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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

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Summary

Background The emergence of paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS) led to the widespread use of anti-inflammatory treatments in the absence of evidence from randomised controlled trials (RCTs). We aimed to assess the effectiveness of intravenous methylprednisolone compared with intravenous immunoglobulins.

Methods This is an open-label, multicentre, two-arm RCT done at ten hospitals in Switzerland in children younger than 18 years hospitalised with PIMS-TS (defined as age <18 years; fever and biochemical evidence of inflammation, and single or multiorgan dysfunction; microbiologically proven or putative contact with SARS-CoV-2; and exclusion of any other probable disease). Patients were randomly assigned 1:1 to intravenous methylprednisolone (10 mg/kg per day for 3 days) or intravenous immunoglobulins (2 g/kg as a single dose). The primary outcome was length of hospital stay censored at day 28, death, or discharge. Secondary outcomes included proportion and duration of organ support. Analyses were done by intention-to-treat. The study was registered with Swiss National Clinical Trials Portal (SNCTP000004720) and ClinicalTrials.gov (NCT04826588).

Findings Between May 21, 2021, and April 15, 2022, 75 patients with a median age of 9·1 years (IQR 6·2–12·2) were included in the intention-to-treat population (37 in the methylprednisolone group and 38 in the intravenous immunoglobulins group). The median length of hospital stay was 6·0 days (IQR 4·0–8·0) in the methylprednisolone group and 6·0 days (IQR 5·0–8·8) in the intravenous immunoglobulins group (estimated effect size –0·037 of the $\log_{10}$ transformed times, 95% CI –0·13 to 0·065, p=0·42). Fewer patients in the methylprednisolone group (ten [27%] of 37) required respiratory support compared with the intravenous immunoglobulin group (21 [55%] of 38, p=0·025). Need and duration of inotropes, admission to intensive care units, cardiac events after baseline, and major bleeding and thrombotic events were not significantly different between the study groups.

Interpretation In this RCT, treatment with methylprednisolone in children with PIMS-TS did not significantly affect the length of hospital stay compared with intravenous immunoglobulins. Intravenous methylprednisolone could be an acceptable first-line treatment in children with PIMS-TS.

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Introduction

The emergence of the COVID-19 pandemic across the globe was followed, in April 2020, by clusters of children presenting with a new inflammatory disease, characterised by fever, multisystem involvement, and elevated inflammation parameters, with similarities to Kawasaki disease.[1–3] This entity has been labelled paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), or multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C). Disease criteria, including confirmed or suspected infection with SARS-CoV-2 and increased inflammation parameters, in the presence of mucocutaneous, circulatory, respiratory, or neurological symptoms, supported clinicians in making a diagnosis of PIMS-TS, enabling therapeutic management. Although some early reports observed recovery in patients without anti-inflammatory treatment,[4] treating patients became common practice because the disease was considered severe, with many affected requiring admission to a paediatric intensive care unit (PICU) for cardiovascular and respiratory support.[5–7] In the absence of evidence from randomised controlled trials (RCTs), PIMS-TS management has been guided by expert opinion and consensus guidelines, and inference from Kawasaki disease trials, rather than PIMS-TS-specific evidence. These guidelines recommend the use of intravenous glucocorticoids and

Research in context

Evidence before this study

The emergence of the COVID-19 pandemic was followed by clusters of children presenting with a new inflammatory disease labelled paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2 (PIMS-TS), or multisystem inflammatory syndrome in children associated with COVID-19 (MIS-C). In the absence of evidence based on randomised controlled trials (RCTs), clinical practice has been guided by expert opinion and consensus recommendations. In a PubMed search using the terms ("intravenous immunoglobulins" OR "methylprednisolone" OR "trial") AND ("Paediatric multisystem inflammatory disease, COVID-19 related" OR "Paediatric Inflammatory Multisystem Syndrome") for studies published between April 1, 2020, and Oct 31, 2022, with no language restrictions, no study was identified reporting on results of randomised comparison of anti-inflammatory treatments for children with PIMS-TS. Six observational studies of patients with PIMS-TS were found, which analysed effectiveness of glucocorticoids, intravenous immunoglobulins, or intravenous immunoglobulins combined with glucocorticoids. Intravenous immunoglobulins in combination with glucocorticoids versus intravenous immunoglobulins alone showed similar or superior effectiveness in relation to a range of outcomes, including measures of inflammation, requirement for respiratory support, vasopressor treatment, and hospital length of stay.

Added value of this study

This is the first reported RCT comparing the two most used anti-inflammatory treatments in children diagnosed with PIMS-TS. In this RCT, treatment with intravenous methylprednisolone once daily over 3 days compared with intravenous immunoglobulins was associated with similar length of hospital stay. Bayesian analyses confirmed these results. Secondary analyses on the need for respiratory support at any time indicated a possible benefit associated with methylprednisolone, albeit confounded by covariate imbalance at baseline. These findings are supported by the observational Best Available Treatment Study, which did not find evidence for differences in recovery for glucocorticoids alone, compared with intravenous immunoglobulins alone.

Implications of all the available evidence

Due to the small sample size of this trial, independent confirmation from larger interventional trials, including the UK RECOVERY trial with subsequent meta-analysis, is needed. In addition, long-term follow-up of these cohorts to investigate the incidence of persistent cardiac anomalies, in particular coronary artery aneurysms, is required. Given the scarce availability of intravenous immunoglobulins around the world, our findings add evidence that intravenous methylprednisolone could be an acceptable first-line treatment in children with PIMS-TS, in addition to supportive care, considering that it is more affordable and more widely available globally than intravenous immunoglobulins.

intravenous immunoglobulins as mainstays of initial therapy, with consideration for biological disease-modifying anti-rheumatic drugs, namely anakinra, tocilizumab, or infliximab, in more severe or refractory cases.[8–11]

Up to now, there remains uncertainty about the effectiveness of glucocorticoid monotherapy as the initial treatment approach in PIMS-TS. Observational data indicate that even though both intravenous immunoglobulins monotherapy and intravenous immunoglobulins in combination with glucocorticoids are effective in PIMS-TS, glucocorticoids alone compared with intravenous immunoglobulins monotherapy might result in similar recovery.[12–15] Due to the scarce availability of intravenous immunoglobulins, especially in low-income and middle-income countries, a randomised comparison of anti-inflammatory treatments for children with PIMS-TS is urgently needed. The Swissped RECOVERY trial was aimed at assessing the effectiveness of intravenous methylprednisolone versus intravenous immunoglobulins in hospitalised children with PIMS-TS.

