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Safety of intravenous use of anakinra in pediatric inflammatory conditions: a retrospective multicenter study

Marta Klanjscek[1], Matteo Trevisan[2], Serena Pastore[3], Manuela Pardeo[2], Alberto Tommasini[1,3], Roberta Caorsi[4], Gianluca Dell'Orso[5], Sarah Abu Rumeileh[6], Chiara Conti[7], Carmelita D'Ippolito[8], Manuela Cortesi[9], Natasha Maximova[3], Marco Cattalini[9,10], Gabriele Simonini[6], Marco Gattorno[4], Fabrizio De Benedetti[2], Andrea Taddio[1,3*] and Claudia Bracaglia[2]

Abstract

Purpose Anakinra is a recombinant human interleukin-1 receptor antagonist primarily administered by subcutaneous injection for the treatment of autoinflammatory conditions. Intravenous use of anakinra is only sparsely described in the literature. The aim of this study was to assess the safety of intravenous use of anakinra in a cohort of pediatric patients.

Methods This is a multicenter, retrospective cohort study. All patients who received intravenous anakinra from January 1st, 2017, to February 29th 2024 were enrolled. Collected data comprised: demographic characteristics, underlying clinical conditions, infusion-related data, anakinra-related adverse events and clinical response.

Results The case series included 113 patients: 64 (56.6%) with underlying rheumatologic diseases, 27 (23.9%) with onco-hematologic diseases, 22 (19.5%) with severe systemic infections. Fifty-nine patients (52.2%) were admitted to intensive care units. The intravenous anakinra dose ranged from 2 to 20 mg/kg/day, and treatment duration ranged from 1 to 80 days. Adverse events were observed in 10 of 113 treated children (8.8%). The most common events were transient elevation of liver or pancreatic enzymes in seven patients (6.2%) and maculopapular rash in two patients (1.2%). One patient (0.9%) experienced an anaphylactoid reaction immediately after the infusion. Sixteen patients (14.2%) died. Among those who died, ten were receiving ongoing anakinra treatment, with a median treatment duration of 27 days (range 2–42), while six patients had discontinued the drug several days earlier.

Conclusion Intravenous administration of anakinra appears to be safe and not associated with severe adverse events. Reported side effects were transient, not life-threatening, and resolved either with specific treatment or after drug discontinuation. Intravenous anakinra may therefore be considered a safe therapeutic option for selected life-threatening acute clinical conditions.

Keywords Anakinra, Intravenous, Side effect, Children

*Correspondence:
Andrea Taddio
andrea.taddio@burlo.trieste.it

Full list of author information is available at the end of the article

Introduction

Anakinra is a recombinant human interleukin-1 (IL-1) receptor antagonist that blocks the action of IL-1, a cytokine that plays a central role in innate immune activation and in the immune responses to foreign antigens.

In pediatrics, anakinra has been approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis, neonatal-onset multisystem inflammatory disorder (NOMID), and deficiency of IL-1Receptor Antagonist (DIRA) [1]. In addition, the European Medicines Agency (EMA) has approved its use for Still's Disease [2].

IL-1 overactivation is implicated in the pathogenesis of several chronic inflammatory conditions [3] including idiopathic recurrent pericarditis, genetically undefined autoinflammatory diseases, and gout flares, as well as in acute inflammatory conditions such as macrophage activation syndrome (MAS), multisystem inflammatory syndrome in children (MIS-C), cytokine release syndrome (CRS), severe COVID-19, and sepsis [4–8] where anakinra may play a therapeutic role.

The recommended route of administration of anakinra is subcutaneous; however, in acute and severe clinical settings requiring higher dosages, the subcutaneous route may be suboptimal. In these situations, achieving adequate drug concentrations can be challenging, and the presence of edema and/or anasarca - common in critically ill patients – may further impair drug absorption despite multiple daily injections [9]. This is supported by pharmacokinetic data showing that maximum plasma concentration (Cmax) of anakinra is 24–29 times higher following intravenous administration compared with subcutaneous injection [10], while the time to reach Cmax after subcutaneous administration ranges from 3.7 to 4.3 h [11]. The intravenous half-life of anakinra is shorter than that observed with subcutaneous administration, with an estimated terminal half-life of approximately 2.64 h versus 4–6 h, respectively [10]. The faster elimination and shorter washout time associated with intravenous administration may be advantageous in situations where infection is a concern, as treatment can be discontinued more rapidly [10]. Furthermore, intravenous administration allows higher peak concentrations to be achieved more quickly [11].

