

Cardiac assessment and inflammatory markers in children with paediatric inflammatory multisystem syndrome temporally associated with SARS-CoV2 (PIMS-TS) treated with methylprednisolone versus intravenous immunoglobulins: 6-month follow-up outcomes of the randomised controlled Swissped RECOVERY trial



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Summary

Background Previous findings from the Swissped RECOVERY trial showed that patients with Pediatric Inflammatory Multisystem Syndrome–Temporally Associated with SARS-CoV-2 (PIMS-TS) who were randomly assigned to intravenous immunoglobulins or methylprednisolone have a comparable length of hospital stay. Here, we report the 6-month follow-up outcomes of cardiac pathologies and normalisation of clinical or laboratory signs of inflammation from this study population.

Methods This pre-planned follow-up of patients with PIMS-TS included the Swissped RECOVERY Trial reports on the 6-month outcomes of the cohort after randomisation, with a focus on cardiac, haematological, and biochemical findings. The trial was an investigator-initiated randomised multicentre open-label two-arm trial in children and adolescents hospitalised with PIMS-TS at ten hospitals in Switzerland. Cardiological assessments and laboratory analyses were prospectively collected in the intention-to-treat analysis on pre-defined intervals after hospital discharge. Differences between randomised arms were investigated using Chi-square test for categorical and Wilcoxon test for continuous variables. The trial is registered with the Swiss National Clinical Trials Portal (SNCTP000004720) and [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT04826588) (NCT04826588).

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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 immunoglobulin group). During follow-up, the incidence of abnormal left ventricular systolic function, coronary artery aneurysms (CAA), and other signs of inflammation were comparable in both groups. However, we detected cardiac abnormalities with low incidence and a mild degree grade of pathology. CAAs were observed in 2/38 children (5.3%) in the IVIG group and 1/37 children (2.7%) in the methylprednisolone group at 6-month follow-up (difference proportion 0.75; 95% confidence interval (CI) –0.05 to 1.0; $p = 0.39$).

Interpretation Methylprednisolone alone may be an acceptable first-line treatment as left ventricular systolic dysfunction and clinical/laboratory evidence for inflammation quickly resolved in all children. However, our findings need further confirmation through larger studies as our sample size is likely to be of insufficient power to address rare clinically relevant adverse outcomes.

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Keywords: Children; Immunoglobulins; PIMS-TS; Methylprednisolone; RCT; Coronary artery aneurysm

Research in context

Evidence before this study

Pediatric Inflammatory Multisystem Syndrome–Temporally Associated with SARS-CoV-2 (PIMS-TS; also termed Multisystem Inflammatory Syndrome in children associated with COVID-19; MIS-C) has emerged as a serious illness affecting children worldwide. Due to its resemblance to Kawasaki disease, consensus guidelines have recommended the use of intravenous immunoglobulins in combination with methylprednisolone for treating children with PIMS-TS. Given the scarcity and costs of immunoglobulins, the Swissped RECOVERY trial was designed to assess the effectiveness of immunoglobulins compared with more affordable and widely available methylprednisolone in children with PIMS-TS. Using the terms (“PIMS-TS” OR “MIS-C” OR “trial”) AND (“intravenous immunoglobulins” OR “methylprednisolone” OR “treatment”) without language restrictions, our PubMed research on studies published between April 1, 2020 and June 26, 2023, identified only the Swissped RECOVERY Trial that prospectively compared the effectiveness of immunoglobulins vs. methylprednisolone alone.

Added value of this study

In this analysis of the open-label multicentre randomised controlled Swissped RECOVERY trial, longitudinal follow-up of cardiac and inflammatory findings of 75 (100%) enrolled children is reported for 6 months after randomisation. Pre-planned 6-month outcomes included follow-up data with focus on ongoing PIMS-TS symptoms and functional status. As part of our post-hoc analysis, the proportion of patients with cardiac pathologies is categorised with respect to the extent of left ventricular systolic ejection fraction (LVEF) reduction and coronary artery enlargement. Our echocardiographic and laboratory follow-up demonstrated comparable outcomes with relation to the incidence of

abnormal left ventricular systolic function, coronary artery aneurysms and biomarker levels between patients randomised to immunoglobulins vs. methylprednisolone. Our findings are supported by the 2021 and the updated 2023 observational Best Available Treatment Study (BATS) publications, which retrospectively assessed treatment effectiveness in a large cohort of patients with PIMS-TS. In these studies, the incidence of left ventricular systolic dysfunction and of coronary artery aneurysms was comparable during short-term follow-up in the groups treated with immunoglobulins alone or steroids alone.

