

Immunomodulatory therapy in children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS, MIS-C; RECOVERY): a randomised, controlled, open-label, platform trial



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Summary

Background Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS), also known as multisystem inflammatory syndrome in children (MIS-C) emerged in April, 2020. The paediatric comparisons within the RECOVERY trial aimed to assess the effect of intravenous immunoglobulin or corticosteroids compared with usual care on duration of hospital stay for children with PIMS-TS and to compare tocilizumab (anti-IL-6 receptor monoclonal antibody) or anakinra (anti-IL-1 receptor antagonist) with usual care for those with inflammation refractory to initial treatment.

Methods We did this randomised, controlled, open-label, platform trial in 51 hospitals in the UK. Eligible patients were younger than 18 years and had been admitted to hospital for PIMS-TS. In the first randomisation, patients were randomly assigned (1:1:1) to usual care (no additional treatments), usual care plus methylprednisolone (10mg/kg per day for 3 consecutive days), or usual care plus intravenous immunoglobulin (a single dose of 2 g/kg). If further anti-inflammatory treatment was considered necessary, children aged at least 1 year could be considered for a second randomisation, in which patients were randomly assigned (1:2:2) to usual care, intravenous tocilizumab (12 mg/kg in patients <30 kg; 8mg/kg in patients ≥30 kg, up to a maximum dose of 800 mg), or subcutaneous anakinra (2 mg/kg once per day in patients ≥10 kg). Randomisation was by use of a web-based simple (unstratified) randomisation with allocation concealment. The primary outcome was duration of hospital stay. Analysis was by intention to treat. For treatments assessed in each randomisation, a single Bayesian framework assuming uninformative priors for treatment was used to jointly assess the efficacy of each intervention compared with usual care. The trial was registered with ISRCTN (50189673) and ClinicalTrials.gov (NCT04381936).

Findings Between May 18, 2020, and Jan 20, 2022, 237 children with PIMS-TS were enrolled and included in the intention-to-treat analysis. Of the 214 patients who entered the first randomisation, 73 were assigned to receive intravenous immunoglobulin, 61 methylprednisolone, and 80 usual care. Of the 70 children who entered the second randomisation (including 23 who did not enter the first randomisation), 28 were assigned to receive tocilizumab, 14 anakinra, and 28 usual care. Mean age was 9·5 years (SD 3·8) in the randomisation and 9·6 years (3·6) in the second randomisation. 118 (55%) of 214 patients in the first randomisation and 39 (56%) of 70 patients in the second randomisation were male. 130 (55%) of 237 patients were Black, Asian, or minority ethnic, and 105 (44%) were White. Mean duration of hospital stay was 7·4 days (SD 0·4) in children assigned to intravenous immunoglobulin and 7·6 days (0·4) in children assigned to usual care (difference -0·1 days, 95% credible interval [CrI] -1·3 to 1·0; posterior probability 59%). Mean duration of hospital stay was 6·9 days (SD 0·5) in children assigned to methylprednisolone (difference from usual care -0·7 days, 95% CrI -1·9 to 0·6; posterior probability 87%). Mean duration of hospital stay was 6·6 days (SD 0·7) in children assigned to second-line tocilizumab and 9·9 days (0·9) in children assigned to usual care (difference -3·3 days, 95% CrI -5·6 to -1·0; posterior probability >99%). Mean duration of hospital stay was 8·5 days (SD 1·2) in children assigned to anakinra (difference from usual care -1·4 days, 95% CrI -4·3 to 1·8; posterior probability 84%). Two persistent coronary artery aneurysms were reported among patients assigned to usual care in the first randomisation. There were few cardiac arrhythmias, bleeding, or thrombotic events in any group. Two children died; neither was considered related to study treatment.

Interpretation Moderate evidence suggests that, compared with usual care, first-line intravenous methylprednisolone reduces duration of hospital stay for children with PIMS-TS. Good evidence suggests that second-line tocilizumab reduces duration of hospital stay for children with inflammation refractory to initial treatment. Neither intravenous immunoglobulin nor anakinra had any effect on duration of hospital stay compared with usual care.

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Research in context

Evidence before this study

Paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS, also known as multisystem inflammatory syndrome in children [MIS-C]) has been treated mainly based on expert opinion and on evidence from retrospective case series and one small randomised controlled trial. We searched PubMed for studies published between April 1, 2020, and April 10, 2023, using the terms (“intravenous immunoglobulins” OR “methylprednisolone” OR “tocilizumab” OR “anakinra” OR “trial”) AND (“Paediatric multisystem inflammatory disease” OR “Paediatric Inflammatory Multisystem Syndrome”) with no language restrictions. Six observational studies analysed the effectiveness of glucocorticoids or intravenous immunoglobulins and other anti-inflammatory treatments. Although at high risk of bias, retrospective observational data from large cohorts reported conflicting conclusions. One study showed a lower rate of treatment failure with intravenous immunoglobulin plus corticosteroids compared with intravenous immunoglobulin alone, with no long-term cardiovascular complications or persistent inflammatory syndromes. A cohort of 518 children from centres in the USA had better outcomes with intravenous immunoglobulin plus corticosteroids versus intravenous immunoglobulin alone. The Best Available Treatment Study included 614 children from 32 countries and did not find any evidence that recovery from PIMS-TS differed after primary treatment with intravenous immunoglobulin alone versus intravenous immunoglobulin plus corticosteroids versus corticosteroids alone; children who received no immunomodulatory treatment took longer to improve. A meta-analysis of the largest non-randomised observational

cohort studies concluded that intravenous immunoglobulin plus glucocorticoids was associated with improved cardiovascular dysfunction compared with intravenous immunoglobulin alone and that treatment with glucocorticoids alone was not associated with improved cardiovascular dysfunction compared with intravenous immunoglobulin alone or intravenous immunoglobulin plus glucocorticoids. Finally, in one randomised controlled trial with 75 children with PIMS-TS, duration of hospital stay did not differ between methylprednisolone and intravenous immunoglobulin treatment groups.

Added value of this study

We found modest evidence that methylprednisolone reduces duration of hospital stay for children with PIMS-TS and good evidence that second-stage tocilizumab reduces duration of hospital stay for children with PIMS-TS refractory to initial treatment. However, both treatments were associated with increased use of inotropes. We found no evidence of benefit for intravenous immunoglobulin, and the anakinra versus usual care comparison included too few patients for us to draw reliable conclusions.

Implications of all the available evidence

The RECOVERY trial shows, for the first time, that methylprednisolone and tocilizumab are superior to usual care for children with PIMS-TS. These randomised data should inform updates of clinical guidelines. These results also show that it is feasible to recruit children into trials during a pandemic to generate reliable evidence.

