Early anakinra treatment improves cardiac outcome of multisystem inflammatory syndrome in children, regardless of disease severity

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[‡]See Supplementary Data S1, available at *Rheumatology* online, for a list of the Italian Society of Pediatric Rheumatology (ReumaPed).

Rheumatology key messages

- Early treatment with anakinra improves the cardiac outcome for patients with MIS-C.
- Anakinra is effective, irrespective of disease severity.
- Corticosteroids are effective in reducing the rate of treatment failure.

Abstract

Objective: The main aim of this study was to define the best treatment option for multisystem inflammatory syndrome in children (MIS-C) and to analyse the role of anakinra.

Methods: This is a multicentre retrospective cohort study. Patients were treated according to the attending physician's decision. The patients were divided into four groups on the basis of the first treatment at time of admittance: (i) IVIG, (ii) IVIG and methylprednisolone (≤2 mg/kg/day), (iii) IVIG with high-dose methylprednisolone (>2 mg/kg/day) and (iv) anakinra with or without IVIG and/or methylprednisolone. Primary outcomes were defined as the presence of at least one of the following features: death, the failure of initial treatment, meaning the need for additional treatment for clinical worsening and cardiac involvement at the end of follow-up.

Results: Two hundred thirty-nine patients were recruited. At univariate analysis, persistent heart involvement at discharge was more frequent in those not receiving anakinra as initial treatment (3/21 *vs* 66/189; $P = 0.047$). After comparisons between the four treatment regimens, adjusting for the propensity score, we observed that early treatment with anakinra was associated with a lower probability of developing persistent heart disease at the end of follow-up (odds ratio: 0.6; 95% CI: 0.4–1.0).

Conclusion: We report that early treatment with anakinra is safe and very effective in patients with severe MIS-C. In addition, our study suggests that early treatment with anakinra is the most favourable option for patients with a higher risk of developing a severe disease outcome.

Keywords: anakinra, MIS-C, children, cardiac outcome, SARS-CoV-2

Introduction

It has been widely reported that SARS-CoV-2 infection has a less severe course in children; however, it can drive a systemic inflammatory response, also known as Paediatric Multisystem Inflammatory Syndrome Temporally associated with COVID-19 (PIMS-TS) or Multisystem Inflammatory Syndrome in Children (MIS-C) [1]. MIS-C was initially defined by the UK Royal College of Paediatrics and Child Health (RCPCH) [2], the US Center for Disease Control and Prevention (CDC) [3] and WHO [4]. Although MIS-C seems to share some clinical manifestations with Kawasaki disease (KD) [5], the key features are the presence of persistent fever, the involvement of multiple organ systems and the prevalence of myocarditis, pericarditis, and shock. The occurrence of coronary abnormalities is possible, but rarer than in patients with KD.

In the last 2 years, we have had the opportunity to collect data from patients with MIS-C, to better describe its clinical manifestations, laboratory expression, and clinical outcome, which is benign for most patients [6]. No clear data are available about the best treatment approach: while the use of immunoglobulin is widely accepted [7], mainly based on the similarities with KD, studies on CSs efficacy have yielded conflicting results [8, 9] and the role of biologic drugs (in particular, the role of IL1 blocking agents) has not yet been defined.

The main aim of this study was to define the better treatment option in MIS-C children and in particular to analyse the role of anakinra in this subgroup of patients.

Methods

Study design and patient selection

This is a multicentre retrospective cohort study promoted by the Italian Society of Pediatric Rheumatology. The study record review was approved by the Institutional Review Board (IRB) of the coordinating center IRCCS Burlo Garofolo (IRCCS Burlo Garofolo-03/2020). Children hospitalized between 1 February 2020 and 31 May 2021 with the clinical diagnosis of MIS-C were enrolled.

MIS-C patients were identified by fulfilment of the RCPCH clinical definition, which is the following: persistent fever (>48 h); lymphopenia and evidence of single or multi-organ dysfunction, with additional clinical, laboratory or imaging data and exclusion of any other microbial cause; SARS-CoV-2 PCR testing may be positive or negative [2].

In particular, cardiac involvement was considered present if at least one of the following conditions was fulfilled: cardiac dysrhythmia or arrythmia; ejection fraction of <55%; pulmonary oedema due to left heart failure; coronary artery z scores of ≥2.5; pericarditis or pericardial effusion; elevated troponin (based on the upper limit of normal for the laboratory running the assay); receipt of vasopressor or vasoactive support; receipt of cardiopulmonary resuscitation (CPR).

Data collection

Demographic, clinical and laboratory data at the time of admittance (within 48 h from admittance), and patients' outcomes were collected in an online anonymized database, which was built for the study purpose using REDCap electronic data capture tools hosted at IRCCS Burlo Garofolo [10, 11].