Implications of all the available evidence

Irrespective of first anti-inflammatory or immunomodulatory treatment, inflammation quickly resolves in children treated for PIMS-TS. Timely initiation of treatment appears to be key, ideally before any coronary artery dilatation occurs. Our randomised controlled trial demonstrates that methylprednisolone alone is probably an acceptable first-line treatment. However, in both groups we detected cardiac abnormalities with low incidence and a comparatively mild degree grade of pathology, and as such our findings in a cohort of 75 children need further confirmation through larger studies such as the UK RECOVERY trial. Interestingly, our follow-up analysis demonstrated two smaller coronary artery aneurysms in the immunoglobulin group and one large/giant late-occurring coronary artery aneurysm in the methylprednisolone group at the 6 months follow-up examination. Future studies will also have to investigate whether abnormal coronary artery wall morphology and endothelial dysfunction in the coronary arteries of patients with PIMS-TS do equally reliably resolve as the coronary artery enlargement itself.

Introduction

Paediatric Inflammatory Multisystem Syndrome—Temporally Associated with SARS-CoV-2 (PIMS-TS; also termed Multisystem Inflammatory Syndrome in children associated with COVID-19; MIS-C) has emerged following the initial wave of SARS-CoV-2 infections as a rare serious illness affecting children worldwide. Due to its resemblance to Kawasaki disease (KD), consensus guidelines have initially recommended the use of intravenous immunoglobulins (IVIG) in combination with steroids for treating children with PIMS-TS.^{1–3} Large retrospective, observational studies demonstrated that cardiac outcome (in terms of normalisation of left ventricular ejection fraction) and inflammatory outcome (such as the resolution of fever) were improved in children treated with the combination of IVIG and methylprednisolone (MPS) when compared to children treated with IVIG alone.^{4,5} However, given the scarcity and costs of IVIG across the globe, establishing the effectiveness of the more affordable and widely available MPS compared with IVIG represented a clinically relevant question. The multicentre, open-label randomised controlled Swissped RECOVERY trial⁶ included 75 children in the intention-to-treat analysis and demonstrated that hospitalised children with PIMS-TS randomised to first treatment with MPS (10 mg/kg once daily for 3 days) had a similar length of hospital stay (primary outcome) and less need for respiratory support (secondary outcome) compared to children treated with IVIG (single dose of 2 g/kg).⁷

In the literature, retrospective evidence obtained on quite small numbers of patients indicates that in most children cardiac abnormalities and inflammatory markers rapidly normalise within 2–3 months after hospital admission.^{8–10} This pre-planned follow-up of patients with PIMS-TS included the Swissped RECOVERY Trial reports on the 6-month outcomes of the cohort after randomisation with particular focus on cardiac, haematological, and biochemical findings.

Methods

Study design

Swissped RECOVERY was an investigator-initiated randomised multicentre open-label two-arm trial in children and adolescents hospitalised with PIMS-TS conducted at ten paediatric hospitals in Switzerland. Hospitalised children diagnosed with PIMS-TS were eligible for a 1:1 randomisation to be treated with IVIG (2 g/kg as a single dose) or intravenous MPS (10 mg/kg/day once daily for 3 days). The study protocol, including primary and secondary outcomes, key inclusion/exclusion criteria, sample size determination, randomisation and masking/blinding, sensitivity analyses, and post-hoc analyses have been published previously.⁶

In brief, the pre-planned 6-month outcomes included standardised assessment of ongoing PIMS-TS

symptoms and fatigue as well as behavioural and functional status.⁶ The 75 patients with PIMS-TS included in the intention-to-treat analysis were followed-up after discharge until 6-month follow-up.