Despite these advantages, the intravenous use of anakinra remains poorly documented in clinical practice. The safety profile of intravenous anakinra was first evaluated in 1992 by Granowitz et al., who administered doses ranging from 1 to 10 mg/kg to 25 healthy adults, observing no differences in homeostasis or laboratory parameters compared to saline-treated controls [12]. In 1993, 14 healthy adult volunteers received anakinra following intravenous administration of *Escherichia Coli* endotoxin, demonstrating potential benefits in sepsis without observed side effects [13]. The first randomized control trial in adults was published in 1994 by Fisher et al., demonstrating safety and tolerability in 99 patients with sepsis or septic shock [14]. These findings were subsequently confirmed in a larger cohort of 893 adult patients with sepsis treated with an initial anakinra dose of 100 mg/day [8], and in further studies by the same group [15]. Although these studies demonstrated good tolerability, no survival benefit was shown.

Initial pediatric reports focused on subcutaneous anakinra for the treatment of macrophage activation syndrome (MAS) or hemophagocytic lymphohistiocytosis (HLH) [16], with subsequent expansion to other rheumatologic conditions such as Kawasaki Disease [17]. Given the limitations of subcutaneous administration in critically ill patients and evidence of improved blood-brain barrier penetration with intravenous administration, the intravenous route has gained increasing relevance in pediatric practice [9, 18].

Retrospective reports have described intravenous anakinra use in patients with MAS at doses of 2 mg/kg per dose (max 100 mg every 12 h) or higher (up to 100 mg every 6 h) in patients already receiving chronic subcutaneous anakinra [19]. Transient elevations in liver enzymes were reported, with no cases of anaphylaxis. Mortality rate was 26.3% occurring in patients with severe underlying conditions, refractory disease, or prior immunosuppressive therapy.

Yang et al. reported the use of intravenous anakinra in 14 pediatric patients with MIS-C, HLH, systemic juvenile idiopathic arthritis (sJIA) and other hyperinflammatory conditions at doses of 2–3 mg/kg every 12 h for a mean duration of 3.5 days, without reported adverse events [20].

Licciardi et al. observed transient transaminases elevation in 30.8% of 13 cases of MIS-C patients treated with intravenous anakinra, compared with 9.1% of those treated subcutaneously [18, 21]. Other reported adverse events include injection-site (with subcutaneous administration), headache, hypercholesterolemia, increased infection risk, neutropenia, thrombocytopenia, allergic reactions, transaminases elevation, and rash.

During the COVID-19 pandemic, intravenous anakinra was approved for hyperinflammatory conditions related to SARS-CoV-2 infection [2], with safety and efficacy rapidly documented in adults with moderate-to-severe COVID-19 and pulmonary involvement [22]. Its use was also reported in refractory pediatric MIS-C. In a study by Caglayan et al., including 378 patients, 82 received anakinra in combination with immunoglobulins and corticosteroids, 12 of whom were treated intravenously, with a favorable safety profile [23]. Additional studies confirmed good safety in pediatric MIS-C patients treated with intravenous anakinra [6, 24].

The primary aim of this study was to evaluate the safety of intravenous anakinra in a large pediatric cohort with inflammatory conditions. A secondary aim was to assess clinical response where data were available.

Materials and methods

This multicenter retrospective cohort study included all patients under 18 years of age who received intravenous anakinra between January 1st, 2017, and February 29th 2024 at five tertiary centers: Institute for Maternal and Child Health, IRCCS "Burlo Garofolo"; Division of Rheumatology, IRCCS Ospedale Pediatrico Bambino Gesù; Unit of Rheumatology and Autoinflammatory Diseases of IRCCS Giannina Gaslini; Rheumatology Unit, IRCCS Anna Meyer, ERN ReCONNET Center, NEUROFARBA Department, University of Florence and Pediatric Clinic of ASST Spedali Civili and University of Brescia.