Patients were treated according to the attending physician's decision, but the main options were the variable administration of IVIG, systemic CSs, and anakinra. Patients were divided into four groups on the basis of the first treatment they underwent at the time of admittance: (i) IVIG, (ii) IVIG plus low-dose methylprednisolone (≤2 mg/kg/day), (iii) IVIG plus high-dose methylprednisolone (>2 mg/kg/day) and (iv) anakinra with or without other drugs (IVIG and/or methylprednisolone). Treatment failure was defined as the need for intensification of treatment after initial treatment.

Outcome

The primary outcomes were defined as death, or the failure of first treatment (considered as: the drugs used in the first 48 h from admittance, the needing of additional treatment for clinical worsening based on treating physician decision within 72 h from the starting treatment, and cardiac involvement at time of discharge). Cardiac involvement at time of discharge was defined as follows: valvular insufficiency and/or heart insufficiency and/or pericarditis and/or any abnormalities of the coronary arteries. Secondary outcomes included the length of hospitalization, the use of vasoactive agents, paediatric intensive care admittance, and/or ventilatory support. Time of discharge was defined as the last 48 h before the discharge.

Statistical analysis

The descriptive analysis was reported using frequency and percentage for the categorical variables and median and interquartile range (IQR) for continuous variables. χ^2 or Fisher exact tests were applied to establish associations between two categorical variables, as appropriate.

Standard mean differences (SMDs) were calculated to evaluate possible imbalances in the baseline characteristics between the therapy groups. Identified groups of therapies were (i) IVIG + high-dose CSs *vs* IVIG + low-dose CSs and (ii) IVIG + CSs + anakinra *vs* IVIG + CSs. Baseline characteristics included both demographic variables and clinical and laboratory manifestations at the onset: age, sex, ethnicity, time from fever onset to hospital arrival, CRP, need for vasoactive

agents, ventricular ejection fraction of <55%, need for ventilatory support, need for intensive care, at least one heart involvement, at least one neurological involvement, at least one lung involvement.

To balance the differences in the baseline characteristics between the therapy groups, propensity score was applied. Propensity score was calculated by logistic regression, using as the dependent variable the therapy groups, and as independent variables the baseline characteristics with SMD > 0.1.

An inverse probability of treatment weighting (IPTW) logistic regression model was constructed to establish associations between each outcome (as described above) and the therapy group. Models were weighted by the appropriate inverse of propensity score and adjusted by baseline variables with a residual imbalance (i.e. SMD > 0.15) after applying the propensity score.

P-values of <0.05 were considered as indicating statistical significance. All analyses were performed using SAS software, Version 9.4 (SAS Institute Inc., Cary, NC, USA) [12].

Results

Baseline population characteristics

A total of 239 patients were enrolled (104 females; 135 males). The median age of onset was 8 years (IQR: 4–11), and most patients were of Caucasian ancestry (190/239; 79.5%). In the 3 months before MIS-C presentation, 93 out of 239 (38.9%) patients presented at least one symptom possibly related to COVID-19 infection; 69 patients (28.9%) reported a clinical COVID-19 diagnosis, while 118 patients (49.4%) reported a contact with a COVID-19 patient. All patients presented either a positive RT-PCR nasal swab, a serological test positivity, recent clinical history compatible with SARS-CoV-2 infection or a recent contact with a person with a SARS-CoV-2 infection. The RT-PCR nasal swab test result was positive for SARS-CoV-2 in 65 patients (27.2%); 188 patients were tested for SARS-CoV-2 serology and 164 patients were positive (87.2%); 45/164 presented IgM positivity and 159/164 IgG positivity); 37 patients presented both RT-PCR and serological test positivity. In the whole study population, evidence of recent SARS-CoV-2 infection was detected in 192 patients (80%).

Clinical and laboratory manifestations

At the time of admission, all patients had fever; skin involvement was present in 64.4% of patients, mucositis in 64.4% and conjunctivitis in 56.1%. Gastrointestinal symptoms were present at onset in 72.8% of children, while lymphadenopathy was present in 30.1% of children. Lung involvement was present in 33.5% of patients; oxygen supplementation was required in 15.5% and non-invasive/invasive ventilatory support was needed in 7.1% and 1.7% of patients, respectively. At the time of admission, all patients underwent a heart US; cardiac involvement was present in 70.7% of patients: 64 patients (26.8%) had myocarditis; 32 (13.4%) had pericarditis; 46 (19.3%) had valvular insufficiency; 30 (12.6%) had a coronary abnormality, while 39 (16.4%) displayed heart failure. Hypotension and non-cardiogenic shock were observed in 46 patients (19.3%).