Ethics

The study was approved by the lead ethics committee (Ethics Committee Northwest/Central Switzerland; EKNZ, Project ID: 2021-00362); and other responsible ethics committees in Switzerland and registered on the Swiss National Clinical Trials Portal (SNCTP000004720) and clinicaltrials.gov (NCT04826588). Prospective written informed consent from parents (and from the patients if aged 14 years or older) was obtained prior to the start of the study.

Follow-up procedures

After randomisation on day 0, follow-up was aligned with clinical routine-monitoring and data were collected prospectively at weeks 1–3 (early follow-up), weeks 4–8 (intermediate follow-up), and weeks 9 post discharge until 6 months after randomisation (late follow-up) ([Supplementary Table S1](#)). Follow-up included a clinical, cardiac and laboratory assessment. The cardiac and/or laboratory assessments were conducted at the discretion of the treating team. As a result, echocardiograms and/or laboratory analyses were omitted in cases where children were evidently in good health (i.e., absence of fever, presence of physical and mental well-being) and had previously had normal findings. These are marked with N.A. in the [Supplementary Tables](#).

Cardiac assessment

Data were collected from serial echocardiographic, electrocardiographic as well as biochemical assessments for all participants in whom the clinical team ordered the examinations as part of the routine care on the pre-specified follow-up dates. Interpretation of the raw data for the echocardiographic and electrocardiographic examinations captured in the REDCap electronic data base¹¹ was performed based on the following definitions for the left ventricular systolic ejection fraction (LVEF): a normal left ventricular systolic function was defined as a LVEF of $\geq 55\%$, a “mild systolic dysfunction” as an LVEF of 40% to $<55\%$, a “moderate systolic dysfunction” as an LVEF of 30% to $<40\%$ and, finally, a “severe systolic dysfunction” as an LVEF of less than 30%.^{12,13} Coronary artery changes including dilatation and aneurysms were characterised using the AHA classification¹⁴ based on the captured Z scores and coronary artery dimension. A Z-Score always <2 was defined as “without coronary involvement”, a Z Score of 2 to <2.5 was defined as a coronary artery dilatation (“dilatation only”), a Z Score of ≥ 2.5 but <5 was defined as a “small aneurysm”, a Z Score of ≥ 5 but <10 and an absolute CA dimension of <8 mm was defined as a “medium aneurysm”, and, finally, a Z Score of ≥ 10 or an absolute CA dimension of

≥ 8 mm was defined as a “large/giant aneurysm”. All arrhythmias or ECG abnormalities observed by the cardiologists were documented by asking for the presence of arrhythmias and/or tachycardias and by enabling a further description of the arrhythmias in a free text box in the REDCap electronic data base during our follow-up. In addition, NT-proBNP and troponin were monitored over time in both treatment groups.

Laboratory assessment of inflammation

To document the resolution of biochemical and haematological signs of inflammation, we recorded blood counts, C-reactive protein (CRP), D-Dimer, Ferritin, Alanin-Aminotransferase (ALT) and albumin serum concentration in those children that appeared clinically unwell at early, intermediate, and late follow-up.

Definition of outcomes

As part of the pre-planned analysis,⁶ the proportion of patients (N, %) with ongoing PIMS-TS symptoms and fatigue as well as behavioural and functional status were recorded. As part of our post-hoc analysis, the proportion of patients with cardiac pathologies was categorised with respect to the extent of left ventricular systolic ejection fraction (LVEF) reduction and coronary artery enlargement.

Statistical analysis

Study data were collected and managed using REDCap electronic data capture tools.¹¹ Follow-up data were summarised using the number (percentage) for categorical variables and the median (inter-quartile range [IQR]) for continuous variables. Whisker Box Plots were omitted in cases where ≤ 5 measurements were available. Summary statistic comparisons between groups were performed using the chi-square test for categorical variables and the Wilcoxon test for continuous variables. As children that were clinically healthy were not followed with serial echocardiographic or laboratory analyses, we did not perform statistical analyses like Repeated Measure ANOVA analysis but preferred descriptive statistics instead. All analyses were based on the complete case data only and were performed using the statistical software R (version 4.0.3, R Development Core Team, Vienna, Austria).¹⁵

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 for publication.