Methods

Study design

Swissped RECOVERY is an investigator-initiated, randomised, multicentre, open-label, two-arm trial in children and adolescents hospitalised with PIMS-TS done at ten paediatric hospitals in Switzerland. Patients with PIMS-TS diagnosed in line with the Swiss PIMS-TS guidelines, which apply the UK Royal College of Paediatrics and Child Health's case definition,[8,16] were recruited in emergency departments, wards, and PICUs of hospitals in Aarau, Basel, Bern, Bellinzona, Fribourg, Geneva, Lausanne, Lucerne, St Gallen, and Zurich. The design of Swissped RECOVERY was informed by a trial on children with PIMS-TS in the UK,[17] which was done within the RECOVERY trial (NCT04381936). In the UK RECOVERY trial, no treatment was defined as the standard of care group. By contrast, in the Swissped RECOVERY trial, treatment with intravenous immunoglobulins was defined as standard of care, because withholding any anti-inflammatory treatment was considered unethical due to observational evidence of effectiveness of anti-inflammatory treatment, and lack of equipoise for any compared with no treatment.[12–14] The study was approved by the lead ethics committee (Ethics Committee Northwest and Central Switzerland; appendix p 3), and other responsible ethics committees in Switzerland. The trial was registered on the Swiss National Clinical Trials Portal (SNCTP000004720) and ClinicalTrial.gov (NCT04826588) before commencement. An independent data monitoring committee monitored trial safety and evaluated the need for early trial

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See **Online** for appendix

termination. The study protocol was published before completion of recruitment.[18]

Participants

Children younger than 18 years with a clinical diagnosis of PIMS-TS admitted to hospital were eligible if the treating physician considered that the patient required intravenous anti-inflammatory treatment. The presumptive diagnosis of PIMS-TS was based on the following case definitions: (1) younger than 18 years; (2) fever and biochemical evidence of inflammation, and single or multiorgan dysfunction; (3) microbiologically proven or putative contact with SARS-CoV-2; and (4) exclusion of any other probable disease (appendix pp 3–4).[8] Patients were excluded if the treating clinician identified a medical history that might put the patient at significant risk in case of study participation; if there was a specific contraindication to one of the treatment groups; or if there was a clinical indication that a specific treatment group had to be administered. Furthermore, neonates with a corrected gestational age of 44 weeks or younger were excluded. Prospective written informed consent from parents (and by patients if aged 14 years or older) was required. In instances where timely informed consent was not achievable, a deferred consent approach was used, in which written consent from the parents or guardians and patients was obtained after enrolment.[19]

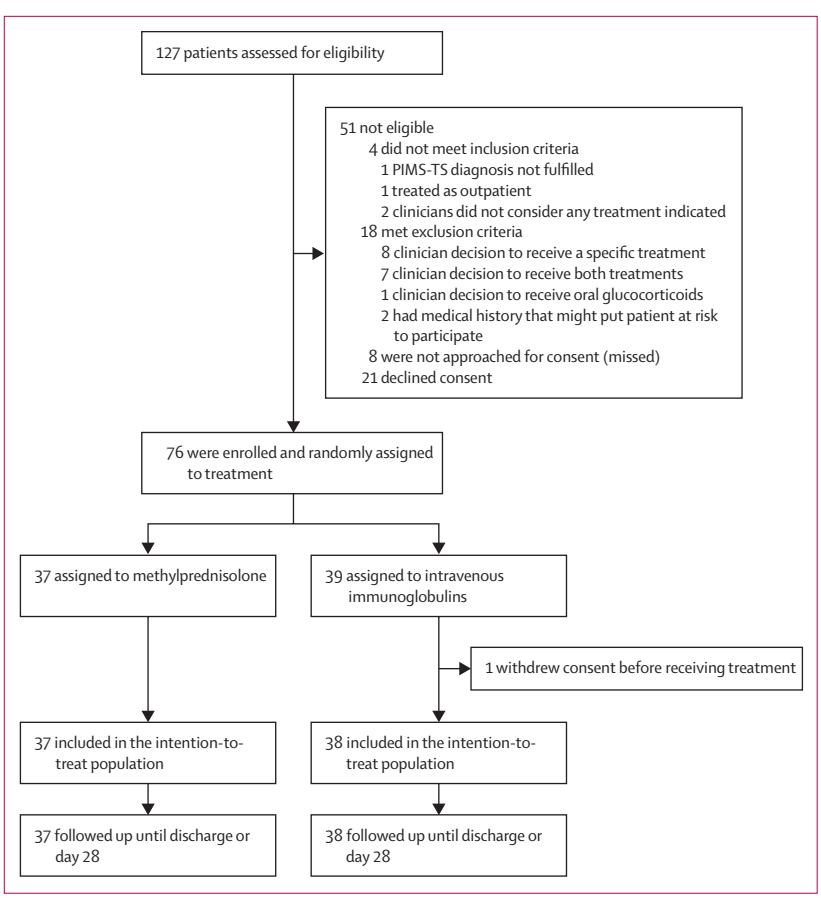

Figure 1: **Trial profile**
PIMS-TS=paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2.

Randomisation and masking

Study patients were randomly assigned 1:1 to intravenous methylprednisolone or intravenous immunoglobulins by online randomisation through the electronic data capture system REDCap hosted by the University Children's Hospital Basel.[20] The computer-generated randomisation list used random permuted blocks of 30 patients without stratification by site. No masking was done, aligned with an open-label pragmatic trial design, and due to the logistic challenges associated with blinding intravenous immunoglobulins and methylprednisolone.