Laboratory examinations at the time of admission showed a significant lymphopenia (median 1070/mmc; IQR: 700–1950/mmc), thrombocytopenia (median 203 000/mmc; IQR: 121 000–275 000/mmc) and increase in inflammatory markers: CRP (median 146.5 mg/l; IQR: 97.00–227.1 mg/l), ESR (median: 53.5 mm/h; IQR: 32–74 mm/h), and ferritin (median 540 ng/ml; IQR: 287.5–915.5 ng/ml). Myocardial enzymes were also elevated: NT-proBNP (Brain Natriuretic Peptide) (median 3364.5 pg/ml; IQR: 873.9–9222.5 pg/ml), BNP (557.5 pg/ml; IQR: 135–1110 pg/ml), troponin I (median 84.7 ng/l; IQR: 26–398 ng/l), troponin T (median 24.6 ng/l; IQR: 8–62.5 ng/l) and e hs-troponin (median 33 ng/l; IQR: 11.7–110.1 ng/l). The clinical and laboratory manifestations are fully described in Table 1.

Concerning the treatment at time of admission: 24 patients (10%) were treated only with IVIG; 127 patients (53%) were treated with IVIG and high-dose CSs; 48 patients (20%) were treated with IVIG and low-dose CSs; and 21 patients (9%) were treated with anakinra in association with IVIG and CSs (19 patients) or only with CSs (2 patients). Of the remaining 19 patients (8%), 4 were treated only with ASA and CSs, and 15 were treated only with CSs.

Cardiac involvement during hospitalization and at the end of follow-up

During the hospitalization, 187 patients (78.2%) showed cardiac involvement: 72 (30.1%) presenting with myocarditis, 60 (25.1%) with valvular insufficiency, 56 (23.4%) with hypotension and/or non-cardiogenic shock, 52 (21.8%) with heart failure, 40 (16.7%) with pericarditis, 27 (11.3%) with coronary dilation, 12 (5%) with coronary aneurysms, 7 (2.9%) with cardiac arrhythmia, and 2 patients had a cardiac arrest (0.8%).

Among our population, only one patient died of cardiac arrest, after 2 months of hospitalization in the Pediatric Intensive Care Unit, where he had received treatment only with CSs. All the other MIS-C patients were discharged from hospital in good clinical condition. One hundred and ninety patients underwent a heart ultrasonography at the time of discharge; of these, 83 patients (34.3%) had at least one heart ultrasonography abnormality at the time of discharge: in particular, left atrial dilation in 2 patients; pericarditis in 15, valvular insufficiency in 40 patients, low ventricular ejection in 11 patients, coronary abnormalities in 12 and coronary aneurysms in 5. Thirteen patients showed persistent, although improved, heart failure.

Outcomes

Concerning the primary outcomes, death was observed in a single patient out of 239 MIS-C subjects enrolled in the study. There were no differences in outcomes if patients without laboratory evidence of SARS-CoV-2 infection were excluded.

Laboratory parameters

From univariate analysis, persistent heart involvement at discharge was not associated with any clinical or laboratory test alteration at the time of diagnosis. Only lower levels of lymphocytes (median 1140/mmc; IQR: 8870–170/mmc *vs* 815/mmc; IQR: 17–3410; $P = 0.047$) and higher levels of BNP (median 1903 pg/ml; IQR: 17–5000 pg/ml *vs* 1903 pg/ml; IQR: 534–5194; $P = 0.046$) were statistically associated with failure of the first treatment option.

Treatment approaches

The univariate analysis showed that initial treatment with anakinra (3/21 *vs* 66/169; $P = 0.047$) was associated with a

Table 1. Demographic, clinical and laboratory manifestations of study population at onset