Results

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 immunoglobulin group). During the 6 months of follow-up, the level of attrition in the follow-up period was as expected ([Supplementary Table S1](#)); however, follow-up information was at least once available for 37/38 (97.3%) patients in the IVIG arm, and 37/37 (100%) patients in the MPS arm ([Fig. 1](#), [Supplementary Table S1](#)).

LV systolic dysfunction

There were no abnormalities in the LV systolic function (“abnormal contractility”) in any of the patients examined by echocardiography during early, intermediate, and late follow-up ([Fig. 2A](#), [Supplementary Table S2](#)).

Coronary artery aneurysms (CAA)

Regardless of the treatment received, normalisation of coronary artery abnormalities occurred rapidly in most children subjected to echocardiographic examination. We observed CAAs in 2/38 children (5.3%) in the initially assigned IVIG group and 1/37 children (2.7%) in the MPS group on late follow-up CAAs were observed in 2/38 children (5.3%) in the IVIG group and 1/37 children (2.7%) in the methylprednisolone group at 6-month follow-up (difference proportion 0.75; 95% confidence interval (CI) –0.05 to 1.0; $p = 0.39$) ([Fig. 2B](#), [Supplementary Table S2](#)). While the Z-Scores appeared to be somewhat lower in children randomised to IVIG than to MPS, the numbers were low, and no statistically significant differences were detectable (early follow-up: IVIG: Z-Score 2.94 [IQR: 2.94, 2.94] vs. MPS: Z-Score 6.36 [IQR: 4.88, 7.85], $p = 0.22$); (intermediate follow-up: IVIG: Z-Score 3.50 [IQR: 3.50, 3.50] vs. MPS: Z-Score 5.26 [IQR: 3.88, 6.63], $p = 0.99$); (late follow-up: IVIG: Z-Score 4.40 [IQR: 4.35, 4.45] vs. MPS: Z-Score 10.90 [IQR: 10.90, 10.90], $p = 0.22$) ([Fig. 2C](#), [Supplementary Table S2](#)).

Arrhythmias and conduction abnormalities

We did not observe any arrhythmias in the two treatment groups during our follow-up ([Supplementary Table S2](#)). As such, the arrhythmias described during the initial hospital stay (one child with incomplete right bundle branch block in the IVIG group, and one child each with an atrioventricular block grade I or an intermittent junctional arrhythmia, respectively, in the MPS group) were evidently transient with no need of an ECG examination on any of the follow-up dates.

Biochemical assessment of cardiac function

Consistent with similar LV systolic function, we found no difference in the concentration NT-proBNP and Troponin between the two groups at any time point ([Supplementary Table S3](#), [Supplementary Figure S1A and B](#)).

Haematological and biochemical resolution of inflammation

The analysis of blood counts and biochemical inflammatory markers including statistical analyses are

