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LETTER TO EDITOR

Successful Treatment with SCIG of a Child with Refractory Chronic ITP

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To the Editor

Immune thrombocytopenia (ITP) is mediated by autoantibodies and characterized by destruction and impaired production of platelets. Primary ITP is a rare, idiopathic autoimmune disorder with an incidence of 3–5 per 100,000 children per year [1], whereas secondary ITP is related to coexisting conditions such as immunodeficiency, rheumatological disorders, infectious diseases, and others [2]. Persistence over 12 months is referred to as chronic ITP (cITP) and bears a significant disease burden due to hemorrhagic, thrombotic, or therapy-associated complications. Besides corticosteroids, intravenous immunoglobulins (IVIG) are a standard first-line therapy for ITP. It is assumed that IVIG positively affects the platelet count and the bleeding diathesis by immunomodulation and stimulation of thrombopoiesis [3].

In patients with humoral immune deficiencies requiring IgG substitution, the subcutaneous application route of Ig (SCIG) has demonstrated a range of benefits compared to the intravenous route. However, except for a retrospective study in the context of humoral immunodeficiencies and cytopenias, SCIG has been poorly investigated for the treatment of autoimmunity and ITP [4–7]. Second- and third-line approaches for cITP include splenectomy, immunosuppressive drugs, and thrombopoietin receptor agonists [1, 8] with an array of adverse effects and risks.

Patient Report

We report the course of a currently 8-year-old girl with cITP that first manifested in her second year of life. She presented with recurrent thrombocytopenia (lowest platelet count 0×10^9/L) and considerable bleeding tendency (diffuse petechiae, large hematomata, epistaxis, mucosal bleeding). Laboratory investigations (Table 1) excluded an underlying primary immunodeficiency, including autoimmune lymphoproliferative syndrome and common variable immunodeficiency, or bone marrow abnormalities, hypogammaglobulinemia, rheumatological disorders, or an active infectious disease. As a potential infectious association, cytomegalovirus (CMV) was repeatedly found in urine at variable copy numbers, and, at two occasions, also in plasma (Fig. 1b) albeit without other clinical signs of illness. Importantly, at the initial diagnostic work-up, anti-CMV IgG was positive, but anti-CMV IgM and virus nucleic acid detection in plasma were negative. Antiviral treatment was initiated upon an increase in copy numbers under immunosuppression with anti-CMV IgG, ganciclovir, valganciclovir, and cidofovir (sequentially) over 8 months and did not show any effect on the platelet count but yielded a persistent reduction of viral load.

Repeated courses of IVIG (0.5 g/kg) were regularly followed by an excellent increase of platelet counts ($> 100 \times 10^9$/L), which, however, could not be maintained for more than 7 to 14 days. Neither short-term steroid therapy (1–2 mg/kg for 1–3 days) nor long-term (initially, same dose for > 4 weeks, then tapered) showed any stable response. Because of Rh negativity, anti-D immunoglobulin treatment was not applicable. Therefore, further therapeutic attempts were undertaken: mycophenolate-mofetil (MMF, 1200 mg/m^2/d) was terminated after 2 months because of increasing CMV viral load in blood (from 0 to 1600 copies/ml) and urine (from 1200 to 43,000 copies/ml); weekly romiplostim (85–170 μg/m^2 over

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Table 1 Immunological and other diagnostic work-up

Methods	Findings
Virus nucleic acid (PCR) testing (plasma, except stated otherwise); Infection serology (before IgG replacement therapy)	Positive or negative: CMV (see Fig. 1 for time course in urine and blood); CMV-IgG positive, IgM negative. Negative: EBV, parvovirus B19, HHV6, adenovirus, HSV-1, HSV-2, VZV, enterovirus, HBV, HCV, and HIV
Serum immunoglobulins: IgG, A, M, D, E, and IgG- and IgA-subclasses	Normal (before start of IgG replacement therapy)
Complement activity (CH50, C3, and C4)	Normal
Flow cytometry: B cells, B-memory cell subsets, T cells, naïve and activated T cells, DNT cells, $TCRgd^+$ T cells, NK-cells, and monocytes	Normal (repeated occasions)
Autoimmune screening: ANA, ENA, ds-DNA-Ab, TG-Ab TR-Ab, TPO-Ab, Insulin-Ab, IA2, IAA, GAD, cardiolipin-Ab, and ß2-glycoprotein Ab	Normal/negative
Bone marrow	Normocellular, trilinear differentiating hematopoiesis, megakaryocytes increased in number, and compatible with ITP
Chest X-ray	Normal

DNT, $CD4^-\,CD8^-\,CD3^+\,TCRab^+$ double negative T cells; *$TCRgd^+$ T cells*, T cell receptor gamma-delta-positive T cells