Procedures

After randomisation, the trial treatment was prescribed by the treating clinician or a dedicated trial member to be administered without delay through a peripheral or central venous access line. Patients received either intravenous methylprednisolone 10 mg/kg per dose (maximum dose 1000 mg per day) once daily for 3 days (no tapering thereafter) or intravenous immunoglobulins 2 g/kg per dose (maximum dose 100 g) as a single dose given as a slow infusion in line with the institutional standard operating procedures (infusion duration 12 h±4 h). The methylprednisolone dose and the intravenous immunoglobulins dose were aligned with the UK RECOVERY trial. The study protocol did not mandate other management procedures, such as organ support, fluids, anticoagulation, or antimicrobial use, which could be delivered as per local practice. Treating clinicians could administer additional anti-inflammatory treatment not intended in the protocol when they considered it to be indicated. The study protocol recommended, however, to observe patients for at least 24 h after starting the randomised treatment before considering additional anti-inflammatory treatment. All non-randomised anti-inflammatory treatments were considered intercurrent events, including treatment with anakinra, additional use of oral glucocorticoids, doses of the randomised treatment not intended in the protocol, fewer doses of the randomised treatment as intended in the protocol, administration of intravenous immunoglobulins in the methylprednisolone group, and vice versa. Intercurrent events were reviewed by an endpoint review committee masked to the treatment group. Data on vital signs, organ function and support, laboratory parameters, additional specific examinations such as electrocardiograms, echocardiograms, and administered treatments were prospectively collected on days 0, 1, 2, 3, 4–5, 6–7, and 8–14, or until discharge.

Outcomes

The primary outcome was the length of hospital stay, defined as the time in days from hospital admission to

discharge or death, with censoring at 28 days. Time from randomisation to discharge was also assessed. Secondary outcomes included all-cause mortality; proportion of patients needing organ support operationalised as respiratory support (ie, invasive ventilation, continuous positive airway pressure, biphasic positive airway pressure, and high and low flow supplemental oxygen), inotropes, renal replacement, and extracorporeal membrane oxygenation; duration of organ support; and proportion of patients with cardiac pathologies defined as coronary artery enlargement (Z score ≥2), left ventricular ejection fraction less than 55%, or arrhythmia at any time after randomisation. Predefined safety outcomes (major bleeding or thrombotic events, or both) and severe adverse events likely to be related to the study treatment were recorded.

Statistical analysis

The statistical analysis plan was defined a priori (appendix pp 21–40), following, wherever possible, the statistical analysis plan defined for the UK-based trial available online.[17] The primary analysis, done with data from the intention-to-treat (ITT) study population, compared the log-transformed time from admission to discharge (death or censoring) of the two groups using a two-sided *t* test. For the period of the trial, it was estimated that approximately 50 and 120 children could be recruited. According to expert opinion, approximately 80 children in total were estimated to be a feasible total target sample size to recruit, with two intervention groups of 40 patients each. This would have 80% power to detect a difference in length of stay of 2·5 days between the trial arms, assuming a two-sided 5% statistical significance level.

Baseline (randomisation) and follow-up patient characteristics were summarised with the n (%) for categorical variables and the median (IQR) for continuous variables. Summary statistic comparisons between groups were done with the χ^2 test for categorical variables, and the Wilcoxon test for continuous variables (unless stated otherwise). Kaplan-Meier plots assessed time from admission to discharge between the trial arms with the log-rank test used to test for differences. Furthermore, univariable and multivariable Cox proportional hazards models were fitted and adjusted for the treatment groups, sex, age (in years), and BMI. For binary outcomes, univariable and multivariable logistic regression models investigated the same baseline risk factors.

To enable consolidation and comparison with the paediatric UK RECOVERY trial,[17] a Bayesian analysis of the primary outcome was done (appendix pp 4–5). In brief, we compared the two treatment groups by considering the difference between the respective mean of the posterior time to discharge distribution (and associated 95% credibility intervals). If the probability that the methylprednisolone group had a better outcome than the immunglobulin group (ie the difference in length of stay was negative) was 95% or larger, then this would signify a very strong signal of benefit. A probability between 80% and 95% would be interpreted as a strong signal, whereas a probability of 70–80% would constitute

	Total (n=75)	Methylprednisolone (n=37)	Intravenous immunoglobulins (n=38)
Age, years	9·1 (6·2–12·2)	8·9 (6·2–12·9)	9·4 (6·8–11·6)
Sex			
Female	19 (25%)	8 (22%)	11 (29%)
Male	56 (75%)	29 (78%)	27 (71%)
Weight, kg	30 (20–39)	30 (19–43)	30 (23–37)
BMI, kg/m²*	16·3 (14·7–18·9)	16·3 (14·9–19·1)	16·0 (14·6–18·7)
Underlying chronic diseases	8 (11%)	3 (8%)	5 (13%)
Ethnicity†			
White	59 (79%)	31 (84%)	28 (74%)
Asian	6 (8%)	4 (11%)	2 (5%)
Black, African, or Caribbean	4 (5%)	1 (3%)	3 (8%)
Mixed or multiple	4 (5%)	1 (3%)	3 (8%)
Other	2 (3%)	0 (0%)	2 (5%)
SARS-CoV-2 history			
Known exposure to SARS-CoV-2	46 (61%)	21 (57%)	25 (66%)
Previous SARS-CoV-2 PCR positive	28 (37%)	11 (30%)	17 (45%)
Vital signs			
Heart rate, bpm	124 (67–179)	124 (106–138)	125 (105–140)
Respiratory rate, bpm	30 (17–60)	30 (27–35)	29 (24–36)
Transcutaneous oxygen saturation, %	97 (78–100)	98 (97–99)	96 (95–98)
Central capillary refill time, s	2 (0–4)	2 (2–3)	2 (2–3)
Clinical characteristics			
Fever (≥38°C for ≥24 h) in the past 7 days	72 (96%)	36 (97%)	36 (95%)
Cardiovascular symptoms			
Arterial hypotension	22 (29%)	12 (32%)	10 (26%)
Shock	12 (16%)	6 (16%)	6 (16%)
Tachycardia	27 (36%)	13 (35%)	14 (37%)
Gastrointestinal symptoms			
Diarrhoea	31 (41%)	16 (43%)	15 (39%)
Nausea and vomiting	47 (63%)	20 (54%)	27 (71%)
Abdominal pain	40 (53%)	21 (57%)	19 (50%)
Mucocutaneous symptoms			
Bilateral conjunctivitis	36 (48%)	20 (54%)	16 (42%)
Palmoplantar erythema and swelling	21 (28%)	8 (22%)	13 (34%)
Rash	42 (56%)	21 (57%)	21 (55%)
Enoral erythema and strawberry tongue	18 (24%)	10 (27%)	8 (21%)
Lymphadenopathy	21 (28%)	13 (35%)	8 (21%)
Neurological symptoms			
Altered mental status	7 (9%)	3 (8%)	4 (11%)
Headache	25 (33%)	14 (38%)	11 (29%)
Meningism	7 (9%)	5 (14%)	2 (5%)
Respiratory symptoms			
Cough	16 (21%)	9 (24%)	7 (18%)
Symptoms of respiratory distress	11 (15%)	5 (14%)	6 (16%)
Hypoxia (need for oxygen)	6 (8%)	1 (3%)	5 (13%)