Demographic characteristics	
Female/Male	104/135
Ethnicity, *n* (%)	
Caucasian ancestry	190 (79.5)
African	26 (10.9)
Asian	17 (7.1)
Latin-American	6 (2.5)
Age at onset, median (IQR), years	8 (4–11)
Clinical manifestations	
At least one skin involvement, *n* (%)	**155 (64.9)**
Maculopapular rash	106 (44.4)
Multiform erythema	23 (9.6)
Perineal erythema	3 (1.3)
Scarlattinoform rash	8 (3.4)
Palmoplantar erythema	41 (17.2)
At least one mucosal involvement, *n* (%)	**154 (64.4)**
Cheilitis	97 (40.6)
Oral changes	90 (37.7)
At least one ocular involvement, *n* (%)	**135 (56.5)**
Conjunctivitis	134 (56.1)
At least one neurological involvement, *n* (%)	**112 (46.9)**
Headache	42 (17.6)
Aseptic meningitis	11 (4.6)
Irritability	56 (23.4)
At least one gastrointestinal involvement, *n* (%)	**174 (72.8)**
Diarrhoea	105 (43.9)
Vomiting	73 (30.6)
Abdominal pain	112 (46.9)
Colecyts hydrops	6 (2.5)
Acute pancreatitis	3 (1.3)
Hepatomegaly	30 (12.6)
Splenomegaly	21 (8.8)
At least one lung involvement, *n* (%)	**80 (33.5)**
Dyspnea	27 (11.3)
Tachypnea	28 (11.7)
Lobar pneumonia	12 (5.0)
Interstitial pneumonia	22 (9.2)
Oxygen supplementation	37 (15.5)
Non-invasive/Invasive ventilation	21 (8.8)
At least one heart involvement, *n* (%)	**169 (70.7)**
Myocarditis	64 (26.8)
Pericarditis	32 (13.4)
Valvular insufficiency	46 (19.3)
Coronary dilation	22 (9.2)
Coronary aneurism	8 (3.4)
Heart failure	39 (16.4)
Hypotension/Non-cardiogenic shock	46 (19.3)
Cardiac arrest	2 (0.8)
At least one osteoarticular involvement, *n* (%)	**30 (12.6)**
Arthritis/arthralgia	19 (8.0)
Myositis	4 (1.7)
Lymphadenopathy, *n* (%)	**72 (30.1)**
Laboratory exams (normal values)	**Median (IQR)**
Leucocytes (5-19.5 10^3/mmc)	10 795 (7750-13 615)
Neutrophils (1-9 10^3/mmc)	8280 (5650-10450)
Lymphocytes (2.5-16.5 10^3/mmc)	1070 (700-1950)
Monocytes (0.2-1.10 10^3/mmc)	400 (220-780)
Haemoglobin (9-13.5 g/dL)	11.3 (10.4-12.3)
Platelets (100-400/mmc)	203 000 (121 000-275 000)
ALT (10-50 U/L)	26 (18-44)
AST (28-41 U/L)	34 (23-50)
GammaGT (39-308 U/L)	23 (15-48)
Creatinine (0.17-0.43 mg/dL)	0.5 (0.4-0.8)
Sodium (136-145mEq/L)	134 (131-136)
Clorus (98-107mEq/L)	99 (96-102)
Potassium (3.4-4.5mEq/L)	4 (3.5-4.3)
CRP (<5mg/L)	146.5 (97.0-227.1)
IgA (*mg/dL)	102 (77-173)
IgG (*mg/dL)	731.5 (591.5-993.5)
IgM (*mg/dL)	98.5 (74-136.5)
Proteins (5.9-7.3 g/dL)	6.3 (5.5-6.9)
Albumin (3.1-5.2 g/dL)	3.1 (2.7-3.6)
CPK (39-308 U/L)	66.5 (41-148)
pH (7.32–7.42)	7.42 (7.38–7.46)
pCO_2 (41–51mmHg)	35 (31–39)
Bicarbonates (22–29 mmol/l)	22.9 (21.1–25.4)
Lactic acid (<3.1 mmol/l)	1.4 (1.2–1.9)
Troponin I (<40 ng/l)	84.7 (26–398)
Troponin T (14 ng/l)	24.6 (8–62.5)
Hs-troponin (<11 ng/l)	33 (11.7–110.1)
Triglycerides (<150 mg/dl)	184 (131–251)
ESR (<28 mm/h)	53.5 (35–74)
Cholesterol (<190 mg/dl)	111 (86–129)
Fibrinogen (170–420 mg/dl)	582 (468–717)
INR	1.2 (1.1–1.4)
aPTT (0.8–1.20 ratio)	1.2 (1.1–1.3)
ATIII (79–120%)	81 (73–93)
C3 (90-180 mg/dl)	134 (89–153)
C4 (10-40 mg/dl)	23.5 (13–32)
Ferritin (30-400 ng/ml)	540 (287.5–915.5)
D-dimer (<500 ng/ml)	2222 (1185.5–3821.5)
NT-proBNP (<400 pg/ml)	3364.5 (873.9–9222.5)
BNP (<100 pg/ml)	557.5 (135–1110)

ALT: alanine aminotransferase; AST: aspartate aminotransferase; CRP: c-reactive protein; CPK: creatine phosphokinase; ESR: erythrocyte sedimentation rate; INR: international normalized ratio; APTT: activated partial thromboplastin time; AIII: antithrombin III; BNP: brain natriuretic peptide.

lower number of subjects who developed heart involvement at the time of discharge (Table 2).

Tables 3 and 4 show imbalance in several baseline characteristics between therapy groups, but after applying the propensity score method the differences between treatment approaches for most of the considered variables were reduced.

Also, the propensity score confirmed that anakinra use was associated with a lower probability of having persistent heart disease at the end of follow-up [$P < 0.06$; odds ratio (OR): 0.6; 95% CI: 0.4, 1.0]. A higher risk of intensive care admittance and use of vasoactive agents also emerged, although that difference was not statistically significant.