Introduction

Paediatric multisystem inflammatory syndrome temporally associated with SARS-CoV-2 (PIMS-TS) was first described in April, 2020.¹⁻³ The condition is also widely referred to as multisystem inflammatory syndrome in children (MIS-C) associated with COVID-19. Patients younger than 18 years present with clinical and laboratory evidence of multisystem inflammation, erythematous mucocutaneous changes, and organ dysfunction particularly affecting the brain, heart, and gut. When first described, 40% of patients required critical care support for shock and cardiac dysfunction, and 12–15% developed coronary artery aneurysms.⁴ Similarities between PIMS-TS and other childhood conditions such as toxic shock syndrome and Kawasaki disease led clinicians to use immunomodulatory therapies believed to be efficacious in treating these conditions.⁴ National and international guidelines were rapidly developed based on expert consensus, and an urgent need for evidence-based treatment was recognised.^{5,6} The mainstay of treatment was supportive care including, when required, organ

support such as vasoactive medications and immunomodulatory therapies.

Observational data from Europe and the USA in the first months of the COVID-19 pandemic suggested that symptoms resolved after treatment with intravenous immunoglobulin and corticosteroids. However, some children who only received supportive care recovered without apparent sequelae.^{4,7,8} A smaller group of children with refractory inflammation were treated in intensive care with a variety of biologics targeting the cytokines interleukin (IL)-1 β , tumour necrosis factor, and IL-6. Similar findings were made in subsequent observational studies.⁹⁻¹² Before possible treatments had sufficient supporting evidence, the primary question from clinicians, particularly in settings where intravenous immunoglobulin was unavailable or unaffordable, was whether children and young people given corticosteroids only had worse outcomes than those also given intravenous immunoglobulin. Whether further or alternative immunomodulatory treatment altered the course of illness was also unknown.

The Randomised Evaluation of COVID-19 therapy (RECOVERY) trial is an investigator-initiated, individually randomised, controlled, open-label, adaptive platform trial to evaluate the effects of potential treatments in patients of all ages admitted to hospital for COVID-19. We used the RECOVERY trial platform to assess the effect of intravenous immunoglobulin or corticosteroids compared with usual care on length of stay in hospital for children with PIMS-TS. We included a second round of randomisation for children with inflammation refractory to first-line treatment, assessing usual care compared with tocilizumab (an anti-IL-6 receptor monoclonal antibody) and anakinra (an anti-IL-1 receptor antagonist).

Methods

Study design

Patients younger than 18 years with PIMS-TS were included in RECOVERY from May 9, 2020. Specialists in paediatric infectious diseases, cardiology, rheumatology, respiratory, critical care, neonatology, and pharmacy formed a working group that developed paediatric arms of the RECOVERY trial specifically to establish best treatments for COVID-19 and subsequently PIMS-TS. Details of the trial design and results for other treatments have been reported.^{13–21} 51 of 177 hospitals in the UK supported by the National Institute for Health Research (NIHR) Clinical Research Network participated in the first randomisation for the initial treatment of PIMS-TS, and 25 hospitals participated in the second randomisation for patients with PIMS-TS requiring further treatment.

The trial was coordinated by the Nuffield Department of Population Health at the University of Oxford (Oxford, UK), the trial sponsor. The trial was conducted in accordance with the principles of the International Conference on Harmonisation–Good Clinical Practice guidelines and approved by the UK Medicines and Healthcare products Regulatory Agency and the Cambridge East Research Ethics Committee (ref: 20/EE/0101). The protocol and statistical analysis plans are available in the appendix and on the study website.

Participants

Patients younger than 18 years who had been admitted to hospital were eligible to participate in the study, if they had clinically suspected PIMS-TS according to the Royal College of Paediatrics and Child Health's criteria,⁵ unless the attending clinician deemed that their medical history put the patient at significant risk if they were to participate in the trial. Children could participate in both randomisation stages if they had previously received intravenous immunoglobulin or methylprednisolone as part of usual care, but they would not receive that same drug once enrolled. Patients with suspected Kawasaki disease were excluded. Patients with known hypersensitivity to human immunoglobulins, selective IgA deficiency, or hyperprolinaemia type I or II were

excluded from the comparison of intravenous immunoglobulin with usual care. Children younger than 1 year were not eligible for the second randomisation. Children weighing less than 10 kg were not eligible for the anakinra comparison. Written informed consent was obtained from all parents or legal guardians, or from patients aged 16 and 17 years if they were well enough to provide informed consent. Assent was obtained from children younger than 16 years who were well enough.

Randomisation and masking

A web-system was used to provide simple randomisation (without stratification or minimisation), with allocation concealment until randomisation had been completed. In the first randomisation, eligible patients were randomly assigned (1:1:1) to usual care, usual care plus methylprednisolone sodium succinate, or usual care plus intravenous immunoglobulin. The trial design allowed children to be randomly assigned to the comparison of the other treatment if the child had already received one of the trial treatments, but as in the RECOVERY trial with adults, treatments were tested independently. Allocated treatment was prescribed by the managing doctor. Patients could enter the second randomisation phase if clinicians deemed that they required additional anti-inflammatory treatment. In the second randomisation, children were initially randomly assigned (1:1) to usual care or usual care plus tocilizumab. On Feb 2, 2021, the second randomisation scheme changed so that patients were randomly assigned (1:2:2) to usual care, usual care plus tocilizumab, or usual care plus anakinra. The change in randomisation scheme followed the development of a Bayesian statistical analysis plan that accounted for the probable small recruitment compared with adult arms of the trial and the opportunity this gave to boost recruitment by increasing the chances of randomisation to an active treatment group. Detailed protocol amendments are listed in the appendix (pp 31, 109).

Children with mild to moderate PIMS-TS were deemed unlikely to be suitable for random assignment to second-stage interventions, unless there was clinical deterioration or failure to respond to first-stage treatment and evidence of ongoing fever and inflammation. Children with more severe disease who did not respond to first-stage interventions and had ongoing fever and inflammation were eligible for the second randomisation (appendix pp 56–80).

Participants and local study staff were not masked to the assigned treatment. The steering committee, investigators, and all others involved in the study (except the independent data monitoring committee) were masked to the results before final analysis.

Procedures

Baseline data were collected with a web-based case report form and included demographic details, level of respiratory support, major comorbidities, suitability of

For more on the RECOVERY trial see <https://www.recoverytrial.net/>

the study treatment for a particular patient, and treatment availability at the study site (appendix p 34–35).

In the first randomisation, patients received either usual care, usual care plus intravenous methylprednisolone sodium succinate 10 mg/kg (maximum 1 g) once a day for 3 consecutive days, or usual care plus a single dose of intravenous immunoglobulin (2 g/kg) as soon as possible after random assignment. In the second randomisation, patients received either usual care or a single dose of intravenous tocilizumab (12 mg/kg in patients <30 kg; 8 mg/kg in patients ≥30 kg; up to a maximum dose of 800 mg) as soon as possible after random assignment. After Feb 2, 2021, the second randomisation changed to usual care, tocilizumab (same dose as previously), or subcutaneous anakinra (2 mg/kg once per day in patients ≥10 kg) for 7 days or until discharge, whichever came first.