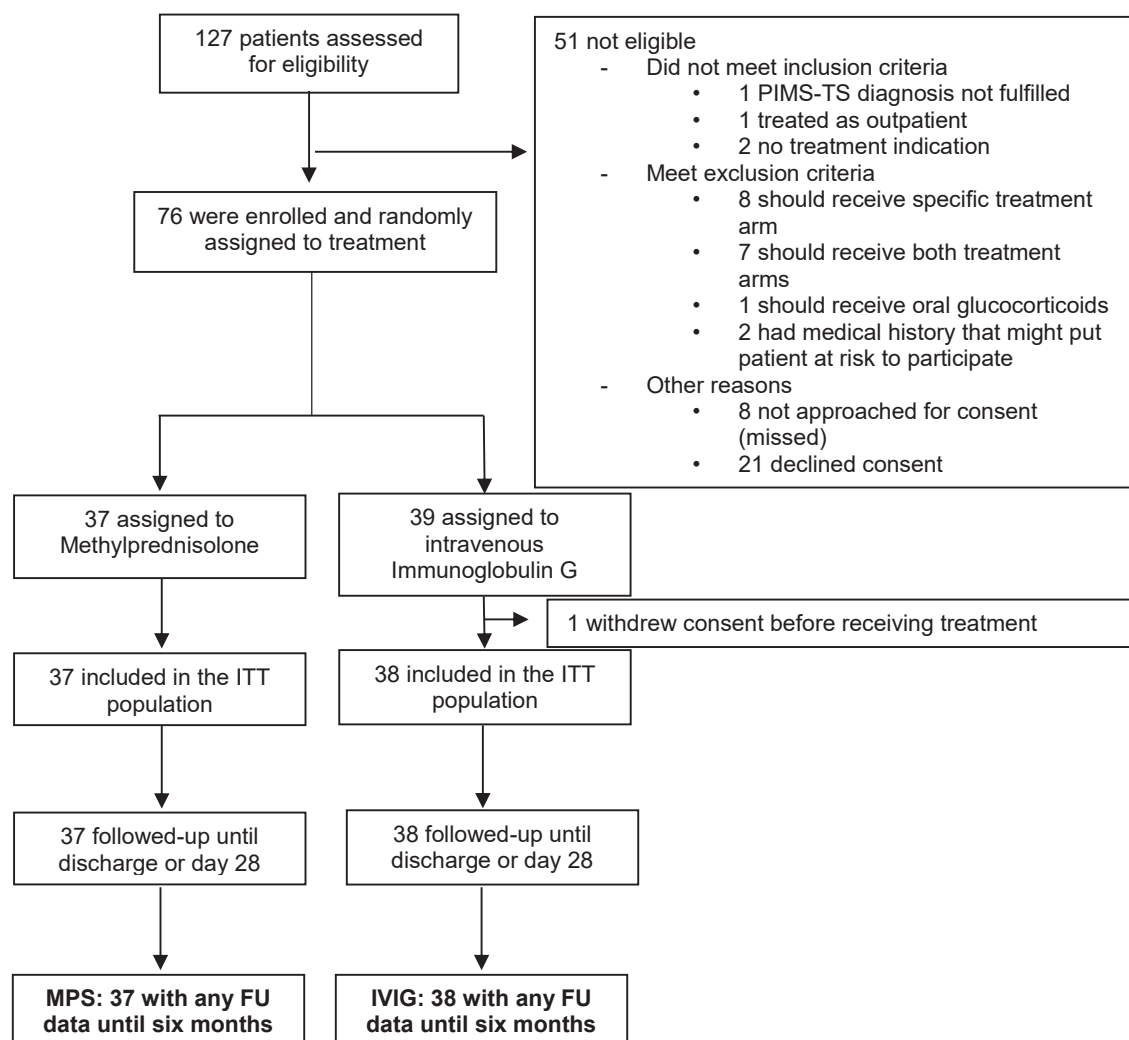


Fig. 1: Study flow chart. Figure shows the Swissped RECOVERY study cohort until discharge/death or censored at 28 days and during the follow-up (described in this publication). ITT: intention-to-treat; MPS: methylprednisolone; IVIG: intravenous immunoglobulins.

summarised in [Supplementary Table S3](#) and [Supplementary Figures S2–S4](#). There were no differences between the two treatment arms for neutrophil/lymphocyte and thrombocyte counts ([Supplementary Figure S2](#)), for CRP, D-Dimer and Ferritin ([Supplementary Figure S3](#)), or for albumin and ALT serum concentrations ([Supplementary Figure S4](#)) during follow-up.

Discussion

The follow-up analyses of the 6-month cardiac and laboratory inflammatory outcomes of children with PIMS-TS who were initially randomly allocated (1:1) to receive immunoglobulins or methylprednisolone provide prospective evidence that regardless of the initial assignment to IVIG or MPS, LV systolic dysfunction or CA

dilatations/aneurysms mostly resolve within the first few days or weeks of the acute illness. In addition, we do not find any evidence for persisting arrhythmias or other conduction abnormalities in our cohort that have earlier been reported in patients with PIMS-TS during the initial phase of the disease.^{4,16,17}