Patients were identified through hospital pharmacy records documenting off-label anakinra dispensing. Treatment decisions were made by the attending physician based on clinical indications. In this cohort, the decision to administer anakinra intravenously rather than subcutaneously was based on the need to treat acute conditions, to use high drug doses to achieve elevated serum levels rapidly, and often for many consecutive days. Since the intravenous route of administration was considered an off-label prescription, in all patients, a favorable opinion was obtained from the local or hospital ethics committee for the use of anakinra in modalities outside of those regulated and approved.

The study was approved by the Institutional Review Board (IRB) of the coordinating center IRCCS Burlo Garofolo (IRCCS Burlo Garofolo-03/2020); According to Italian legislation, given the retrospective nature of the study and the maintenance of patient anonymity, obtaining informed consent is not required.

Collected data included: demographic characteristics, underlying clinical conditions, infusions details (dosage; duration; concomitant therapies), adverse events and clinical response.

For patients with underlying immunorheumatologic conditions, clinical improvement was defined as recovery from the ongoing acute condition. In the remaining patients, clinical improvement was defined based on the effect observed on the underlying indication for anakinra administration, namely the hyperactivation of systemic inflammation occurring in the context of infectious or onco-hematologic conditions. Accordingly, clinical improvement was considered to be an amelioration of vital signs, laboratory parameters, and baseline clinical status, as assessed by the treating physician.

Laboratory parameters were not systematically analyzed in their entirety; however, all abnormalities potentially attributable to the drug were carefully evaluated.

Table 1 Clinical conditions that needed intravenous treatment with anakinra

Diseases treated with IV anakinra	Number of patients ($n = 113$)
MIS-C	35
HLH (without infectious subset)	15
HLH (during sepsis)	9
HLH (during localized infection)	6
Sepsis (without HLH)	2
MAS	11
Disseminated infectious diseases (non-bacterial)	5
Kawasaki disease	7
Pericarditis	2
Periodic-recurrent fever	7
Sistemic JIA	2
IL-6 in cerebrospinal fluid	1
GVHD/engraftment syndrome	5
Anti-inflammatory effect during blinatumomab-induced hyperinflammation syndrome	2
Hyperinflammation (oncological setting)	4

MIS-C = Multisystem inflammatory syndrome in children; HLH = Hemophagocytic Lymphohistiocytosis according to the HLH-2004 criteria, MAS = Macrophage Activation Syndrome referring to secondary form of HLH occurring in the context of rheumatologic diseases, JIA = Juvenile Idiopathic Arthritis; GvHD = Graft versus Host Disease.

Results

A total of 113 patients were enrolled; 69 were male (61%) and 44 were female (39%). The mean age at initiation of anakinra treatment was 7.62 years (6-1783 days). In all patients, the use of intravenous anakinra was supported by clinical and laboratory evidence of an hyperinflammatory syndrome. Among these patients, 64 (56.6%) had immune-rheumatologic diseases, 27 patients (23.9%) had hemato-oncologic conditions, and 22 patients (19.5%) presented with hyperinflammation in the context of a documented infection. Fifty-nine patients (52.2%) were admitted at intensive care units (ICUs), and 54 of them were already in the ICU before starting anakinra. The main underlying conditions and indications for intravenous anakinra are summarized in Table 1.

Intravenous anakinra administration and concomitant immunomodulatory therapies

The median intravenous anakinra dose was 8.2 mg/kg/day (range 2–20 mg/kg/day), and the median treatment duration was 20 days (range 1–80 days). Ninety-one patients (80.5%) received concomitant glucococorticoids, and 29 (25.6%) were treated with intravenous immunoglobulins. Only four patients (3.5%) did not receive any additional immunomodulatory therapy during anakinra treatment.