Follow-up information was completed when participants were discharged from hospital or at 28 days after randomisation (appendix p 37–44). At least 6 weeks after randomisation (during a routine in-person follow-up hospital appointment or telephone call), a follow-up form was completed for all participating children (appendix p 46–53). Information collected included vital signs, results of routine acute and follow-up tests (including C-reactive protein [CRP], electrocardiograms, and echocardiograms), other supportive care treatments for PIMS-TS (eg, aspirin), receipt of respiratory or renal support, duration of admission, and length of stay in paediatric high-dependency or intensive care. Some of this information was collected on an additional paediatric case record form.

Outcomes

Outcomes were initially assessed 28 days after randomisation. The primary outcome was duration of hospital stay. Secondary outcomes included number of days on inotropes and baseline-adjusted CRP values on day 3. Prespecified subsidiary clinical outcomes included need for inotropes, presence and persistence of coronary artery aneurysms or left ventricular dysfunction, number of days in intensive care, readmission to hospital within 8 weeks of discharge, use of additional antibiotics post-discharge, and time to escalation of immunosuppressive treatment. The statistical analysis plan also specified duration of invasive or non-invasive mechanical ventilation and area under the curve of CRP values between days 1 and 8, but these analyses were not completed due to the very small numbers of patients needing ventilatory support or with available CRP data beyond day 3. Suspected serious adverse reactions were reported in an expedited manner, in compliance with regulatory requirements.

Statistical analysis

All analyses were done in the intention-to-treat population and in accordance with the prespecified Statistical Analysis Plan for the PIMS-TS population (appendix p 101). For the

primary and secondary outcomes (and the subsidiary outcome of days on intensive care), a Bayesian framework was used to jointly assess the efficacy of each intervention compared with a common group of children assigned to usual care. This was done separately for treatments in the first and second randomisations. For the other outcomes, Bayesian analyses were also done, but only comparing each treatment with its own control (including only patients for whom the active treatment was both available and suitable as a treatment). The posterior distribution of the difference between the outcome of an active treatment and the outcome of usual care was calculated. If the probability that the active group had a better outcome than the usual care group (ie, the difference in outcome is negative—denoted posterior probability in the results) was 95% or larger, this signified a very strong signal of benefit. A probability between 80% and 95% was interpreted as a strong signal, and a probability of 70–80% constituted a moderate positive signal. A probability of 30% or less was taken as a signal for possible harm. Sensitivity analyses for primary and secondary outcomes comparing each treatment group to its own control were also done.

To analyse the primary outcome (duration of hospital stay), an age-adjusted Bayesian negative binomial model was used. Non-informative prior distributions were used for each treatment indicator and age, while the prior distribution for the intercept was informed by UK national surveillance data. The secondary outcome (number of days on inotropes) was analysed using the same model but with a different prior distribution for the intercept, which was also informed by UK national surveillance data. CRP values on day 3 were analysed on the log scale with a Bayesian linear model that adjusted for the log baseline CRP value and age. Non-informative normal priors were used for all parameters.

Prespecified secondary and subsidiary clinical outcomes were analysed according to their type. Count data, such as duration of stay in a paediatric intensive care unit, were analysed with the same model as the primary endpoint but with different prior distributions on the intercept. Binary outcomes were analysed using a Beta-Binomial model with a Beta(1,1) prior distribution, and a Bayesian Cox proportional hazards model with non-informative priors (ie, normal for the regression coefficients and gamma prior for the baseline hazard) was used for the outcome of time to next escalation of immunosuppressive treatment.

The full database is held by the study team, which collected the data from study sites and did the analyses at the Nuffield Department of Population Health, University of Oxford (Oxford, UK).

As stated in the protocol, appropriate sample sizes could not be estimated when the trial was being planned at the start of the COVID-19 pandemic. Recruitment to the intravenous immunoglobulin and corticosteroid comparisons to usual care ended on July 16, 2021, and recruitment to the tocilizumab and anakinra comparison to usual care ended on Jan 20, 2022, when clinical cases

stopped being seen routinely in the UK. The statistical analysis plan was finalised on Aug 31, 2021 (without any knowledge of the study results). The trial steering committee and all other individuals involved in the trial were masked to outcome data until after the completion of follow-up.

Analyses were done in SAS version 9.4. The trial is registered with ISRCTN (50189673) and ClinicalTrials.gov (NCT04381936).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between May 18, 2020, and Jan 20, 2022, 244 children with PIMS-TS were assessed for eligibility. Seven patients were excluded and 237 were enrolled (figure). 23 patients entered the second randomisation directly and 214 patients entered the first randomisation, 73 of whom were randomly assigned to intravenous immunoglobulin, 61 to methylprednisolone, and 80 to usual care. 70 children entered the second randomisation, 28 of whom were randomly assigned to tocilizumab, 14 to anakinra, and 28 to usual care. One patient withdrew consent after the second randomisation. 237 patients were included in the intention-to-treat analysis.

Baseline characteristics were similar in all groups (table 1). Mean age was 9.5 years (SD 3.8) in the first randomisation and 9.6 years (3.6) in the second randomisation. 118 (55%) of 214 patients in the first randomisation and 39 (56%) of 70 patients in the second randomisation were male. 130 (55%) of 237 patients were from Black, Asian, or minority ethnic groups, and 105 (44%) were White.

Median time from symptom onset to treatment assignment was 6 days (IQR 5–8) in the first randomisation and 7 days (5–8) in the second randomisation. Median time from hospital admission to treatment assignment was 1 day (1–2) and 2 days (1–3) in the first and second randomisation, respectively. CRP, creatinine, and D-dimer test results and respiratory support were similar between groups within and across comparisons (table 1). Previous diseases and drug treatments are shown in table 1.

Compliance with assigned therapy was generally very good in the treatment groups (table 2), but a substantial proportion of patients assigned to usual care in the first randomisation received an off-protocol study treatment after randomisation (table 2). 19 (35%) of 55 patients assigned to usual care in the intravenous immunoglobulin comparison received intravenous immunoglobulin, and 33 (50%) of 66 patients assigned to usual care in the methylprednisolone comparison received corticosteroids. Compliance was better in the second randomisation, in which no patients in the usual care group of the tocilizumab comparison received tocilizumab and

three (25%) of 12 patients in the usual care group of the anakinra comparison received anakinra.