High-dose CSs were found to be associated with a lower probability of having treatment failure ($P < 0.0001$; OR: 0.4; 95% CI: 0.2, 0.6) and with a higher probability of having heart disease presence at the end of follow-up (Tables 5 and 6).

Discussion

MIS-C is an inflammatory systemic response to SARS-CoV-2 infection in children. Although some clinical manifestations are similar to KD, MIS-C has some specific clinical manifestations such as a more severe systemic inflammatory response with a higher rate of intensive care admittance and, in some cases, a fatal course [13]. In addition, MIS-C has a distinct heart involvement characterized by myocardial inflammation, heart failure, and valvular insufficiency, rather than classic coronary artery abnormalities, which is the most known clinical complication during KD [1].

Table 2. Univariate analysis of association between treatment option at time of admission and outcomes

	Corticosteroids + IVIG ($n = 169$)	Corticosteroids + IVIG + anakinra ($n = 21$)[a]	*P* value
Heart involvement at the end of follow-up, *n* (%)	66 (39.1)	3 (15)	0.047
Use of vasoactive agents during hospitalization; *n* (%)	21 (12.4)	8 (40)	0.001
Need of ventilatory support, *n* (%)	33 (19.5)	7 (35)	0.11
Intensive care admittance, *n* (%)	45 (26.6)	10 (50)	0.03

[a] 19 patients were treated with anakinra, CSs and IVIG; 2 patients were treated with anakinra and CSs.

Although MIS-C is now a well described and accepted clinical condition, its treatment is still debated. Since MIS-C shares clinical manifestations with KD, the first-line treatment generally adopted in clinical practice is based on IVIG infusion; however, CSs are often associated with IVIG because of the unusual severity of the inflammatory response [7]. The role of CSs treatment has not been clearly elucidated to date, as well as the use of other immunomodulant agents. Belhadier *et al.* demonstrated that adding CSs to immunoglobulins is associated with a shorter time to recovery of cardiac function in patients with MIS-C [14]; similarly, Son *et al.* and Ouldali *et al.* also showed that initial treatment with IVIG plus glucocorticoids, rather than initial treatment with IVIG alone, was associated with a lower risk of new or persistent cardiovascular dysfunction and a shorter duration of fever, respectively [8, 15].

On the other hand, McArdle *et al.* showed no evidence that recovery from MIS-C differed after primary treatment with IVIG alone, IVIG plus glucocorticoids, or glucocorticoids alone [9]; while Villacis-Nunez *et al.* demonstrated that glucocorticoids alone may be considered a reasonable treatment option for those patients with milder disease [16]. These discrepancies rely upon heterogeneity within the different studies in terms of recruitment criteria, outcomes explored, and methodology adopted, and no definite criteria are yet available for defining disease severity and treatment response. Given the available evidence, recent clinical recommendations have suggested the use of CSs and IVIG as first-line treatment [7, 17].

IL1 blockade has been increasingly used by paediatric rheumatologists in recent years to treat hyperinflammatory conditions of variable aetiology, and it has been recently demonstrated that refractory KD may respond to anti-IL1 treatment with anakinra [18]. Another condition characterized by secretion of cytokines, and which shares some laboratory characteristics with MIS-C, is Macrophage Activation Syndrome (MAS), which can also be treated with anakinra as well [19]. For these reasons anakinra has been used in cases of severe or refractory MIS-C, with a good response; however, the rate of the evidence is based on case reports, small case series, or descriptive case collection [20–23].

In our experience, MIS-C has an abrupt onset with severe manifestations, but usually a benign course in its acute phase, if recognized in a timely fashion and treated aggressively. Heart involvement may be the worst manifestation, and it is evident that heart involvement is the one that may influence survival rate and long-term complications [24, 25]. Myocarditis was the most common manifestation among our patients. Valvular insufficiency was mainly diagnosed based on US imaging, and its high incidence in our cohort may be related to the high incidence of myocarditis (and valvular insufficiency may be interpreted as a consequence of the myocarditis).

For the first time, we showed that the early use of anakinra at the time of admission was protective against heart involvement at time of discharge. The use of the propensity score suggests that this is independent of disease severity at onset, of the use of vasoactive drugs, and of intensive care admittance. This could be due to the fact that, in the absence of defined clinical guidelines, the choice of anakinra was totally in the hands of the treating physician and based on the severity of the clinical manifestations. Another hypothesis is that anakinra efficacy is more evident in patients with higher levels of inflammation, in which case the contribution of anakinra in controlling inflammation is more relevant.

Moreover, although the evaluation of the safety of anakinra was not the main aim of this study, no patient presented any side effects from anakinra infusion.