Adverse events and clinical response

Adverse events were observed in 10 out of 113 children (8.8%). Five patients required discontinuation of the anakinra infusion due to adverse events that could not be otherwise managed, and treatment was not resumed either intravenously or subcutaneously. In this subgroup, the median anakinra dose was 9.5 mg/kg/day (range 3–15 mg/kg/day). Specifically, the three patients who developed infusion reactions requiring treatment discontinuation had received doses of 3 mg/kg,10 mg/kg and 10 mg/kg respectively; two of them had previously received subcutaneous anakinra as chronic therapy or on-demand therapy. These cases are summarized in Table 2.

Sixteen patients (14.2%) died. Among them, ten were receiving ongoing anakinra treatment, with a median treatment duration of 27 days (range 2–42), while six had discontinued the drug several days earlier. None of the deaths were attributed to anakinra administration. The clinical characteristics of deceased patients are summarized in the Table 3. According to the treating physician's assessment, 97 patients (85.8%) showed a clinical and/or laboratory improvement after initiation ok anakinra.

Subgroup analysis

Patients were stratified according to the underlying clinical condition for which intravenous anakinra was administered.

Patients with immune-rheumatological conditions

Patients with immuno-rheumatological conditions represent the largest subgroup including 64 patients. HLH, MAS, Kawasaki disease, and MIS-C were defined according to established diagnostic criteria [25–27]. The median age at treatment initiation was 8.4 years (range 0.75-16 years), and 34 patients (54%) were treated in the ICU.

The mean anakinra dose was 8.38 mg/kg/day (range 2.2–20 mg/kg/day), with a mean treatment duration of 17 days (range 1–80 days).

Adverse events included transient transaminase elevation in three patients (4.7%), skin rash in two (3.1%), hypotension and vomiting in two (3.1%), and transient amylase elevation in one (1.6%). Five patients discontinued treatment due to adverse events.

Recovery was documented in 58 patients (92%) according to treating physician. Three patients (4.7%), showed no clinical improvement, while 2 (3.1%) experienced partial improvement. No deaths were reported in this subgroup.

Patients with hemato-oncologic conditions

Twenty-seven patients had underlying hemato-oncologic diseases. The median age at treatment initiation was 6.5 years (range 1–17 years), and ten patients (37%) required ICU admission.

The mean anakinra dose was 6.28 mg/kg/day (range 1–10 mg/kg/day), with a mean treatment duration of 20.19 days (range 4–79 days). No adverse events were reported.

Clinical improvement was observed in 22 patients (84,6%). In one case, response was not evaluable due to early death. Six patients (22%) died as a result of complications related to the underlying disease.

Patients with infectious diseases

Twenty-two patients developed hyperinflammatory syndromes in the context of infections; 11 had sepsis complicated by HLH. The mean age was 4.5 years (range 1.5–14 years). The mean anakinra dose was 8.58 mg/kg/day (range 4–15 mg/kg/day), and the mean treatment duration was 25.33 days (range 1–60 days). Three patients (13.6%) developed adverse events, consisting of transient elevation of liver enzymes. Five patients (22.7%) were treated in the ICU, and ten patients (45.5%) died. Among those who died, five had congenital, acquired, or iatrogenic immunodeficiency, and one had cystic fibrosis. Eleven patients (50%) showed clinical improvement according to the treating physician.

Discussion

The primary aim of this study was to evaluate the safety of intravenous anakinra in a large pediatric cohort by analyzing reported adverse events. We collected data from 113 patients treated across five centers over a seven-year period.

Adverse events were observed in 8.8% of patients, a higher proportion than reported in previous studies, which generally included smaller sample sizes. Direct comparison is challenging, as many prior reports

Table 2 Side effects reported during intravenous anakinra administration

Side effect	Number of cases reported	Intervention required for resolution
Transient elevation of liver or pancreatic enzymes	7/113 (6.2%)	2 patients discontinued the treatment. In 5 patients spontaneous resolution.
Maculopapular rash 20 min after the infusion	2/113 (1.7%)	Treatment discontinuation
Hypotension and vomiting at the beginning of the infusion	1/113 (0.9%)	Intravenous administration of antihistamine and glucocorticoids in addition to treatment discontinuation

Table 3 Table of patients deceased in our cohort who underwent anakinra treatment