Mean duration of hospital stay was 7.4 days (SD 0.4) in children assigned to intravenous immunoglobulin and 7.6 days (0.4) in children assigned to usual care (difference -0.1 days, 95% credible interval [CrI] -1.3 to 1.0 ; posterior probability 59%; table 3). The difference in the number of days on inotropes was 0.0 (-0.4 to 0.4 ; posterior probability 45%). 25 (34%) of 73 patients assigned to intravenous immunoglobulin and 19 (35%) of 55 patients assigned to usual care needed any inotropes (risk ratio 1.0, 95% CrI 0.6 to 1.6; posterior probability 53%; table 4). Natural log CRP values were higher in children assigned to intravenous immunoglobulin than in children assigned to usual care (difference 0.2, -0.1 to 0.4 ; posterior probability of benefit 9% [ie, 91% posterior probability of harm]; table 3).

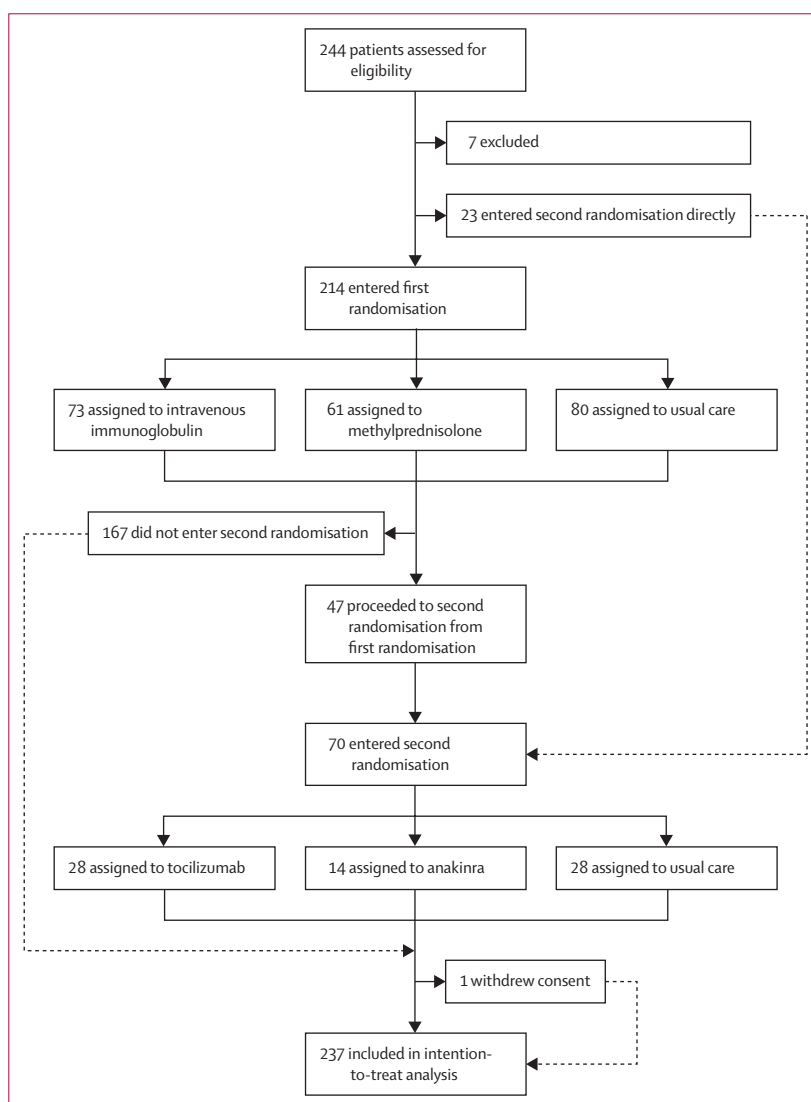


Figure: Trial profile

	First randomisation				Second randomisation			
	Intravenous immunoglobulin vs usual care		Methylprednisolone vs usual care		Tocilizumab vs usual care		Anakinra vs usual care	
	Intravenous immunoglobulin (n=73)	Usual care (n=55)	Methylprednisolone (n=61)	Usual care (n=66)	Tocilizumab (n=28)	Usual care (n=28)	Anakinra (n=14)	Usual care (n=12)
Age, years	9.2 (3.6)	9.7 (3.9)	10.0 (3.9)	9.0 (3.9)	9.4 (3.8)	9.7 (3.3)	9.9 (3.8)	9.2 (3.6)
Sex								
Male	38 (52%)	32 (58%)	32 (52%)	39 (59%)	14 (50%)	16 (57%)	9 (64%)	6 (50%)
Female	34 (47%)	23 (42%)	29 (48%)	27 (41%)	14 (50%)	12 (43%)	5 (36%)	6 (50%)
Ethnicity								
Black, Asian, and minority ethnic	43 (59%)	31 (56%)	36 (59%)	36 (55%)	18 (64%)	13 (46%)	8 (57%)	4 (33%)
White	29 (40%)	24 (44%)	24 (39%)	30 (45%)	10 (36%)	15 (54%)	6 (43%)	8 (67%)
Unknown	1 (1%)	0	1 (2%)	0	0	0	0	0
Time since symptom onset, days	6 (5-7)	6 (5-8)	7 (4-8)	6 (4-8)	7 (5-9)	7 (5-9)	5 (5-7)	10 (8-44)
Time since hospital admission, days	1 (1-2)	1 (1-2)	1 (1-2)	2 (1-3)	2 (1-3)	2 (1-4)	1 (1-2)	4 (2-6)
Biochemistry								
C-reactive protein, mg/L	177 (114-254)	176 (140-243)	191 (113-263)	172 (128-253)	240 (142-282)	194 (151-286)	213 (168-239)	166 (126-194)
Creatinine, µmol/L	50 (42-59)	48 (39-68)	45 (35-73)	46 (32-60)	53 (41-68)	42 (33-62)	50 (43-99)	37 (30-60)
D-dimer, ng/mL	1910 (628-4029)	1373 (633-3338)	1709 (10-3317)	1593 (832-3895)	3201 (906-5572)	2456 (1232-4910)	3290 (2032-4000)	2563 (1071-6196)
Respiratory support								
No oxygen	60 (82%)	46 (84%)	48 (79%)	54 (82%)	17 (61%)	17 (61%)	9 (64%)	8 (67%)
Oxygen only	7 (10%)	3 (5%)	4 (7%)	4 (6%)	5 (18%)	6 (21%)	2 (14%)	1 (8%)
Non-invasive ventilation	4 (5%)	5 (9%)	4 (7%)	5 (8%)	2 (7%)	3 (11%)	1 (7%)	2 (17%)
Invasive mechanical ventilation	2 (3%)	1 (2%)	5 (8%)	3 (5%)	4 (14%)	2 (7%)	2 (14%)	1 (8%)
Previous diseases								
Diabetes	1 (1%)	0	0	1 (2%)	0	0	1 (7%)	0
Heart disease	0	0	1 (2%)	0	0	0	0	0
Chronic lung disease	1 (1%)	0	0	0	0	0	0	0
Tuberculosis	0	0	0	0	0	0	0	0
HIV	0	0	0	0	0	0	0	0
Severe liver disease	0	0	0	0	0	0	0	0
Severe kidney impairment*	0	0	0	1 (2%)	0	0	0	0
Any of the above	2 (3%)	0	1 (2%)	2 (3%)	0	0	1 (7%)	0
Previous drug treatment†								
Corticosteroids	14 (19%)	14 (25%)	1 (2%)	2 (3%)	10 (36%)	12 (43%)	3 (21%)	9 (75%)
Intravenous immunoglobulin	0	0	20 (33%)	23 (35%)	10 (36%)	12 (43%)	3 (21%)	7 (58%)
Remdesivir	0	0	0	0	0	0	0	0
Inotropes	11 (15%)	10 (18%)	10 (16%)	13 (20%)	19 (68%)	11 (39%)	6 (43%)	5 (42%)
SARS-CoV-2 test result								
Positive	11 (15%)	10 (18%)	10 (16%)	16 (24%)	5 (18%)	8 (29%)	3 (21%)	1 (8%)
Negative	60 (82%)	42 (76%)	48 (79%)	47 (71%)	21 (75%)	17 (61%)	10 (71%)	8 (67%)
Unknown	2 (3%)	3 (5%)	3 (5%)	3 (5%)	2 (7%)	3 (11%)	1 (7%)	3 (25%)