(Table 1 continues on next page)

	Total (n=75)	Methylprednisolone (n=37)	Intravenous immunoglobulins (n=38)
(Continued from previous page)			
Main laboratory characteristics*			
White cell count, ×10⁹/L, ref 4·5–13·5	9·4 (6·5–12·6)	8·6 (6·3–11·3)	10·9 (7·4–13·6)
Platelet count, ×10⁹/L, ref 150–450	146 (106–216)	135 (99–191)	156 (118–256)
Lymphocytes, ×10⁹/L, ref 1·5–6·8	0·7 (0·5–1·3)	0·7 (0·5–1·2)	0·8 (0·6–1·3)
C-reactive protein, mg/L, ref <10	162 (101–228)	142 (98–200)	171 (114–242)
D-dimers, ng/mL, ref 190–500	2650 (1613–5470)	2800 (1513–5000)	2485 (1630–5627)
Ferritin, µg/L, ref 14–124	549 (243–851)	445 (217–594)	704 (306–1068)
Troponin, ng/L	19 (6–37)	13 (6–32)	24 (6–61)
N-terminal prohormone of brain natriuretic peptide, pg/mL	3104 (906–7382)	2394 (5–25735)	4191 (77–64982)
Post-hoc PIMS-TS phenotype‡			
Shock	20 (27%)	10 (27%)	10 (26%)
Kawasaki disease-like	31 (41%)	15 (41%)	16 (42%)
Undifferentiated	24 (32%)	12 (32%)	12 (32%)

Data are n (%) or median (IQR). bpm=beats per minute. PIMS-TS=paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *BMI missing one value, otherwise missingness shown in the appendix (p 7). †Ethnicity data entered by study coordinators based on information available at time of consenting. ‡According to Schlapbach and colleagues.[8]

Table 1: **Demographic, clinical, and main laboratory characteristics at baseline**

a moderate positive signal. A probability of 30% or less would be taken as a signal for harm. Prespecified differences in length of stay were also investigated according to age category, ethnicity, sex, PICU admission (at baseline and at any time), and phenotype (PIMS-TS with shock, Kawasaki disease-like PIMS-TS, and undifferentiated PIMS-TS).[18] Furthermore, the longitudinal trajectory of biomarkers was plotted.

All analyses were based on the complete case data only. For frequentist statistics, a p value of less than 5% was considered statistically significant. The trial statistician was fully masked up to database closure, and thereafter to the specific treatment groups for the primary analysis. The analysis was done with the statistical software R (version 3.6.1) and OpenBUGS for the Bayesian analysis.[21]

Role of the funding source

The funders of the study had no role in the trial design, data collection, data analysis, data interpretation, or writing of the manuscript and the decision to submit.

Results

Between May 21, 2021, and April 15, 2022, a total of 127 patients with PIMS-TS were assessed for eligibility, of whom 76 were enrolled, provided informed consent, and were randomly (1:1) allocated to either the methylprednisolone (n=37) or the intravenous immunoglobulins group (n=39; figure 1, appendix p 6). Parents of one patient withdrew consent before the initiation of treatment, leaving 75 patients in the ITT study population. All 37 patients in the methylprednisolone group included in the ITT study population received methylprednisolone; 37 (97%) of 38 patients in the intravenous immunoglobulins group in the ITT population received intravenous immunoglobulins. No children died during the study, with discharge time administratively censored at 28 days for only one patient. The study population had a median age of 9·1 years (IQR 6·2–12·2), and 19 (25%) of 75 were female (table 1). An underlying chronic disease was present in eight (11%) of 75 children. At baseline, 72 (96%) of 75 patients reported fever (≥38°C for more than ≥24 hours) in the past 7 days, and the majority presented with lymphopenia, increased inflammatory parameters, and elevated N-terminal prohormone of brain natriuretic peptide (table 1, appendix p 7). Almost all patients (70 [93%] of the 75 analysed patients) were randomly assigned within a day of admission; four patients were randomly assigned within 2 days and one patient within 6 days.

The median time from admission to discharge was 6·0 days (IQR 4·0–8·0) for the methylprednisolone group and 6·0 days (IQR 5·0–8·8) for the intravenous immunoglobulins group (table 2, figure 2A, appendix p 14). There was no significant difference in the $\log_{10}$ transformed mean times between the two trial groups (p=0·42). The between-group difference in admission to discharge estimated from the Bayesian posterior distribution model was of a similar magnitude (mean difference –0·68 days with the methylprednisolone group having shorter length of stay, 95% credible interval –2·3 to 1·0; figure 2B), indicating a moderate benefit in favour of the methylprednisolone group according to the a priori definitions for this analysis (80%). There was no difference between the treatment groups from unadjusted survival models (hazard ratio 0·87, 95% CI 0·63–1·2, p=0·41; figure 2C, appendix pp 8–9, 15).