Comparing our findings with the existing literature proves challenging, as no study has yet prospectively examined "treatment effectiveness". However, in the 2021 and the updated 2023 observational Best Available Treatment Study (BATS) publications, which retrospectively assessed "treatment effectiveness" in a large cohort of 2009 patients with PIMS-TS, the incidence of LV systolic dysfunction and of CAAs was comparable between the treatment groups treated with "IVIG alone" or "steroids alone".^{18,19} Considering that a key concern of BATS was the extent to which a retrospective

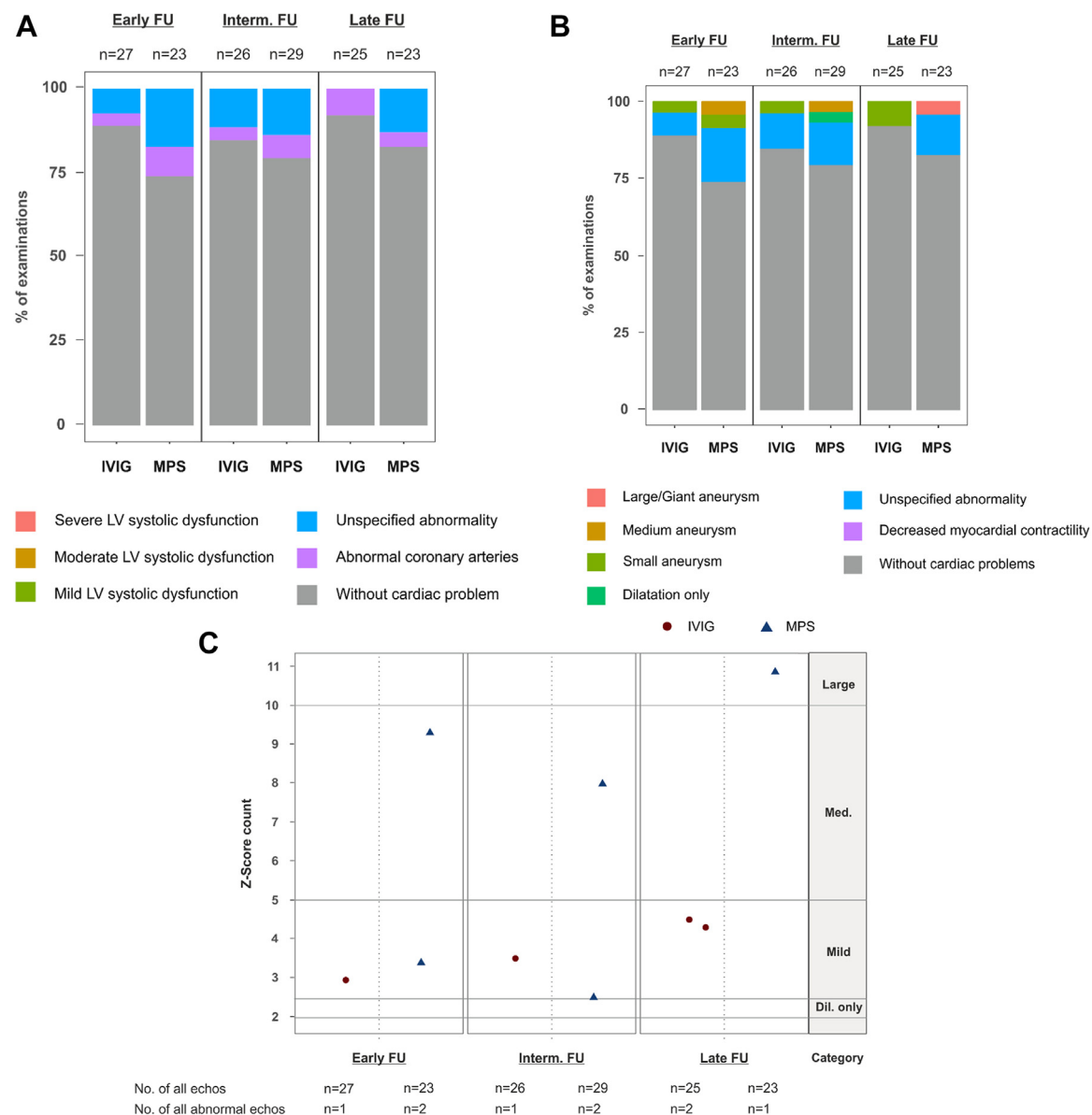


Fig. 2: Early, intermediate, and late cardiac Follow-up examinations: Left ventricular (LV) systolic function and coronary artery (CA) involvement. (A) Echocardiographic findings during Follow-up (FU) in children with PIMS-TS treated with intravenous immunoglobulins (IVIG) or methylprednisolone (MPS) as per protocol. Stacked bar charts depicting the percentage of examinations with varying degrees of LV systolic dysfunction, abnormal coronary arteries, normal function, or “unspecified” abnormalities at the indicated time points. (B) Stacked bar charts depicting the percentage of children with varying degrees of coronary artery enlargement (large/giant, medium or small aneurysms, “dilatation only”), with other cardiac abnormalities (“unspecified” or decreased myocardial contractility) or without any cardiac abnormalities at the indicated time points. Note that “unspecified” in this context refers to abnormalities other than “decreased myocardial contractility”, “abnormal coronary arteries” or “pericardial effusion”. Number of children with echocardiograms is indicated in the headings of the Figures. (C) Z Score counts in all echocardiograms during FU with documented abnormal coronary artery size. Categorisation into coronary artery “dilatation only”, “mild”, “medium” or “large” CAA, respectively, was done using the AHA classification.

comparison of outcomes after non-randomised choice of treatment would be sufficient to guide global clinical practice, our study does in part provide important prospective evidence that methylprednisolone alone may be

sufficient as first-line therapy to control PIMS-TS-induced inflammation.

The overall low incidence and the comparatively low grade of any cardiac abnormalities in our patient cohort