Underlying clinical condition	Sex	Age at the beginning of the treatment (years)	Concurrent infection	Indication for anakinra use	Concomitant immunomodulators	Dosage (mg/kg/day)	Clinical response	Side effects	Treatment duration (days)	Outcome	Timing of death-anakinra infusion	Admission to ICU
Ewing sarcoma after bone marrow transplant	F	17	Disseminated aspergillosis	HyperinflInflammation from underlying therapy	Mycophenolate mofetil, Ruxolitinib, Methyl-prednisolone	2,5	not evaluable	no	4	Deceased due to chronic respiratory failure in pulmonary fibrosis	After the discontinuation	no
Thalassemia post-transplant (matched unrelated donor)	F	1	Adenovirus infection	Hyperinflammation during viral infection	Tacrolimus, methylprednisolone	10	improved	no	16	Deceased for complications occurred from the 2nd transplant, performed after IL-1 treatment	After the discontinuation	no
NBAS (Neuroblastoma Amplified Sequence) deficiency and suspected immunodeficiency	F	0.3	Isolation of Pneumocistis jirovecii/metapneumovirus from bronchoalveolar lavage, Stafilococcus Aureus and Klebsiella sepsis	Secondary HLH (Hemophagocytic Lymphohistiocytosis)	Methylprednisolone	5	no	no	38	Deceased for septic shock	Ongoing therapy	Yes (prior to the initiation of anakinra)
Cystic fibrosis, liver and pancreas transplant	F	17	Pseudomonas Aeruginosa sepsis	Secondary HLH	Methylprednisolone, cyclosporine	11	no	no	5	Deceased for sepsis/multiple organ failure	Ongoing therapy	Yes (prior to the initiation of anakinra)
CHARGE syndrome	F	1	Isolation of Pseudomonas and Serratia from tracheal aspirate during endocarditis	Secondary HLH	Methylprednisolone	15	improved	no	23	Deceased for cardiac arrest, Candida endocarditis	Ongoing therapy	Yes (prior to the initiation of anakinra)
DRESS syndrome (Drug reaction with eosinophilia and systemic symptoms)	F	14	Klebsiella sepsis	Secondary HLH	Methylprednisolone, mepolizumab, immunoglobulins	5,7	no	no	42	Deceased for refractory HLH	Ongoing therapy	Yes (prior to the initiation of anakinra)
Previously healthy	M	3	EBV (Epstein Barr virus) infection	Secondary HLH	Emapalumab, rituximab, cyclosporine, methylprednisolone	11	no	no	30	Deceased for refractory HLH	Ongoing therapy	Yes (prior to the initiation of anakinra)
Centromeric Instability syndrome with immunodeficit	F	0.6	Pseudomonas Aeruginosa sepsis	Primary HLH	Immunoglobulins	10	no	no	30	Deceased (unspecified cause)	Ongoing therapy	no
Previously healthy	M	1	Streptoccoccus Pyogenes sepsis	Secondary HLH	Immunoglobulins, methylprednisolone	10	improved	no	25	Deceased (unspecified cause)	Ongoing therapy	no
Previously healthy	F	8	Parvovirus B19 infection	Secondary HLH	Methylprednisolone, immunoglobulins	10	improved	no	4	Deceased (unspecified cause)	Ongoing therapy	no
Chronic Granulomatous Disease post HSCT (Hematopoietic Stem Cell Transplant)	F	15	Disseminated Candida Albicans	ARDS (Acute Respiratory Distress Syndrome)	Cyclosporine, thalidomide, corticosteroids	7,5	resolution	no	30	Deceased some time after the clinical episode due to extensive chronic GVHD	After the discontinuation	Yes (prior to the initiation of anakinra)
LLA-B (B-cell Acute Lymphoblastic Leukemia) post-HSCT	M	7	Klebsiella Pneumoniae sepsis	Hyperinflammation during sepsis	Cyclosporine, methylprednisolone, ruxolitinib	9	resolution	no	10	Deceased due to a relapse	After the discontinuation	no
Diamond-Blackfan anemia post-HSCT	M	11	No	Persistent fever after infusion of antiviral T lymphocytes	Hydrocortisone/methylprednisolone/dexamethasone, ruxolitinib	7,5	improved	no	33	Deceased due to GvHD and sepsis	After the discontinuation	no
Relapsed LLA-T (T-cell Acute Lymphoblastic Leukemia)	M	2	No	ARDS post-chemotherapy	Corticosteroids	10	resolution	no	29	Deceased due to extensive chronic GVHD	After the discontinuation	Yes (prior to the initiation of anakinra)
LLA-B post-HSCT	M	3	No	Severe systemic inflammatory complication with endothelial damage (engraftment evolving into graft-versus-host disease)	Methylprednisolone, ruxolitinib	3	no	no	35	Deceased (unspecified cause)	Ongoing therapy	Yes (after the initiation of anakinra)