It is important to underline that Caglayan *et al.* recently reported 82 patients affected by MIS-C and treated with anakinra; among this population, 1.8% died [26]. These data seem to be contrasting with our results, in which anakinra was observed to be safe and seemed to be protective against cardiac outcome; however, in the manuscript by Caglayan *et al.* the median time to anakinra treatment varied from 1 to 14 days from time of admittance, while in our study all patients recruited were treated in the first 48 h. We believe that, since MIS-C is a very acute disease, prompt treatment is very important in defining the clinical outcome.

The efficacy of anakinra should not be surprising, since its use has been demonstrated to be of help in severe KD [18], but it is important to emphasize that while some authors consider MIS-C a unique disease, others consider it to be part of the KD spectrum [27] or a variable of the Kawasaki Shock Syndrome, the most severe clinical course of KD [28], both conditions in which a more aggressive treatment plan is considered acceptable. Indeed, some preliminary evidence has already been published on the efficacy of anakinra in more severe MIS-C patients [29–30].

The use of CSs has also been debated in MIS-C treatment; although several studies have tried to clarify the use of CSs in MIS-C, their role still remains unclear. Moreover, the best dosage protocol for CSs in MIS-C has never been discussed. For the first time, we have tried to determine whether high- or low-dose CSs may best influence MIS-C outcome. Our data did not demonstrate any significant difference in heart involvement at the end of follow-up, intensive care admittance, vasoactive drug use, or ventilatory need, based on the steroids dosing. However, high doses of CSs were associated with a lower probability of having treatment failure at the time of admission; in other words, the patients who were initially treated with high CSs were less likely to have treatment failure

Table 3. Propensity score analysis. Baseline Characteristics of Children according to First-line Therapy Group: IVIG plus high or low dose corticosteroids

	Before IPTW propensity method			After IPTW propensity method		
	IVIG + high-dose CSs (*n* = 127)	**IVIG + low-dose CSs (*n* = 48)**	**SMD**	**IVIG + high-dose CSs (*n* = 159.5)**	**IVIG + low-dose CSs (*n* = 146.9)**	**SMD**
Variables						
Age at onset, median (IQR)	8 (4–11)	8 (5–10)	0.003	7 (4–11)	8 (5–10)	−0.042
Sex, *n* (%)			−0.134			−0.163
F	55 (43.3)	24 (50.0)		68.9 (43.2)	75.4 (51.3)	
M	72 (56.7)	24 (50.0)		90.6 (56.8)	71.5 (48.7)	
Ethnicity, *n* (%)			0.516			0.679
Caucasian	96 (75.6)	44 (91.6)		118.8 (74.5)	138.2 (94.1)	
African	20 (15.8)	1 (2.1)		26.0 (16.3)	0 (0.0)	
Asian	3 (2.4)	1 (2.1)		3.8 (2.4)	4.7 (3.2)	
Middle-eastern	4 (3.1)	1 (2.1)		6.0 (3.8)	1.5 (1.0)	
Other	4 (3.1)	1 (2.1)		4.8 (3.0)	2.4 (1.6)	
Time from fever onset to hospital arrival (d), median (IQR)	5 (4–6)	4 (2–5)	0.349	4 (4–6)	4 (3–5)	0.085
CRP, median (IQR)	135.0 (80.6–202.0)	181.5 (110.5–238.0)	−0.402	141.1 (89.0–205.0)	144.5 (107.7–213.0)	−0.074
Need for vasoactive agents, *n* (%)	17 (13.4)	2 (4.2)	0.330	17.4 (10.9)	9.9 (6.7)	0.148
Ventricular ejection fraction <55%, *n* (%)	39 (30.7)	16 (33.3)	−0.056	50.2 (31.5)	40.3 (27.5)	0.089
Need for ventilatory support, *n* (%)	8 (6.5)	4 (4.4)	−0.076	10.0 (6.3)	6.4 (4.5)	0.077
Need for intensive care, *n* (%)	23 (20.2)	11 (23.9)	−0.090	33.6 (21.0)	27.9 (19.0)	0.051
At least one heart involvement, *n* (%)	91 (71.7)	39 (81.3)	−0.228	121.5 (76.2)	114.9 (78.2)	−0.049
At least one neurological involvement, *n* (%)	62 (48.8)	28 (58.3)	−0.192	82.1 (51.5)	81.0 (55.2)	−0.074
At least one lung involvement, *n* (%)	40 (31.5)	19 (39.6)	−0.170	52.4 (32.9)	50.5 (34.4)	−0.033

IPTW: inverse probability of treatment weighting; SMD: standard mean difference.