might have resulted from the gradually milder becoming phenotype²⁰ but also a high grade of awareness and early diagnosis of affected children. Irrespective of the choice of first-line treatment, timely initiation of anti-inflammatory and/or immunomodulatory treatment may be key, ideally before any coronary artery dilatation occurs (see also retrospective-prospective cohort study on 872 children presented as an Abstract by Tagarro et al. at the 41st Annual ESPID Meeting, 2023, Lisbon, Portugal). In line with the notion that anti-inflammatory/immune-modulatory treatment may not fully prevent the occurrence of CAAs, a recent meta-analysis in 547 patients with PIMS-TS reported persistent coronary artery dilatation or CAAs in 5.2% of children at 6-month follow-up.²¹ Consistent with these findings, our follow-up analysis demonstrated two smaller CAAs in the initially assigned IVIG group and one large/giant CAA in the initially assigned MPS group at 6-month follow-up. It remains open if this rather concerning large/giant CAA and the overall somewhat higher Z Scores in the patients assigned to MPS indicate a lower effectiveness of MPS or simply too small a case number. Knowing that coronary arteries in patients with previous KD may display a persisting abnormal vascular wall morphology and an endothelial dysfunction at the site of regressed coronary aneurysms,^{22,23} future studies will have to show if endothelial dysfunction in the coronary arteries of patients with PIMS-TS does also reliably resolve. In that sense, the previously recommended structured long-term follow-up strategy including repeated cardiologic assessment¹⁻³ appears indispensable despite the overall favourable cardiac outcome of our patients.

Based on previously published data by the PIMS-TS Study Group and EUCLIDS and PERFORM Consortia,²⁴ our interdisciplinary working group decided to include NT-proBNP, troponin, neutrophil, lymphocyte and thrombocyte count, CRP, D-Dimer, ferritin, albumin, and ALT into our follow-up analysis. Here, we document that irrespective of the initially assigned treatment arm, haematological and biochemical markers of inflammation normalise rapidly. In line with this, the observational BATS study did not identify any treatment-related differences in the resolution of CPR, ferritin, and troponin elevations.¹⁹ As such, the question arises if the increasingly frequent (and cost-intensive) determination of laboratory markers of inflammation in every patient with PIMS-TS adds information relevant for clinical-decision making. We observe that laboratory markers importantly support the diagnosis of PIMS-TS and document disease severity on admission, but over time they are of little significance in children in whom fever, and left ventricular systolic dysfunction rapidly resolve.