Table 3 (continued)

Underlying clinical condition	Sex	Age at the beginning of the treatment (years)	Concurrent infection	Indication for anakinra use	Concomitant immunomodulators	Dosage (mg/kg/day)	Clinical response	Side effects	Treatment duration (days)	Outcome	Timing of death-anakinra infusion	Admission to ICU
LLA Pre-B	M	3	No	Hyperinflammatory state after CAR-T therapy	Hydrocortisone, toclizumab	7	no	no	2	Deceased (unspecified cause)	Ongoing therapy	Yes (after the initiation of anakinra)

combined patients treated with intravenous and subcutaneous anakinra without distinguishing adverse events by route of administration. To our knowledge, this represents the largest pediatric cohort treated exclusively with intravenous anakinra.

The most frequent adverse event - the transient transaminases elevation - occurred less frequently in our cohort than in the study by Licciardi et al. (6.2% vs. 30.8%) [21]. This difference may reflect the exclusive inclusion of MIS-C patients and the smaller sample size in that study. In patients with MAS or HLH, transaminase elevation occurred in11.1%, a higher rate than reported by Phadke et al. (5.26%) [19].

Two cases of maculopapular rash (1.7%) were observed and resolved after treatment discontinuation. Both patients recovered fully. Apart from injection-site reactions, systemic skin rash has been very rarely reported with subcutaneous anakinra [22]. One patient experienced an immediate post-infusion reaction characterized by fever, urticaria, hypotension, and vomiting, consistent with an anaphylactoid reaction. This resolved after drug discontinuation and administration of an antihistamines and glucocorticoids and has not been previously reported in the literature. Neutropenia, previously described as a potential adverse event [9], was not observed in our cohort.

Among patients who experienced adverse events, only two of the three patients who required discontinuation due to immediate reactions had prior exposure to subcutaneous anakinra. Although previous exposure followed by a drug-free interval could theoretically favor sensitization, this hypothesis requires further investigation.

Mortality among patients treated with intravenous anakinra for MAS/HLH has been reported at approximately 26.3% [28], whereas mortality in our cohort was slightly lower (19.5%). No deaths occurred among MIS-C patients, died, despite reported mortality rate of 1.4–1.7% [23]. Patients with infection-associated hyperinflammation showed the highest mortality, likely reflecting severe baseline clinical conditions, ICU admission, and underlying immunodeficiency. In this group, a high percentage of patients started anakinra in ICU suggesting a significant pre-existing impairment. Furthermore, 5 of the deceased had congenital, acquired, or iatrogenic immunodeficiency, and one patient was affected by cystic fibrosis, all conditions that predispose to infections, comorbidities, and inherently increase the baseline mortality of affected individuals especially during acute events.

Despite higher mortality in this subgroup, adverse events rates were comparable to those observed in the overall cohort, supporting the hypothesis that deaths were primarily related to disease severity rather than anakinra toxicity.

As a secondary outocome, clinical improvement was observed in 85.8% of patients, particularly among those with immune-rheumatologic conditions. Improvement rates were 94.3% for MIS-C, 50% for HLH, and 100% for MAS, compared with previously reported improvement rates of approximately 80% in MAS treated with intravenous anakinra [24]. We observed a lower mortality rate compared to those reported for the main categories of treated diseases (MIS-C, HLH, MAS).

The strengths of this study include its multicenter design and large sample size. To our knowledge, there are no data on the use of intravenous anakinra in pediatric patients with different diseases. However, its retrospective nature and the wide heterogeneity of the underlying represent important limitations, partially addressed through subgroup analysis.

