrolment in the registry. However, with the development and approval of various therapeutic approaches for these conditions, a decision was made in 2015 to transition the registry into an observational study. This transformation primarily focused on collecting detailed information on the disease course of AIDs and assessing the efficacy and long-term safety of different therapeutic approaches, utilizing the MedDRA standard procedures.

The ability to retrieve retrospective information from patients enrolled before 2015 presented a dual opportunity. Firstly, it allowed for the gathering of accurate and standardized safety information in a large cohort of AID patients using the MedDRA system. Secondly, it facilitated the analysis of the impact of retrospective versus longitudinal data collection on the accuracy of the retrieved information.

As expected, the longitudinal collection of AEs notably augmented the number of events compared to the retrospective collection, particularly affecting drug-related AEs. Furthermore, employing standardized and objective methods for AE collection across various centers helped diminish the likelihood of subjective interpretations by enrolling physicians. This approach facilitated a more uniform data collection process across different diseases and treatments, thereby enhancing the consistency and reliability of the gathered information.

So far, the currently available data on AEs in AID in literature come from retrospective studies, single-centre reports, or small observational studies, mainly focused on the most common AIDs [11–24]. Few information is available for rarer and more recent conditions. As stated previously, for the first time, in the present study safety events were uniformly recorded across various conditions. This approach provided a comprehensive understanding of the overall impact of AEs within the entire spectrum of monogenic and multifactorial AIDs and across different age groups. In general, infectious and infestations, neurological manifestations and surgical or medical procedures were the most frequent reported AEs. Neoplasms were observed in a small group of patients, prevalently in adults. Interestingly, most of them had a very long disease course before the proper diagnosis of AID, supporting the potential role of chronic and subchronic inflammation in the carcinogenesis [25]. Despite the absence of NLRC4 patients in the registry, macrophage activation syndrome was observed in a small proportion of patients, suggesting that it may represent a potentially lethal complication in AID in which this complication is rarely observed (namely MKD) and might represents a common clinical finding in a subgroup of patients with an undefined inflammatory phenotype (reported as undefined AID or SURF), as recently observed in patients with IL-18 related MAS and pulmonary involvement [26, 27].

The present study put also a particular attention on the impact of drug-related AEs in the context of AID. As expected, the longitudinal collection of data prompted to a much higher accuracy in reporting AEs in general and even more for drug-related AEs, that represent the most delicate issue concerning the monitoring of AID patients in daily clinical practice.

The study offers a comprehensive description of the incidence of drug-related AEs across various conditions and treatments commonly utilized in both ultra-rare monogenic and more prevalent multifactorial AIDs.

At present, data concerning drug-related AEs are mainly coming from clinical trials focused on a single agent and on a limited number of conditions (CAPS, FMF, TRAPS, MKD) [19, 23, 28–32]. Data coming from the real life are generally generated from national or international retrospective studies [33–40].

According to a systematic review on the efficacy and safety of treatments used in FMF by Demirkaya et al., information on the safety profile were generally poorly described [11] .

In the narrative review on the use of IL-1 inhibitors in FMF by Hentgen et al., was clearly underlined that current available safety data are usually limited to short-term observations and that long-term data are needed [15]. So far, very few observational studies are ongoing and are generally focused on a single agent [35, 41–43] or on a limited number of patients and conditions [44–47].

In the present study, drug-related AEs were reported in all conditions and has been referred to the wide range of treatments used in the AIDs with a uniform and standardized method as MedDRA. The highest rate of drug-related AEs was observed for classical DMARDs (Methotrexate) and biologics, with a higher incidence for Infliximab, Anakinra and Etanercept. In line with data coming from the clinical trials conducted on AIDs, infections and skin manifestations were the most frequent side effects in real life also [22, 48]. Overall, in 30% of AEs the drug was discontinued.

Colchicine was the drug most commonly used in the cohort of patients analysed, with an overall incidence rate of AE of 2.7 per 100 patients-year, leading to a definitive discontinuation of the drug in 6 patients only. So far, data on discontinuation of the drug after AEs was rather limited in the literature and related to few studies, prevalently for single drugs or conditions during clinical trials [14, 21, 32, 33, 49].

In general, data from the present study confirms the overall good safety profile of the treatments commonly used in AIDs [50]. However, in real life, drug discontinuation after AEs is higher than reported in clinical trials.

Notably, all AEs reported in the Eurofever registry were from moderate to severe. In order to avoid an excessive effort for the centers, mild AEs were not reported by the treating physicians. Potentially this decision may have reduced the number of injection site related reactions reported, as one of

the most common findings known from the previous studies [14, 19, 28, 51].

The present study presents some important limitations. The first limitation was the relatively high percentage of patients with incomplete safety information in our dataset. While all longitudinally enrolled patients provided complete safety information according to the most recent edition of the Medical Dictionary for Regulatory Activities (MedDRA), for all patients enrolled before 2015, investigators had the possibility to retrospectively update the complete information on safety according to MedDRA. This limitation could potentially introduce biases and affect the generalizability of our findings, related to a possible selection of patients followed by centers more prone to include retrospective data on safety or to provide longitudinal data of their patients. However, the geographical distribution of the centers including safety data in the present study was rather wide, indicating a substantial representation of the entire Eurofever network.

A second limitation is the relative short follow-up of patients enrolled in the longitudinal study group. This aspect is due to the laborious transformation of Eurofever from a classical retrospective registry to a modern longitudinal observational study, and in many cases, it mainly reflects the difficulties of the clinical centres to systematically update the information on their patients on at least a yearly basis.

Despite these limitations, the study collects by far the highest number of AID patients collected so far in a longitudinal cohort, providing the incidence of AEs in a variety of conditions treated with different treatments using the standardized MedDRA protocol.

In conclusion, the present study shows the importance of a longitudinal and homogeneous registration of the AEs in rare conditions, with a particular focus on the safety profile of the treatments used in these conditions. Traditional international registries should be transformed in longitudinal observational studies in order to provide relevant clinical information from real life. This effort requires constant and costly logistical organization and the willingness of centres to consistently provide information longitudinally. This represents a critical element for the success of any international initiatives that are essential for rare conditions and that must be supported for its operation and development, possibly in an academic setting with the support of international institutions for rare diseases.

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Declarations

Data Sharing Statement Data are available upon reasonable request. Data are available on reasonable request.

Patient and Public Involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Competing Interests MG: Novartis, SOBI, speakers' fees' consultancies, unrestricted grants to Eurofever. NR: honoraria for scientific consultancies or speaker bureaus from Abbie, AMGEN, Aurinia, Eli Lilly, Galapagos, Guidepoint, Novartis, Pfizer. All other coauthors no interests to declare.

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