Data are mean (SD), n (%), or median (IQR). None of the female patients were pregnant. Both randomisations used a common control group, so 80 and 28 children were assigned usual care in first and second randomisations, respectively. *Estimated glomerular filtration rate <30 mL/min per 1.73 m². †Drugs recorded as being given to participant before randomisation.

Table 1: Baseline characteristics

Mean duration of hospital stay was 6.9 days (SD 0.5) in children assigned to methylprednisolone and 7.6 days (0.4) for children assigned to usual care (difference -0.7 days, 95% CrI -1.9 to 0.6; posterior probability of benefit 87%; table 3). The difference in the number of days on inotropes was 0.1 days (-0.3 to 0.5, posterior

probability of benefit 40%; table 3). 23 (38%) of 61 patients assigned to methylprednisolone and 17 (26%) of 66 patients assigned to usual care needed inotropes (risk ratio 1.5, 95% CrI 0.9 to 2.5; posterior probability of benefit 8% [ie, 92% posterior probability of harm]; table 4). Natural log CRP values were lower in children

	First randomisation				Second randomisation			
	Intravenous immunoglobulin vs usual care		Methylprednisolone vs usual care		Tocilizumab vs usual care		Anakinra vs usual care	
	Intravenous immunoglobulin (n=73)	Usual care (n=55)	Methylprednisolone (n=61)	Usual care (n=66)	Tocilizumab (n=28)	Usual care (n=28)	Anakinra (n=14)	Usual care (n=12)
Patients with compliance data	72	55	61	66	28	28	14	12
Intravenous immunoglobulin	71 (99%)	19 (35%)	19 (31%)	29 (44%)	12 (43%)	14 (50%)	8 (57%)	5 (42%)
Corticosteroids	43 (60%)	32 (58%)	61 (100%)	33 (50%)	13 (46%)	22 (79%)	9 (64%)	9 (75%)
Tocilizumab or sarilumab	8 (11%)	9 (16%)	2 (3%)	11 (17%)	26 (93%)	0	0	0
Anakinra	5 (7%)	1 (2%)	1 (2%)	1 (2%)	0	3 (11%)	11 (79%)	3 (25%)
Other treatments received								
Lopinavir or ritonavir	0	0	0	0	0	0	0	0
Hydroxychloroquine	0	0	0	0	0	0	0	0
Azithromycin or other macrolide	11 (15%)	8 (15%)	9 (15%)	11 (17%)	2 (7%)	5 (18%)	1 (7%)	2 (17%)
Remdesivir	0	0	0	0	0	0	0	0
Casirivimab–imdevimab	0	0	0	0	0	0	0	0
Aspirin	47 (65%)	31 (56%)	29 (48%)	40 (61%)	18 (64%)	17 (61%)	7 (50%)	9 (75%)
Colchicine	0	0	1 (2%)	0	0	0	0	0

Data are n (%). Percentages are calculated based on the number of patients with compliance data.

Table 2: Treatments given after randomisation, by randomised allocation

assigned to methylprednisolone than in children assigned to usual care (difference -0.2 , -0.5 to 0.0 ; posterior probability of benefit 97%; table 3).

Mean duration of hospital stay was 6.6 days (SD 0.7) in children assigned to tocilizumab and 9.9 days (0.9) for children assigned to usual care (difference -3.3 days, 95% CrI -5.6 to -1.0 ; posterior probability of benefit >99%; table 3). However, the difference in the number of days on inotropes was 0.3 days (0.0 to 0.8, posterior probability of benefit 4% [ie, posterior probability of harm 96%]; table 3). Six (21%) of 28 children assigned to tocilizumab and four (14%) of 28 children assigned to usual care needed any inotropes (risk ratio 1.7, 95% CrI 0.5 to 4.7; posterior probability of benefit 25%; table 4). Natural log CRP values were lower in children assigned to tocilizumab than in children assigned to usual care (difference -0.1 , 95% CrI -0.6 to 0.3 ; posterior probability of benefit 73%; table 3).

Mean duration of hospital stay was 8.5 days (SD 1.2) in children assigned to anakinra and 9.9 days (0.9) in children assigned to usual care (difference -1.4 days, 95% CrI -4.3 to 1.8 ; posterior probability of benefit 84%; table 3). The difference in the number of days on inotropes was 0.8 days (0.2 to 1.9; posterior probability of benefit <1% [ie, posterior probability of harm >99%]; table 3). Five (36%) of 14 children assigned to anakinra and two (17%) of 12 children assigned to usual care needed inotropes (risk ratio 2.5, 95% CrI 0.6 to 7.8; posterior probability of benefit 15% [posterior probability of harm 85%]; table 4). Natural log CRP values were higher in children assigned to anakinra than in children assigned to

usual care (difference 0.6, 0.0 to 1.1; posterior probability of benefit 2%; table 3).

There were few adverse safety outcomes. Two persistent coronary artery aneurysms were reported in the usual care group in the first randomisation and none in any of the treatment groups or in the usual care group in the second randomisation (table 4). There were few cardiac arrhythmias, bleeding, or thrombotic events in any group (appendix p 82). Two children died (table 3), they were considered unrelated to study treatment.