Fewer patients on methylprednisolone needed respiratory support at any time (ten [27%] of 37) compared with those on intravenous immunoglobulins (21 [55%] of 38, p=0·025). Considering postrandomisation only, when the treatments could have had an effect, there was a difference in those requiring respiratory support (three [8%] of 37 *vs* 11 [29%] of 38, p=0·040; table 2, figure 2D), although baseline imbalance between the groups must also be considered a confounding factor. Duration of respiratory support, treatment with inotropes, and duration of inotropes were not different between the study groups (table 2, figure 2A). After baseline, 70 echocardiographic examinations were done in 35 of 38 patients randomly assigned to intravenous immunoglobulins, and 74 echocardiographic examinations were done in 35 of 37 patients randomly assigned to methylprednisolone. Nine (24%) of 38 patients randomly assigned to intravenous immunoglobulins had a decreased ejection fraction of less than 55% compared with five (14%) of 37 patients randomly assigned to methylprednisolone (p=0·52; table 2). No patient needed extracorporeal membrane oxygenation or renal replacement therapy. Multivariable logistic regression adjusted for sex, age, and

BMI indicated that the intravenous immunoglobulins group was more likely to receive respiratory support at any time (adjusted odds ratio [OR] 5·0, 95% CI 1·9–13, p=0·030; figure 2D, appendix pp 10–11).

20 (27%) of 75 cases of PIMS-TS were categorised as PIMS-TS shock, 31 (41%) as Kawasaki disease-like PIMS-TS, and 24 (32%) as undifferentiated PIMS-TS. In subgroup analyses, the median time to discharge was shorter in patients with Kawasaki disease-like PIMS-TS randomly assigned to methylprednisolone (5·0 days [IQR 4·0–6·0]) compared with those randomly assigned to intravenous immunoglobulins (6·5 days [IQR 5·8–9·3], p=0·035 [not adjusted for multiple testing]), with no treatment difference for the other phenotypes, and for the other predefined subgroup analyses (appendix pp 12, 14). Exploratory analyses of the trajectories for inflammation markers C-reactive protein, leukocyte, neutrophils, and other laboratory markers did not reveal major differences between patients in the intravenous immunoglobulins group versus those in the methylprednisolone group (appendix pp 16–20).

In total, 76 intercurrent events were reported in 41 patients mainly due to additional not randomised anti-inflammatory treatment (appendix p 12). In the methylprednisolone group, 24 (65%) of 37 patients had intercurrent events, of which 11 (30%) were related to receiving intravenous immunoglobulins and 10 (27%) were related to tapering glucocorticoids. In the intravenous immunoglobulins group, 17 (45%) of 38 patients had intercurrent events, of which 12 (32%) were related to taking methylprednisolone. Figure 3 shows intercurrent events and per-protocol treatment after randomisation until day 6. There was no statistically significant difference between the two groups in terms of intercurrent events (p=0·45; appendix p 12). Similarly, in a predefined per-protocol analysis (ie, while on treatment strategy for the intercurrent event first treatment change [including switching]) of the primary endpoint, there was no difference between the groups (p=0·4; appendix p 12); this analysis only included patients without this postrandomisation event.

Only one (1%) of 75 analysed patients had a thrombotic event (table 2). During the trial period, seven (9%) of 75 patients had severe adverse events, and all were resolved (appendix p 13). None of the severe adverse events were definitively related to the treatment intervention. Of three possibly related severe adverse events, two (hyperglycaemia, and agitation or lethargy) were reported in the methylprednisolone group, and one (hypotensive shock) was reported in the intravenous immunoglobulins group.

	Methylprednisolone (n=37)	Intravenous immunoglobulins (n=38)	Effect size with 95% CI and p value
Primary outcome			
Primary analysis			
Time from admission to discharge, days	6·0 (4·0–8·0)	6·0 (5·0–8·8)	–0·037 (–0·13 to 0·065), p=0·42*
Time from randomisation to discharge, days	5·0 (4·0–7·0)	5·5 (5·0–8·0)	–0·032 (–0·13 to 0·065), p=0·51*
Bayesian analysis adjusted for treatment and age			
Time from admission to discharge, days	6·8 (5·7–8·0)	7·5 (6·3–8·7)	–0·68 (–2·3 to 1·0)†
Time to event analysis (Cox proportional hazards model)			
Time from randomisation to discharge, days	1 (ref)	HR 0·87, 95% CI 0·63–1·2, p=0·41	Adjusted HR 0·89, 95% CI 0·65–1·2, p=0·45‡
Secondary outcomes			
Respiratory support at any time	10 (27%)	21 (55%)	p=0·025§
After randomisation respiratory support¶	3 (8%)	11 (29%)	p=0·040§
Respiratory support at any time, (no=0, yes=1)	1 (ref)	OR 3·2, 95% CI 1·4–7·7, p=0·034	Adjusted OR 5·0, 95% CI 1·9–13, p=0·030‖
Duration of any respiratory support, days**	2·5 (1·3–4·8)	2·0 (1·0–4·0)	0·036 (–0·23 to 0·31), p=0·78*
Inotropes at any time	10 (27%)	15 (39%)	0·37§
Duration of any inotropes, days	2·0 (1·3–3·0)	2·0 (1·5–3·0)	0·058 (–0·24 to 0·36), p=0·67*
Primary intensive care unit admission	15 (41%)	20 (53%)	0·41§
Cardiac events, at any post-baseline visit			
Left ventricular ejection fraction <55%	5 (14%)	9 (24%)	0·52§
Coronary artery enlargement (Z score ≥2)	2 (5%)	4 (11%)	0·67††
Arrhythmia	2 (5%)	1 (3%)	0·54††
Safety outcome			
Major bleeding‡‡ or thrombotic events§§, at any visit after baseline	0 (0%)	1 (3%)	0·99††

Data are n (%) or median (IQR) unless stated otherwise. All-cause mortality, extracorporeal life support, and renal replacement therapy are not shown because there were no events in either group. HR=hazard ratio. OR=odds ratio. *Following the *t* test of the $\log_{10}$ transformed times, negative effect size indicate longer durations for intravenous immunoglobulins. †Mean duration in methylprednisolone group compared with intravenous immunoglobulins group estimated from the posterior distribution with 95% credible interval. ‡Adjusted HR from the Cox proportional hazards model adjusted for treatment group, sex, age, and BMI (sandwich-type standard errors calculated in models to adjust for potential hospital level effects; appendix pp 8–9). §χ^2 test with Yate's continuity correction. ¶Post-hoc analysis. ‖Adjusted OR from the multivariable logistic regression model adjusted for treatment, sex, age, and BMI (sandwich-type standard errors calculated in models to adjust for potential hospital level effects). **Any respiratory support is defined as a need for invasive ventilation, continuous positive airway pressure, biphasic positive airway, and high and low flow supplementary oxygen. ††Fisher's exact test. ‡‡Major bleeding is defined as intracranial bleeding or bleeding requiring transfusion, endoscopy, or surgery. §§Thrombotic events are defined as acute pulmonary embolism, deep vein thrombosis, ischaemic stroke, myocardial infarction, or systemic arterial embolism.