Limitations of the study

This study has several limitations, including the heterogeneity of the cohort, although analyses were also performed within the context of the various subgroups for the purpose of overcoming this limitation. The heterogeneity of the cohort, the concomitant use of other immunomodulators and the absence of a group of patients with similar characteristics treated with subcutaneous anakinra makes it very difficult to evaluate its efficacy, even if it is a secondary outcome. Furthermore, laboratory data for individual patients and the specific effects of anakinra were not available; however, we reported all instances in which potentially attributable changes were observed.

Conclusion

The intravenous use of anakinra in pediatric patients may represent a more manageable alternative for the treatment of certain life-threatening acute clinical conditions, allowing the administration of higher drug doses even in critical care settings. Intravenous anakinra, at doses ranging from 2 to 20 mg/kg/day, appeared to be safe in our patient cohort. Adverse events were transient or pharmacologically manageable. Deaths occurred in patients who were already in critical clinical condition prior to anakinra administration. Regarding secondary outcomes, clinical efficacy was observed primarily in patient groups with underlying immuno-rheumatological or hematological-oncological conditions.

Abbreviations

CAPS	Cryopyrin-associated periodic syndromes
EMA	European Medicines Agency
FDA	Food and Drug Administration
HLH	Hemophagocytic lymphohistiocytosis
IL-1	Interleukin-1
MAS	Macrophage activation syndrome
MIS-C	Multisystem inflammatory syndrome of childhood
COVID-19	COronaVIrus Disease 19
sJIA	Sistemic juvenile idiopathic arthritis

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Author contributions
Andrea Taddio, Claudia Bracaglia, Marta Klanjscek, Fabrizio De Benedetti, Marco Gattorno have made substantial contributions to the conception; Andrea Taddio, Claudia Bracaglia, Marta Klanjscek, Fabrizio De Benedetti, Roberta Caorsi, Marco Gattorno, Matteo Trevisan, Serena Pastore and Manuela Pardeo have made substantial contributions in designing the work; Matteo Trevisan, Gianluca Dell'Orso, Alberto Tommasini, Sarah Abu Rumeileh, Chiara Conti, Carmelita D'Ippolito, Manuela Cortesi, Natasha Maximova, Marco Cattalini e Gabriele Simonini have made substantial contributions in the acquisition, analysis of data and interpretation of data; Andrea Taddio, Claudia Bracaglia and Marta Klanjscek have drafted the work or substantively revised it. All authors reviewed the manuscript. All authors have approved the submitted version (and any substantially modified version that involves the author's contribution to the study) and have agreed both to be personally accountable for the author's own contributions and to ensure that questions related to the accuracy or integrity of any part of the work.

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Data availability
The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
The study record review was approved by the Institutional Review Board (IRB) of the coordinating center IRCCS Burlo Garofolo (IRCCS Burlo Garofolo-03/2020).

Consent for publication
Not applicable.

Competing interests
FDB, RC, CB, MC, GS, MG and AT have received honoraria from SOBI and Novartis.

Author details
[1]Department of Medicine, Surgery and Health Sciences, University of Trieste, Trieste, Italy
[2]Division of Rheumatology, ERN-RITA Center, IRCCS Ospedale Pediatrico Bambino Gesù, Roma, Italy
[3]Institute for Maternal and Child Health, IRCCS "Burlo Garofolo", Trieste, Italy
[4]Center for Autoinflammatory Diseases and Immunodeficiencies, IRCCS Giannina Gaslini, Genova, Italy
[5]Hematology Unit, Department of Pediatric Hematology-Oncology, IRCCS, Istituto Giannina Gaslini, Genova, Italy
[6]Rheumatology Unit, IRCCS Anna Meyer, ERN ReCONNET Center, NEUROFARBA Department, University of Florence, Firenze, Italy
[7]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI), University of Genoa, Genoa, Italy
[8]Pediatric Haematology-Oncology, ASST Spedali Civili di Brescia, Brescia, Italy
[9]Pediatric Clinic, ASST Spedali Civili di Brescia, Brescia, Italy
[10]University of Brescia, Brescia, Italy

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