Analyses with a shared control group rendered similar results to analyses comparing each treatment group with its own control group (appendix p 83).

Discussion

RECOVERY was the first randomised controlled trial to open recruitment to children with respiratory COVID-19 (May, 2020) and with PIMS-TS (August, 2020). This paper reports the full data for two separate randomisations available to clinicians treating PIMS-TS initially or for second-line treatment in the most unwell children.

Before data become available from randomised trials,²² practice was being guided by observational studies.^{9–11,23} Although these studies include large cohorts, they are limited by the absence of randomisation (and hence risk of bias), use of retrospective data, challenges of treatment mixing in single agent groups, heterogeneity of health-care access, and different national treatment guidelines.

In this comparison between intravenous immunoglobulin, methylprednisolone, and no additional treatment (usual care), methylprednisolone shortened

	First randomisation				Second randomisation								
	Intravenous immunoglobulin (n=73)	Methylprednisolone (n=61)	Usual care (n=80)	Intravenous immunoglobulin vs usual care	Methylprednisolone vs usual care	Tocilizumab (n=28)	Anakinra (n=14)	Usual care (n=28)					
	Treatment effect (95% CrI)	PPB	Treatment effect (95% CrI)	PPB	Treatment effect (95% CrI)	PPB	Treatment effect (95% CrI)	PPB					
Primary outcome													
Duration of hospital stay, days*	7.4 (0.4)	6.9 (0.5)	7.6 (0.4)	-0.1 (-1.3 to 1.0)	-0.7 (-1.9 to 0.6)	6.6 (0.7)	8.5 (1.2)	9.9 (0.9)	-3.3 (-5.6 to -1.0)	>99%	-1.4 (-4.3 to 1.8)	84%	
28-day mortality	0	1 (2%)	1 (1%)	0	0	0	
Number of patients discharged from hospital	72 (99%)	60 (98%)	78 (98%)	28 (100%)	14 (100%)	25 (89%)	
Secondary clinical outcomes													
Number of days on inotropes, days*	0.8 (0.1)	0.9 (0.2)	0.8 (0.1)	0.0 (-0.4 to 0.4)	0.1 (-0.3 to 0.5)	0.6 (0.2)	1.1 (0.4)	0.2 (0.1)	0.3 (-0.0 to 0.8)	4%	0.8 (0.2 to 1.9)	<1%	
Baseline-adjusted ln CRP on day 3†	4.8 (0.1)	4.4 (0.1)	4.6 (0.1)	0.2 (-0.1 to 0.4)	-0.2 (-0.5 to 0.0)	4.2 (0.2)	4.9 (0.2)	4.3 (0.2)	-0.1 (-0.6 to 0.3)	73%	0.6 (0.0 to 1.1)	2%	
Subsidiary clinical outcomes													
Duration in ICU, days*	2.0 (0.3)	1.8 (0.3)	2.2 (0.3)	-0.3 (-1.0 to 0.5)	-0.4 (-1.2 to 0.4)	2.0 (0.5)	3.6 (1.1)	2.5 (0.5)	-0.5 (-1.9 to 0.8)	78%	1.1 (-1.0 to 3.7)	17%	

Data are n (%), unless otherwise specified. Paediatric-specific primary outcomes were predefined in the Statistical Analysis Plan. CrI=credible interval. PPB=posterior probability of benefit. IMV=invasive mechanical ventilation. In CRP=natural log of c-reactive protein. ICU=intensive care unit. CAA=coronary artery aneurysm. IVD=left ventricular dysfunction. *An age-adjusted model was used which allowed the joint estimation of the two treatment effects versus usual care (ie, mean difference and 95% CrI) while preserving the principle of randomisation, assuming a common control group. †A linear regression model was used (adjusted for age and baseline ln CRP values) which allowed the joint estimation of the two treatment effects versus usual care (ie, mean difference and 95% CrI) while preserving the principle of randomisation, assuming a common control group. Missing data were estimated using multiple imputations for ln CRP values (before day 4) adjusted for age and sex, and stratified by treatment allocation.

Table 3: Effects of treatments on primary and secondary outcomes

hospital stay, but we found no effect of intravenous immunoglobulin. By contrast with initial case reports and despite a hesitancy among some clinicians to randomly assign patients to usual care only, there were no clinically relevant cardiac aneurysm safety signals in any study group. During the trial recruitment period, most cases of PIMS-TS occurred in children older than 6 years, and in the Omicron SARS-CoV-2 era, most cases treated as Kawasaki disease are now relatively easy to differentiate from PIMS-TS by patient age and clinical presentation. Although some confusion remains,¹² children with more Kawasaki disease-like phenotype can generally be distinguished and treated with intravenous immunoglobulin as first-line treatment. Although PIMS-TS has not been as common for Omicron and subsequent SARS-CoV-2 variants, if PIMS-TS were to recur on a wider global basis, methylprednisolone could be considered the first-line treatment of choice due to treatment effect, affordability, and widespread availability. Although intravenous immunoglobulin is standard treatment for Kawasaki disease,²⁴ we found little evidence to support intravenous immunoglobulin for PIMS-TS. One factor that could have contributed to any difference being small is that a substantial proportion of children randomly assigned usual care also received active treatment (35%). Such crossover in the comparison would have reduced any effect that might have been present (but would also lead to underestimation of any true benefits). Another trial¹⁸ randomly assigned 75 children between intravenous immunoglobulin or methylprednisolone using the same dose regimens as our trial. They found no evidence that methylprednisolone reduced the length of hospital stay compared with intravenous immunoglobulin therapy.

This is the first randomised controlled trial to show that tocilizumab reduces length of hospital stay for children with PIMS-TS, although inotrope use was increased. As tocilizumab is known to increase blood pressure,²⁵ the increased use of inotropes in children treated with tocilizumab is unexplained, although the number of children treated with inotropes was small, so this observation might be due to chance. While it is also possible that children treated with tocilizumab were coincidentally sicker at randomisation than children who received usual care, this is not supported by clinical or biochemical parameters. The number of days since symptom onset and days since hospital admission were the same between groups. Median CRP and D-dimer concentrations were higher in the tocilizumab group, but IQRs overlap. There were too few participants in the anakinra group to provide reliable results. The incidence of PIMS-TS has reduced greatly, and recent data suggest that the severity of PIMS-TS has decreased with each subsequent SARS-CoV-2 variant.¹⁹

Our trial has several limitations. The sample size was small, and substantial use of study treatments in the