Table 2: **Primary, secondary, and safety outcomes**

Discussion

In this open-label, multicentre RCT comparing intravenous methylprednisolone treatment with intravenous immunoglobulins in children with PIMS-TS, both treatments were comparable in terms of length of hospital stay. In a preplanned Bayesian analysis, there was a moderate benefit in terms of a reduced length of stay associated with methylprednisolone treatment (defined as an 80% probability that the methylprednisolone group had a lower length of stay than those in the intravenous immunoglobulins group). In addition, we observed that patients assigned to methylprednisolone

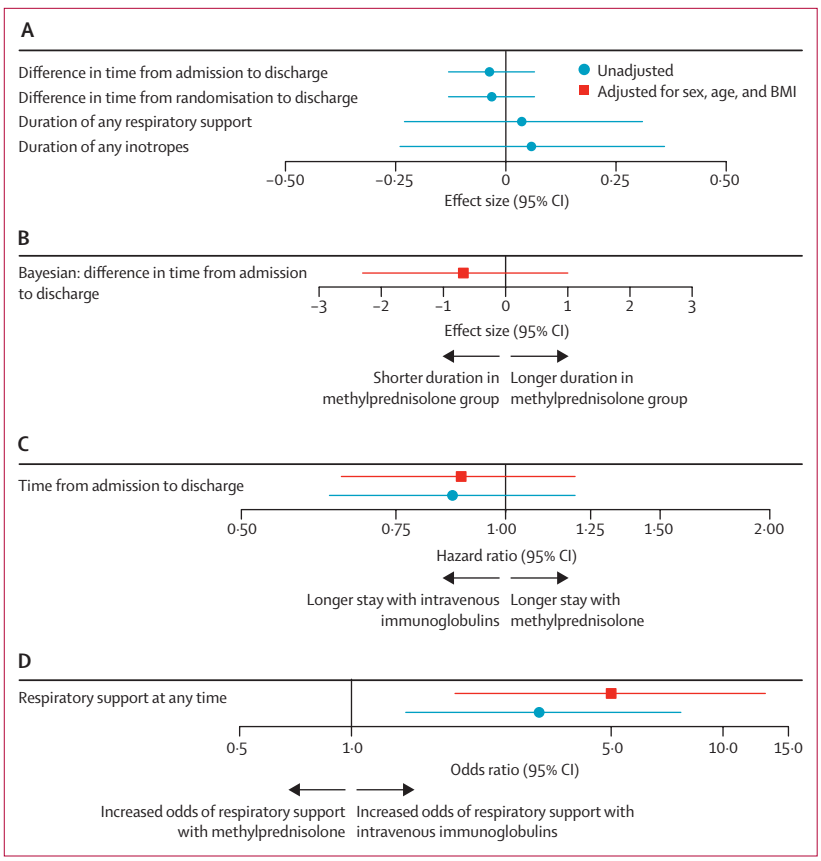

***Figure 2*: Forest plots of estimated effect sizes for the primary and secondary endpoints**
Estimated effect sizes are shown for primary and secondary endpoints in unadjusted analyses (A), Bayesian analyses for the primary endpoint (B), adjusted and unadjusted analyses for the primary endpoint (C), and for the secondary endpoint respiratory support at any time (D). The effect sizes in panel A are evaluated on the $\log_{10}$ scale (since we log before the *t* test), the Bayesian analysis is on the original scale (panel B).

required respiratory support less often at any time compared with patients randomly assigned to intravenous immunoglobulins. We did not observe significant differences in other secondary outcomes, including cardiac events such as coronary artery enlargement, within the 28-day follow-up period.

In the Swissped RECOVERY trial, the analysed patients with PIMS-TS had in general similar clinical and laboratory characteristics but lower proportions of patients admitted to PICUs compared with previously published cohorts.[12–14,22,23] Since the first wave of the pandemic, rates of PICU admission in children with PIMS-TS decreased and intravenous immunoglobulins, glucocorticoids, and anti-platelet medications emerged as the predominant treatments.[24] Six large observational studies have assessed effectiveness of glucocorticoid monotherapy, intravenous immunoglobulins, or intravenous immunoglobulins plus glucocorticoids.[12–15,23,25] Son and colleagues[13] compared 103 propensity-matched patients treated with intravenous immunoglobulins plus glucocorticoids with 103 patients treated with intravenous immunoglobulins alone. Initial treatment with glucocorticoids and intravenous immunoglobulins was associated with lower risk of the composite outcome of cardiovascular dysfunction on or after day 2 than intravenous immunoglobulins alone (17% *vs* 31%, risk ratio 0·56, 95% CI 0·34–0·94). Patients treated with intravenous immunoglobulins plus glucocorticoids had a lower risk of requiring additional anti-inflammatory treatment. Ouldali and colleagues[12] compared 64 patients treated with intravenous immunoglobulins with 32 propensity-matched patients treated with intravenous immunoglobulins plus methylprednisolone. Treatment with intravenous immunoglobulins plus methylprednisolone was associated with lower risk of ongoing fever (OR 0·25, 95% CI 0·09–0·70), reduced use of additional anti-inflammatory treatment, and shorter PICU stay. McArdle and colleagues[14] analysed 614 patients (246 were treated with intravenous immunoglobulins, 208 with intravenous immunoglobulins and glucocorticoids, and 99 with glucocorticoids). Inotropic support or mechanical ventilation on day 2 or later or death was observed in 56 patients receiving intravenous immunoglobulins plus glucocorticoids (adjusted OR for the comparison with intravenous immunoglobulins alone 0·77, 95% CI 0·33–1·82) and in 17 patients who received glucocorticoid monotherapy (adjusted OR 0·54, 95% CI 0·22–1·33). The adjusted OR for reduction in disease severity were similar in the two treatment groups compared with intravenous immunoglobulins alone, indicating similar recovery patterns[14] Villacis-Nunez and colleagues[15] assessed failure of initial therapy for 69 children receiving glucocorticoid monotherapy, 31 receiving intravenous immunoglobulins alone, and 115 receiving glucocorticoids plus intravenous immunoglobulins. After propensity score weighting, initial treatment failure was comparable between the patients in the gluocorticoid and the patients in the intravenous immunoglobulins plus glucocorticoid group. Patients in the intravenous immunoglobulins plus glucocorticoid group had a longer median inpatient stay compared with the glucocorticoid group (6 *vs* 5 days; p=0·001). Harthan and colleagues[23] compared 153 patients receiving intravenous immunoglobulins and glucocorticoids, 33 patients with intravenous immunoglobulins monotherapy, 43 patients with glucocorticoids, and 127 receiving neither intravenous immunoglobulins nor glucocorticoids. Combination therapy was associated with shorter length of PICU stay. However, when comparing hospital length of stay between these groups in mixed linear regression analyses, no significant difference was observed after adjusting for confounding variables. Bagri and colleagues[25] showed in their propensity score matched analysis that patients treated with glucocorticoids (n=45) versus intravenous immunoglobulins combined with glucocorticoids (n=84) did not differ in relation to the need of inotropes or respiratory support 2 days and later after treatment initiation.