The Swissped RECOVERY Trial has been the first randomised trial prospectively assessing treatment effectiveness of immunoglobulins and methylprednisolone

in children with PIMS-TS. During the comparatively long follow-up period of 6 months, the level of attrition in the follow-up period was as expected. We had deemed repeated routine echocardiograms and/or laboratory analyses in children that were evidently in good health not only unethical but also unreasonable in a period of limited resources and had therefore decidedly omitted these. As such, it is important to note that “missingness” during our follow-up period is a sign of good outcome and not a sign of poor quality of our follow-up assessment. In line with our high degree of rigor, follow-up information was at least once available for 97.3% of the patients in the immunoglobulin arm, and 100% of the patients in the methylprednisolone arm.

Unfortunately, we had to limit our cohort size to 75 children included in the intention-to-treat analysis as the incidence of PIMS-TS gradually declined during the early summer months of 2022. This means that the trial is likely to be of insufficient power to address rare adverse outcomes, such as CAA formation or resolution. In addition, cardiologists in some centres did not feel comfortable assessing the eligibility of children with PIMS-TS presenting with CAAs for inclusion into our study, as IVIG would have been the primary drug of choice to prevent and treat CAAs in patients with KD.¹⁴ Hence, we cannot fully exclude the possibility that a certain bias in the composition of our patient cohort existed that limits generalisability of trial findings to patients presenting with CAAs. Collectively, our findings in a cohort of 75 children need further confirmation through larger studies such as the UK RECOVERY trial (NCT04381936).

Over the past 3 years, significant progress has been made in understanding the complex immunological pathology of PIMS-TS. It is now evident that the immune dysfunction pathways in PIMS-TS and KD seem to be related but not identical. This raises the question of whether the similarities between the two diseases are sufficient to justify a similar therapeutic approach. Our follow-up data on 75 patients indicate that intravenous methylprednisolone is likely an acceptable first-line treatment for children with PIMS-TS; however, the role of IVIG and methylprednisolone in preventing and treating moderate to large/giant CAAs remains to be addressed.

Contributors

All authors conceptualised and approved this manuscript. MCA performed data analysis with CS and wrote the first draft of the manuscript. CS provided figures and tables and performed statistical analysis. AA supported statistical analysis. SBD, DW, MHP, GBR, SG, NS and JT critically revised the manuscript. TW, LJS and JB led the trial, and revised the manuscript. MCA and CS accessed and verified all data. All authors approved the final version of the manuscript.

Data sharing statement

Anonymised participant data will be made available upon requests directed to the corresponding author. Proposals will be reviewed and approved by the sponsor, investigator, and collaborators based on scientific merit. After approval of a proposal, data can be shared through a secure Online platform after signing a data access agreement. All data

will be made available for a minimum of 5 years from the end of the trial.

Declaration of interests

LJS was supported by grants from the NOMIS Foundation, the Vontobel Foundation, and the Gaydoul Foundation for this study. Swiss PedNet (<https://www.swisspednet.ch/>) provided infrastructure support for study coordination and monitoring. JB received grant support paid to the institution from the European and Developing Countries Clinical Trials Partnership (PediCaP, RIA2017MC-2023), Horizon 2020 (NeoIPC, grant 965328), the Swiss National Science Foundation (KIDS-STEP, grant 173532), National Institute for Health Research (CAP-IT, project 13/88/11), Innosuisse (SPEARHEAD flagship grant), the Swiss Personalised Health Network (Secretariat for Education Research and Innovation) (SwissPedHealth, award NDS-2021-911), in the past 36 months; consulting fees paid to the institution from Shionogi, Sandoz, Basilea, and GSK; payments to the institution for presentations, lectures, speakers bureaus, manuscript writing or educational events in the past 36 months from Pfizer, Sandoz, and Bayer; participated at independent data monitoring committee boards of Avenir trial (member, expenses), Lakana trial (member, unfunded), CURLY trial (Chair, unfunded) in the past 36 months; is the vice 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. All other authors declare no competing interests.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.eclinm.2023.102358>.

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