	First randomisation						Second randomisation					
	Intravenous immunoglobulin vs usual care			Methylprednisolone vs usual care			Tocilizumab vs usual care			Anakinra vs usual care		
	Usual care (n=73)	Risk or rate ratio (95% CrI)	PPB	Usual care (n=61)	Risk or rate ratio (95% CrI)	PPB	Usual care (n=28)	Risk or rate ratio (95% CrI)	PPB	Usual care (n=14)	Risk or rate ratio (95% CrI)	PPB
Need for inotropes	25/73 (34%)	1.0 (0.6-1.6)	53%	23/61 (38%)	1.5 (0.9-2.5)	8%	6/28 (21%)	1.7 (0.5-4.7)	25%	5/14 (36%)	2.5 (0.6-7.8)	15%
Need for non-IMV	6/67 (9%)	2.5 (0.5-8.7)	18%	2/52 (4%)	0.7 (0.1-2.0)	82%	2/24 (8%)	1.5 (0.2-5.8)	46%	3/11 (27%)	31.7 (0.7-137.3)	7%
Need for IMV	4/71 (6%)	1.3 (0.3-3.9)	51%	3/56 (5%)	1.5 (0.3-4.6)	43%	0/24 (0%)	2/12 (17%)
Need for ICU	44/73 (60%)	1.1 (0.8-1.5)	33%	36/61 (59%)	1.1 (0.8-1.5)	31%	23/28 (82%)	1.2 (0.9-1.7)	11%	10/14 (71%)	1.1 (0.6-1.9)	40%
Presence of CAA	9/73 (12%)	1.9 (0.6-4.8)	19%	3/61 (5%)	0.7 (0.2-1.9)	81%	6/28 (21%)	1.7 (0.5-4.7)	25%	2/14 (14%)	2.4 (0.2-10.1)	36%
Persistence of CAA	0/73 (0%)	0/61 (0%)	0/28 (0%)	0/14 (0%)
Presence of LVD	14/73 (19%)	1.0 (0.5-1.9)	56%	8/61 (13%)	0.7 (0.3-1.5)	83%	9/28 (32%)	1.6 (0.6-3.6)	19%	5/14 (36%)	1.6 (0.5-4.5)	30%
Persistence of LVD	0/73 (0%)	0/61 (0%)	0/28 (0%)	0/14 (0%)
Readmission to hospital	11/73 (15%)	0.7 (0.3-1.4)	84%	13/61 (21%)	1.2 (0.6-2.2)	40%	7/28 (25%)	1.5 (0.5-3.7)	28%	2/14 (14%)	1.3 (0.2-4.4)	56%
Additional antibiotics	2/73 (3%)	2.3 (0.2-10.7)	44%	4/61 (7%)	1.3 (0.3-3.7)	45%	0/28 (0%)	0/14 (0%)
Escalation of immunosuppressive treatment	38/73 (52%)	0.7 (0.4-1.1)	96%	13/61 (21%)	0.2 (0.1-0.4)	>99%	15/28 (54%)	1.0 (0.5-1.9)	60%	9/14 (64%)	2.1 (0.6-5.9)	15%

Data are events/total (%) or mean (SE) unless otherwise specified. All ratios correspond to risk ratios (with 95% credible intervals) with the exception of the outcome of escalation of immunosuppressive treatment which is calculated as a rate ratio (95% CrI). Persistence of CAA or LVD was defined as evidence of CAA or LVD on echocardiography at the clinical follow-up visit before the final study phone call 5-8 weeks after discharge. CrI=credible interval. PPB=posterior probability of benefit. IMV=invasive mechanical ventilation. ICU=intensive care unit. CAA=coronary artery aneurysm. LVD=left ventricular dysfunction.

Table 4: Effect of treatments on secondary clinical paediatric outcomes

usual care groups reduced the ability of the trial to detect plausible effects of treatment. Due to short average durations of hospital stay, we were unable to analyse CRP data at all prespecified timepoints. Despite this, we saw that methylprednisolone and tocilizumab, but not intravenous immunoglobulin, shortened hospital stay, although these treatments were associated with increased use of inotropes. We saw no benefit of intravenous immunoglobulin and had insufficient data on the effects of anakinra group to draw clear, reliable conclusions. A diagnosis of PIMS-TS was made on the basis of clinical criteria, and enrolment criteria were defined before testing for COVID-19 or antibody tests were widely available. Finally, RECOVERY is an unblinded pragmatic clinical trial. While we do not believe decisions on length of surveillance after clinical recovery were affected by trial treatments (due to the way health care is organised in the UK), we cannot completely exclude the possibility that some clinicians might have decided to keep children admitted for surveillance depending on treatment received.

In conclusion, moderate evidence suggests that intravenous methylprednisolone reduces duration of hospital stay versus usual care for children admitted with PIMS-TS, and good evidence suggests that tocilizumab reduces duration of hospital stay compared with usual care for children with inflammation that is refractory to initial treatment. Tocilizumab was associated with increased inotrope use. Neither intravenous immunoglobulin nor anakinra reduced duration of hospital stay.

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This manuscript was drafted and developed by SNF, CEJ, EW, RH, TJ, NS, ES, AVR, further developed by the Writing Committee and Paediatric RECOVERY Working Group, and approved by all members of the trial steering committee. Statistical analyses were performed by TJ, NS, ES, and JRE. The funders had no role in the analysis of the data, preparation and approval of this manuscript, or the decision to submit it for publication. SNF, RH, NS, and TJ vouch for the data and analyses and for the fidelity of this report to the study protocol and data analysis plan. The corresponding authors had full access to all data in the study and had final responsibility for the decision to submit for publication.

Declarations of interest

SNF acts on behalf of University Hospital Southampton NHS Foundation Trust as an investigator or in the provision of consultative advice on clinical trials and studies of COVID-19 and other vaccines funded or sponsored by manufacturers of vaccines and antimicrobials, including