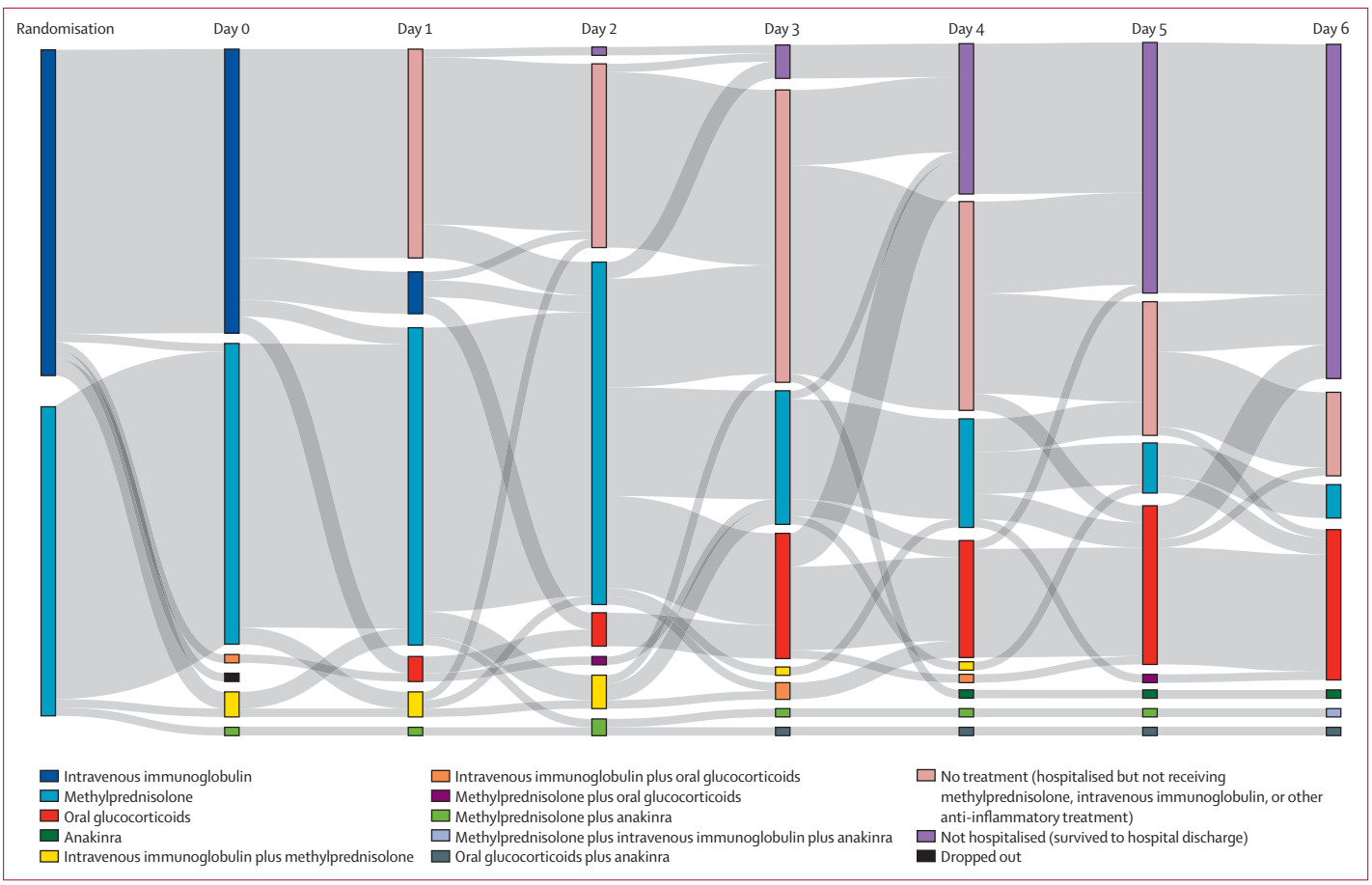

Figure 3: **Sankey diagram of intercurrent events in participants until day 6**
Overview of intercurrent events is shown in participants randomly assigned to the intravenous immunoglobulin or methylprednisolone group until day 6. Intercurrent events are defined as non-per-protocol anti-inflammatory treatments (such as additional anti-inflammatory treatment, more doses of the randomised treatment, intravenous immunoglobulin in the methylprednisolone group, and vice versa). Day 0 was defined as day of randomisation in which the patient received methylprednisolone or intravenous immunoglobulin. For all patients with intercurrent events, the different intercurrent events after randomisation are shown over time (day 0–6). Each day subsumes the intercurrent events occurring in a 24-h period.