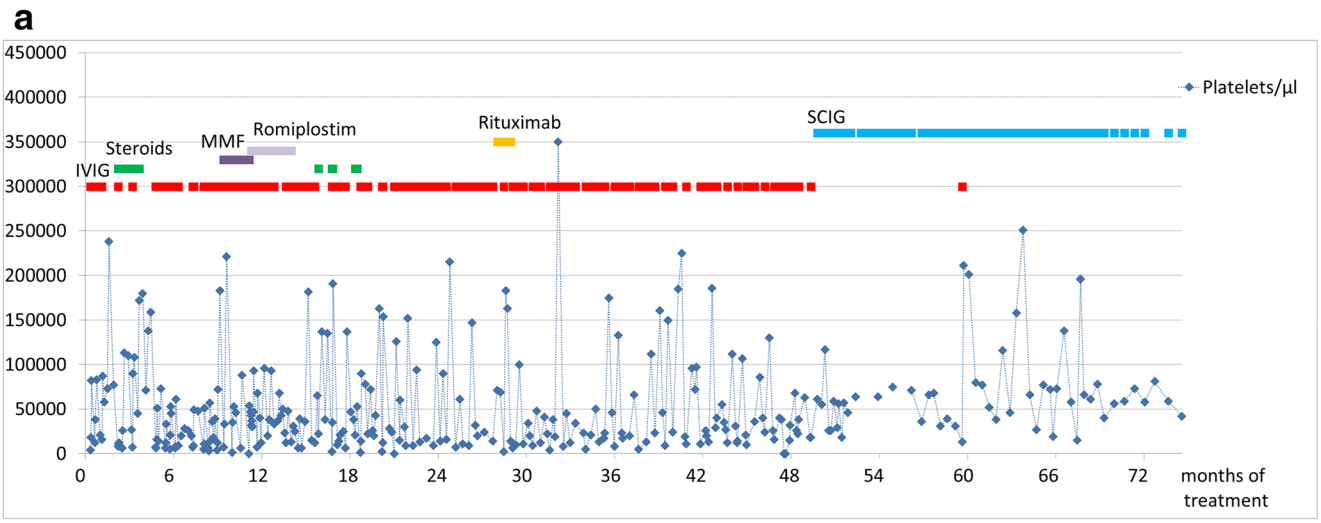
2.5 months), and rituximab (4×375 mg/m^2, one course) did not show any therapeutic success with regard to the platelet count and bleeding tendency.

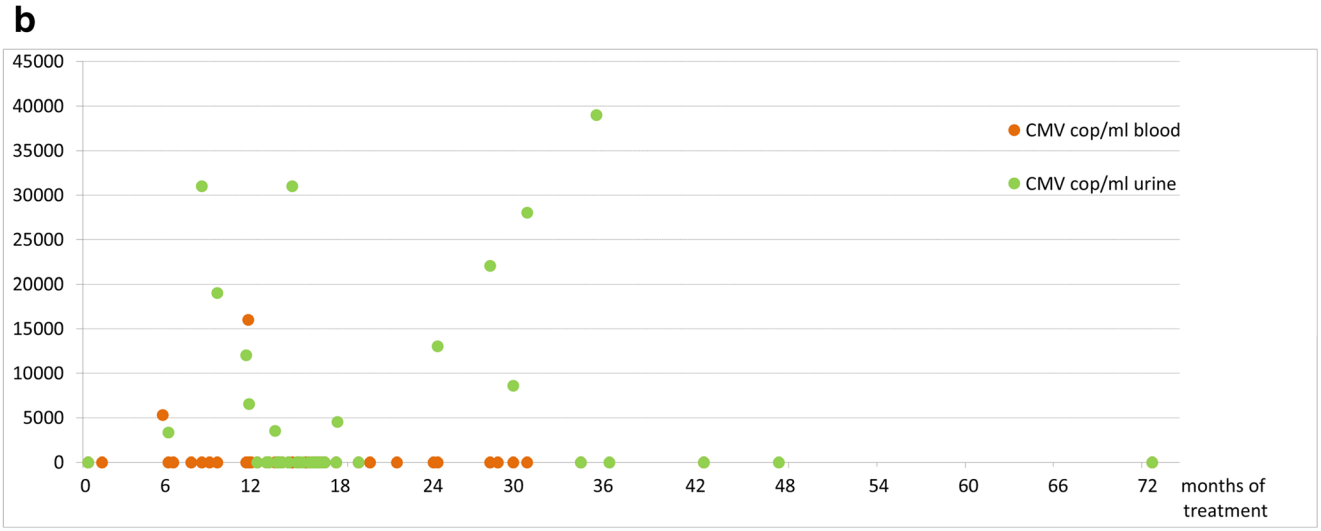
As the patient remained responsive to regular applications of IVIG (0.5 g/kg 2–4 weekly), this treatment was continued as a single agent long-term therapy for 1.5 years (Fig. 1a). Attempts to extend the interval of IVIG administration resulted in a relapse of hemorrhages. In the 5th year of treatment, a compassionate use of SCIG (90 mg/kg/week) was initiated in an attempt to improve the health-related quality of life of the girl and her family. After 6 months of satisfactory response, the interval could be extended to 2 weeks. Four months after stretching to 2-weekly intervals, an accidental delay of administration with additional 4 days was followed by a drop of the platelet counts and a bleeding episode, requiring an acute intervention, in this case with IVIG (Fig. 1a), and suggesting persisting dependency on treatment. Thereafter, the 2-weekly interval was maintained without complications and continued for a total of 12 months. After that period without complications, applications could be further stretched to 3-weekly (75 mg/kg/week) (Fig. 1a). Interestingly, SCIG lead on average to higher platelet counts (mean platelet count = 72×10^9/L, SD = 51×10^9/L) than IVIG (mean platelet count = 48×10^9/L, SD = 58×10^9/L), ($p < 0.05$, Wilcoxon-Test, Fig. 1c). Additionally, the need for hospitalization decreased dramatically after initiation of SCIG—only 0.5 days/year under SCIG—compared to 24.8 days/year from disease onset under IVIG and four second-line therapies, and to 25.5 days/year during IVIG maintenance therapy.