Table 4. Propensity score analysis. Baseline Characteristics of Children according to First-line Therapy Group: IVIG plus corticosteroids and anakinra versus other treatment plans

	Before IPTW propensity method			After IPTW propensity method		
	IVIG + CSs + anakinra (*n* = 21)	**Other therapy[a] (*n* = 218)**	**SMD**	**IVIG + CSs + anakinra (*n* = 155.9)**	**Other therapy[a] (*n* = 198.5)**	**SMD**
Variables						
Age at onset, median (IQR)	10 (5–12)	7 (4–11)	0.331	11 (8–12)	7 (4–11)	0.296
Sex, *n* (%)			0.090			0.597
F	10 (47.6)	94 (43.1)		112.9 (72.4)	87.9 (44.3)	
M	11 (52.4)	124 (56.9)		42.9 (27.6)	110.6 (55.7)	
Ethnicity, *n* (%)			0.152			0.477
Caucasian	16 (76.2)	173 (79.4)		140.6 (90.2)	154.5 (77.8)	
African	2 (9.5)	24 (11.0)		8.8 (5.7)	23. (11.6)	
Asian	1 (4.8)	7 (3.2)		6.4 (4.1)	5.8 (2.9)	
Middle-eastern	1 (4.8)	6 (2.7)		0 (0.0)	6.4 (3.2)	
Other	1 (4.8)	8 (3.7)		0 (0.0)	8.6 (4.4)	
Time from fever onset to hospital arrival (d), median (IQR)	4 (3–5)	5 (3–6)	−0.339	4 (3–5)	4 (3–6)	−0.111
CRP, median (IQR)	188.4 (104.5–282.8)	146.0 (96.6–219.0)	0.254	135.0 (71.5–277.9)	146.0 (98.7–217)	0.000
Need for vasoactive agents, *n* (%)	6 (28.6)	26 (11.9)	0.423	20.5 (13.1)	27.0 (13.6)	−0.013
Ventricular ejection fraction <55%, *n* (%)	7 (33.3)	63 (28.9)	0.096	48.4 (31.0)	63.2 (31.8)	−0.018
Need for ventilatory support, *n* (%)	4 (21.1)	17 (8.3)	0.368	9.5 (6.1)	17.5 (8.8)	−0.103
Need for intensive care, *n* (%)	7 (36.8)	38 (20.9)	0.358	29.5 (18.9)	46.7 (23.5)	−0.112
At least one heart Involvement, *n* (%)	14 (66.7)	155 (71.1)	−0.096	120.5 (77.3)	143.7 (72.4)	0.114
At least one neurological involvement, *n* (%)	9 (42.9)	103 (47.3)	−0.088	40.3 (25.8)	101.5 (51.1)	−0.538
At least one lung involvement, *n* (%)	7 (33.3)	73 (33.5)	−0.003	46.2 (29.7)	66.5 (33.5)	−0.083

IPTW: inverse probability of treatment weighting; SMD: Standard Mean Difference.
[a] Adjusted by sex and ethnicity.

Table 5. Propensity score analysis. Evaluation of the association between IVIG plus high or low dose corticosteroids in relation of the following outcomes: clinical worsening, need for intensive care, ventilatory support, vasoactive agents use, heart disease at last follow-up and length of hospitalization

	Before IPTW propensity method			After IPTW propensity method		
	IVIG + high-dose CSs ($n = 127$)	IVIG + low-dose CSs ($n = 48$)	OR (95% CI)	IVIG + high-dose CSs ($n = 159.5$)	IVIG + low-dose CSs ($n = 146.9$)	OR[a] (95% CI)
OUTCOME						
At least one worsening/poor response, *n* (%)	42 (33.1)	28 (58.3)	0.4 (0.2, 0.7)	55.8 (35.0)	86.3 (58.8)	0.4 (0.2, 0.6)
Need for intensive care, *n* (%)	31 (24.4)	14 (29.2)	0.7 (0.4, 1.6)	39.4 (24.7)	32.9 (22.4)	1.2 (0.7, 2.1)
Need for ventilatory support, *n* (%)	22 (17.3)	10 (20.8)	0.8 (0.3, 1.8)	28.0 (17.5)	27.6 (18.8)	0.6 (0.3, 1.2)
Need for vasoactive agents *n* (%)	19 (15.0)	3 (6.3)	2.3 (0.7, 7.8)	20.9 (13.1)	9.9 (6.7)	2.4 (1.1, 5.4)
Heart disease at the last follow-up, *n* (%)	50 (39.4)	15 (31.3)	1.4 (0.7, 2.9)	64.8 (40.6)	53.4 (36.3)	1.2 (0.7, 1.9)
Length of hospitalization >11 days, *n* (%)	46 (36.2)	32 (66.7)	0.3 (0.1, 0.6)	59.8 (37.5)	93.3 (63.5)	0.3 (0.2, 0.5)

IPTW: inverse probability of treatment weighting; OR, odds ratio.
[a] Adjusted by sex and ethnicity.