Altogether, the available observational data support our findings and suggest that glucocorticoid treatment is comparable to intravenous immunoglobulins in patients with PIMS-TS. In our trial, this finding was consistent across all three a priori defined PIMS-TS phenotypes, including the Kawasaki disease-like group, but the respective subgroup sizes were too small to permit firm conclusions. Our study was unable to address whether intravenous immunoglobulins or methylprednisolone are superior to no anti-inflammatory treatment, because clinicians considered it unethical to withhold treatment for patients with PIMS-TS when designing the study. There remains a need for further research because intravenous immunoglobulins have been widely used in PIMS-TS due to clinical overlap with Kawasaki disease. In Kawasaki disease, intravenous immunoglobulins are recommended as the first-line treatment, although evidence, particularly for long-term effects, is scarce.[4] Considering the scarcity of paediatric data forcing compassionate use of drugs[26,27] in general, and the magnified relevance of this during the pandemic, our study provides urgently needed data on best treatments for a unique paediatric rare disease. Adverse events were scarce compared with previous reports.[28] For some outcomes, such as the need for respiratory support, the data from our trial suggest that treatment with glucocorticoids might be better than intravenous immunoglobulins alone. Treatment with intravenous immunoglobulins can be associated with fluid overload, particularly in children with decreased cardiac function, which potentially could account for the higher respiratory support requirements in our study. However, we did not collect data on fluid balance to be able to assess for this possible association.

Direct comparison of the observed treatment effects in different PIMS-TS studies is not only hampered by variable treatment protocols and variable outcome definitions, but also by considerable contamination with anti-inflammatory treatments. In the BATS study,[14] such

were administered in 136 (25%) of 552 patients in the three treatment groups by day 2, and 238 (43%) patients received additional treatment at any time. Among the patients in the propensity score matched sample who received intravenous immunoglobulins monotherapy in the Overcoming COVID-19 study,[13] 74 (72%) patients received an additional anti-inflammatory treatment, and among those receiving intravenous immunoglobulins and glucocorticoids, 41 (39%) patients received additional anti-inflammatory treatment. In the Swissped RECOVERY trial, intercurrent events were reported more commonly in the patients randomly assigned to the methylprednisolone group compared with intravenous immunoglobulins group. This difference might be explained due to glucocorticoid tapering aligned with the Swiss PIMS-TS guidelines,[8] which was not prescribed in the trial protocol.

The results of two further RCTs investigating optimal anti-inflammatory treatment in PIMS-TS are awaited, including the UK RECOVERY trial (NCT04381936) and the US MISTIC trial (NCT04898231). The UK RECOVERY trial investigated, in children with PIMS-TS, a two-stage randomisation with methylprednisolone, intravenous immunoglobulins, and no anti-inflammatory treatment as first randomisation, and anakinra, tocilizumab, and no anti-inflammatory treatment as second randomisation. The US MISTIC study aims to randomly assign 180 patients to methylprednisolone, anakinra, and infliximab if intravenous immunoglobulins monotherapy is considered clinically insufficient.

Several limitations of the Swissped RECOVERY study need to be stated. First, numbers of eligible patients with PIMS-TS declined considerably during the emergence of the SARS-CoV-2 omicron variant by spring 2022, leading to termination of the trial at 76 (of 80 intended) patients. The sample size was not powered to permit robust conclusions on secondary outcomes and subgroup analyses. Second, several exclusions occurred due to clinicians considering one of the treatments unsuitable before proceeding to possible enrolment or preferring a combination of intravenous immunoglobulins and glucocorticoids. We were not allowed to analyse whether clinical characteristics of patients without consent differed from enrolled patients. Therefore, for future trials, it would be desirable to access deidentified routine clinical data of patients who did not consent to enrol. Third, study treatments in this pragmatic trial were open label with the potential for bias, especially in relation to intercurrent events and therefore a second randomisation stage to additional rescue anti-inflammatory treatment might have been beneficial. Fourth, aligned with the UK RECOVERY study, the primary outcome of length of hospital stay included prerandomisation hospital stay and might have been further affected by conditions not related to disease severity. However, this outcome was chosen because length of hospital stay represents a patient-centred, objective measure strongly related to health-care costs. Finally, the follow-up period was limited to discharge or a maximum of 28 days. Further follow-up is required to delineate the full long-term effects associated with the studied interventions.

In conclusion, in this RCT on children with PIMS-TS, treatment with methylprednisolone resulted in comparable length of hospital stay compared with intravenous immunoglobulins, and might be associated with lower requirement for respiratory support. Intravenous methylprednisolone could be an acceptable first-line treatment for children with PIMS-TS, being considerably more affordable and more widely available globally than intravenous immunoglobulins.[29]

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Contributors
LJS and JAB designed this study, oversaw study setup, conduct, and analysis setup, contributed to the first draft, approved the final version, and take responsibility for the accuracy of reported findings. TW and NS contributed to study design, setup, conduct, and analysis setup, contributed to the first draft, and approved the final version. CS is the data manager for Swissped RECOVERY. AA wrote the statistical analysis plan and did the final analyses. AA and CS contributed to study conduct, and approved the final version. MCA, DGNB, GB-R, MB, SG, HK, M-HP, JT, FV, and PZ recruited patients, collected data, contributed to manuscript writing, and approved the final version. All authors had full access to the presented data in this Article and had final responsibility for the decision to submit for publication.

Declaration of interests
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president of the SwissPedNet (unpaid) and leadership of Severe Bacterial Infection and Antimicrobial Resistance working group of the Penta Foundation (unpaid). TW gave presentations for Novartis (payment to the institution) in the past 36 months. MB received an unrestricted Grant in the past 36 months from DOMARENA Foundation and Consulting fees by MSD; receives payment for Post Graduate Education in Paediatric Infectious Diseases; received support for the European Society For Paediatric Infectious Diseases (ESPID) Annual Meeting as Chair of Educational Committee; is Chair of the ESPID Education Committee and board members of SwissPedNet. All other authors declare no competing interests.

Data sharing

Deidentified participant data will be shared upon reasonable request unless the request is conflicting with ongoing or planned analyses. Requests need to be addressed to the corresponding author and will require approval by the Swissped RECOVERY steering group, and with a signed data access agreement. Researchers with a proposed use, approved by appropriate institutional review boards and the Swissped RECOVERY Steering Committee, can access the data.

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