Janssen, Pfizer, Moderna, AstraZeneca, GlaxoSmithKline, Novavax, Sanofi, Medimmune, Merck, Iliad, and Valneva. He receives no personal financial payment for this work. CEJ acts on behalf of University Hospital Southampton NHS Foundation Trust as an investigator in clinical trials and studies of COVID-19 and other vaccines funded or sponsored by vaccine manufacturers including Moderna, Pfizer, GlaxoSmithKline, Medicago, Minervax, and Novavax. She receives no personal financial payment for this work. CEJ has received personal remuneration for participation in data safety and monitoring boards and for provision of consultative advice to Moderna and Sanofi. EW acts on behalf of Imperial College Healthcare NHS Trust as an investigator in clinical trials and studies of treatments for COVID-19 and other vaccines or treatment trials funded or sponsored by vaccine or drug manufacturers including Moderna, Pfizer, AstraZeneca, Sanofi, and Iliad. She receives no personal financial payment for this work. EW has received personal remuneration for participation in a podcast on the management of COVID-19 from Gilead. AVR has been a consultant or advisor for Eli Lilly, SOBI, and Roche for COVID related trials. AVR has received speaker and consulting fees and Honoraria from Eli Lilly, Roche, Abbvie, Pfizer, Novartis, SOBI, and UCB. ME acts on behalf of Newcastle upon Tyne Hospitals NHS Foundation Trust as an investigator in clinical trials and studies of diagnosis and treatment for COVID-19 and other vaccines or treatment trials funded or sponsored by vaccine or drug manufacturers including Roche, Pfizer, AstraZeneca, and Sanofi. She receives no personal financial payment for this work. SBD acts on behalf of St George's, University of London as an investigator in clinical trials and studies of treatments for COVID-19 and other vaccines or treatment trials funded or sponsored by vaccine or drug manufacturers including Janssen, AstraZeneca, Pfizer, Moderna, Valneva, MSD, Iliad, and Sanofi. SBD has received honoraria from MSD and Sanofi for taking part in Respiratory Syncytial Virus advisory boards. SBD is a member of the UK Department of Health and Social Care (DHSC) Joint Committee on Vaccination and Immunisation (JCVI) RSV subcommittee and a member of the Medicines and Healthcare products Regulatory Agency's (MHRA) Paediatric Medicine Expert Advisory Group (PMEAG), but the views expressed herein do not necessarily represent those of DHSC, JCVI, MHRA, or PMEAG. AB has received consultancy fees from Gilead in relation to treatment of COVID-19 in children. CCR has received honoraria for lectures on behalf of AstraZeneca and Chiesi Pharmaceuticals. TJ is supported by a grant from the UK MRC (MC_UU_00002/14). All other authors declare no competing interests. No form of payment was given to anyone to produce the manuscript. The Nuffield Department of Population Health at the University of Oxford has a staff policy of not accepting honoraria directly or indirectly from industry.

Data sharing

The protocol, consent form, statistical analysis plan, definition and derivation of clinical characteristics and outcomes, training materials, regulatory documents, and other relevant study materials are available online. As described in the protocol, the trial steering committee will facilitate the use of the study data, and approval will not be unreasonably withheld. De-identified participant data will be made available to bona fide researchers registered with an appropriate institution within 3 months of publication. However, the steering committee will need to be satisfied that any proposed publication is of high quality, honours the commitments made to the study participants in the consent documentation and ethical approvals, and is compliant with relevant legal and regulatory requirements (eg, relating to data protection and privacy). The steering committee will have the right to review and comment on any draft manuscripts before publication. Data will be made available in line with the policy and procedures. Those wishing to request access should complete the form and email it to data.access@ndph.ox.ac.uk

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References

- Davies P, Evans C, Kanthimathinathan HK, et al. Intensive care admissions of children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) in the UK: a multicentre observational study. *Lancet Child Adolesc Health* 2020; **4**: 669–77.
- Levin M. Childhood multisystem inflammatory syndrome—a new challenge in the pandemic. *N Engl J Med* 2020; **383**: 393–95.
- Riphagen S, Gomez X, Gonzalez-Martinez C, Wilkinson N, Theocharis P. Hyperinflammatory shock in children during COVID-19 pandemic. *Lancet* 2020; **395**: 1607–08.
- Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA* 2020; **324**: 259–69.
- Harwood R, Allin B, Jones CE, et al. A national consensus management pathway for paediatric inflammatory multisystem syndrome temporally associated with COVID-19 (PIMS-TS): results of a national Delphi process. *Lancet Child Adolesc Health* 2021; **5**: 133–41.
- Henderson LA, Canna SW, Friedman KG, et al. American College of Rheumatology clinical guidance for multisystem inflammatory syndrome in children associated with SARS-CoV-2 and hyperinflammation in pediatric COVID-19: Version 3. *Arthritis Rheumatol* 2022; **74**: e1–20.
- Davies P, du Pré P, Lillie J, Kanthimathinathan HK. One-year outcomes of critical care patients post-COVID-19 multisystem inflammatory syndrome in children. *JAMA Pediatr* 2021; **175**: 1281–83.
- Godfred-Cato S, Bryant B, Leung J, et al. COVID-19-associated multisystem inflammatory syndrome in children—United States, March–July 2020. *MMWR Morb Mortal Wkly Rep* 2020; **69**: 1074–80.
- Ouldali N, Toubiana J, Antona D, et al. Association of intravenous immunoglobulins plus methylprednisolone vs immunoglobulins alone with course of fever in multisystem inflammatory syndrome in children. *JAMA* 2021; **325**: 855–64.
- Son MBF, Murray N, Friedman K, et al. Multisystem inflammatory syndrome in children—initial therapy and outcomes. *N Engl J Med* 2021; **385**: 23–34.
- McArdle AJ, Vito O, Patel H, et al. Treatment of multisystem inflammatory syndrome in children. *N Engl J Med* 2021; **385**: 11–22.
- McCrinkle BW, Harahsheh AS, Handoko R, et al. SARS-CoV-2 variants and multisystem inflammatory syndrome in children. *N Engl J Med* 2023; **388**: 1624–26.
- Horby PW, Mafham M, Bell JL, et al. Lopinavir-ritonavir in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2020; **396**: 1345–52.
- RECOVERY Collaborative Group. Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; **397**: 1637–45.
- Abaleke E, Abbas M, Abbasi S, et al. Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2021; **397**: 605–12.
- RECOVERY Collaborative Group. Colchicine in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet Respir Med* 2021; **9**: 1419–26.
- Abani O, Abbas A, Abbas F, et al. Convalescent plasma in patients admitted to hospital with COVID-19 (RECOVERY): a randomised controlled, open-label, platform trial. *Lancet* 2021; **397**: 2049–59.
- Abani O, Abbas A, Abbas F, et al. Baricitinib in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial and updated meta-analysis. *Lancet* 2022; **400**: 359–68.
- Abani O, Abbas A, Abbas F, et al. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2022; **399**: 143–51.
- Abani O, Abbas A, Abbas F, et al. Casirivimab and imdevimab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet* 2022; **399**: 665–76.
- Horby P, Lim WS, Emberson JR, et al. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med* 2021; **384**: 693–704.
- Welzel T, Atkinson A, Schöbi N, et al. Methylprednisolone versus intravenous immunoglobulins in children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS): an open-label, multicentre, randomised trial. *Lancet Child Adolesc Health* 2023; **7**: 238–48.
- Ouldali N, Son MBF, McArdle AJ, et al. Immunomodulatory therapy for MIS-C. *Pediatrics* 2023; **152**: e2022061173.
- Eleftheriou D, Levin M, Shingadia D, Tulloh R, Klein NJ, Brogan PA. Management of Kawasaki disease. *Arch Dis Child* 2014; **99**: 74–83.
- Roche Products Limited. RoActemra summary of product characteristics (SmPC). May 23, 2023. <https://www.medicines.org.uk/emc/product/9086/smpc> (accessed Aug 3, 2023).