Table 6. Propensity score analysis. Evaluation of the association between IVIG plus corticosteroids and anakinra versus other treatment plans in relation of the following outcomes: clinical worsening, need for intensive care, ventilatory support, vasoactive agents use, heart disease at last follow-up and length of hospitalization

	Before IPTW propensity method			After IPTW propensity method		
	IVIG + CSs + anakinra ($n = 21$)	Other therapy[a] ($n = 218$)	OR (95% CI)	IVIG + CSs + anakinra ($n = 155.9$)	Other therapy[a] ($n = 198.5$)	OR[a] (95% CI)
OUTCOME						
At least one worsening/poor response, *n* (%)	17 (81.0)	85 (39.0)	6.1 (2.0, 18.1)	147.5 (94.6)	76.3 (38.4)	22.6 (10.4, 49.3)
Need for intensive care, *n* (%)	11 (52.4)	57 (26.2)	3.1 (1.2, 7.6)	44.7 (28.7)	55.9 (28.2)	1.3 (0.7, 2.2)
Need for ventilatory support, *n* (%)	7 (33.3)	43 (19.7)	2.1 (0.8, 5.5)	24.9 (16.0)	39.4 (19.9)	1.0 (0.5, 1.9)
Need for vasoactive agents, *n* (%)	8 (38.1)	25 (11.5)	4.8 (1.8, 12.6)	29.5 (19.0)	26.3 (13.2)	1.6 (0.7, 3.3)
Heart disease at the last follow-up, *n* (%)	3 (14.3)	80 (36.7)	0.3 (0.1, 1.1)	44.7 (28.7)	77.1 (38.8)	0.6 (0.4, 1.0)
Length of hospitalization >11 days, *n* (%)	20 (95.2)	99 (45.4)	16.4 (3, 91.5)	155.9 (100.0)	90.8 (45.8)	276.0 (18.0, >999.999)

[a] Adjusted by age at the onset, sex, ethnicity and at least a neurological involvement at the baseline. IPTW: inverse probability of treatment weighting; OR, odds ratio.

during hospitalization. This is a very interesting finding and suggests a protective role of high-dose CSs in MIS-C patients, although it is not clear why CSs were not associated with better outcomes in terms of heart involvement at the end of follow-up, or with any other primary or secondary outcome. This could be due to the number of patients recruited and the heterogeneity of treatments adopted, although the methodology using the propensity score tried to correct this bias. It is also notable that patients failing initial treatment with CSs likely received intensification of treatment with higher doses of CSs or biologic drugs, so it is not possible to clearly evaluate the effect of CSs dosage on clinical outcome. Since in our cohort the vast majority of patients were treated from the beginning with IVIG and CSs, the usefulness of treatment with IVIG alone or CSs alone was not assessed.

The mortality rate in our cohort was low, as only one patient died after 2 months of hospitalization in paediatric intensive care; this contrast with the 70 patients (in 8639 MIS-C cases) who died of MIS-C in the United States [31]. The patient reported on in our study was treated only with CSs, and he had never received IVIG or anakinra.

Our study has some caveats, mainly the relatively low number of patients recruited and its retrospective design. Although the methodology adopted, with the use of the propensity score, tried to correct for the treatment heterogeneity among our population, it may be that the most severe patients benefitted, at least partially, from intensive care unit admittance and the use of vasoactive agents. Unfortunately, a randomized controlled trial to evaluate the real benefit of adding IL1 to treatment for patients with MIS-C seems unpractical. Another aspect of interpretation of the findings lies in the patient's diagnosis, as it has already been demonstrated that the MIS-C criteria may not be highly specific, and some patients with severe acute COVID-19 may satisfy the criteria; therefore, it is not possible to exclude the possibility that a minority of our patients were affected by severe COVID-19 and not by MIS-C. Indeed, the distinction between the two conditions is sometimes very difficult in clinical practice [32], but we believe the suggestion that IL1 blockade might be useful in treating patients with hyperinflammatory conditions related to SARS-CoV-2 infection would be of great value for clinicians attending those patients. This is also in accordance with evidence from adult patients with severe COVID-19, who have been successfully treated with IL1 antagonists [33]. Finally, as MIS-C is a good model of a hyperinflammatory condition with heart involvement, our evidence would also be of interest in the study of other common conditions, such as KD and MAS.

In conclusion, although the best treatment option for MIS-C patients has not been established yet, it is clear that an early aggressive treatment seems to be strongly recommended; in particular early treatment with anakinra seems to be safe and very useful in patients with MIS-C, and anakinra could be considered the best treatment option for those patients with a higher probability of developing severe disease; unfortunately, it is not clear which are the clinical or laboratory characteristics at onset that

may predict a more severe disease course; more data need to be collected in order to try to address these issues.

Supplementary material

Supplementary material is available at *Rheumatology* online.

Data availability

The data that support the findings of this study are openly available in figshare at http://doi.orghttps://figshare.com/articles/dataset/Anakinra_and_MIS-C/22180063.

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