Discussion

While many patients with cITP do not require treatment at all, the purpose of treating cITP in children is to reduce the bleeding tendency and to prevent the risk of life-threatening hemorrhages by maintaining platelet counts sufficiently high while preserving an acceptable health-related quality of life. However, many second-line therapies fail to achieve an adequate response, and most are associated with substantial side effects, the majority of which are due to immunosuppression. This was the case in our patient, who underwent four alternative treatment modalities with little or no effect before being treated with SCIG. We also observed the unusual event of CMV reactivation on MMF treatment. Although normal results from immune phenotypic analyses and the absence of a clinical predisposition towards infections suggested otherwise, and MMF alone may suffice to induce a secondary immunodeficiency with CMV reactivation, this observation might raise concerns for an underlying immune deficiency. This might be addressed by genetic (panel or whole exome sequencing) diagnostics, which was not yet undertaken due to the observed, favorable treatment response with continuous CMV negativity.

The establishment of new, potentially beneficial, therapeutic strategies for cITP through prospective trials is mainly obstructed by the low incidence of this diagnostic entity, an even lower indication to treat. Thus, an individual approach is taken frequently [8]. To date, only few reports on the application of SCIG in cITP have been published: Iuliano et al (2014) included one child in their series of five successfully treated patients; Chapdelaine et al (2012) describe an excellent response in two children with cITP, however, in a setting of a probable underlying humoral immune deficiency [4, 7]. Recently, a large retrospective study and a small patient series showed that in patients with common variable immune deficiency and concomitant ITP, SCIG (with a trough level of > 7 g/l) were at least as effective with regard to immune modulation and treatment of the autoimmune cytopenia as IVIG [5, 6], in line with the potential benefit of SCIG in our observation.





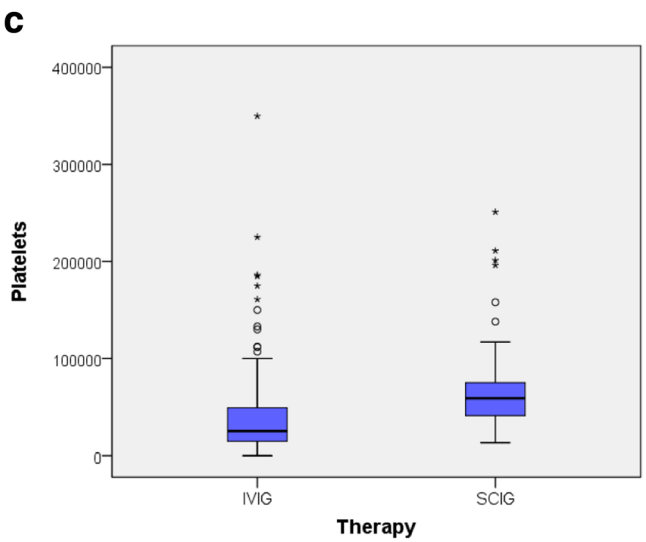


Fig. 1 **a** Platelet count (left *y*-axis) is shown over a treatment period (0 to 75 months, *x*-axis). In addition, the different therapy options: intravenous immunoglobulins (IVIG), corticosteroids, mycophenolat mofetil (MMF), romiplostim, and subcutaneous immunoglobulins (SCIG) are shown. **b** The same time axis as in **a** is used to depict the course of CMV copy numbers detected in plasma and urine. **c** Subcutaneous immunoglobulins (SCIG) lead to higher platelet counts on average (mean platelet count = 72×10^9/L, SD = 51×10^9/L) than intravenous immunoglobulins (IVIG) (mean platelet count = 48×10^9/L, SD = 58×10^9/L), ($p < 0.05$, Wilcoxon-Test)

Given the dependency of the thrombocytopenia on regular administration of IgG despite normal baseline IgG levels, we aimed to achieve more constant serum concentrations of IgG. Those were reached by subcutaneous application, similarly to the use in patients with immune deficiencies. Surprisingly, even lower doses of SCIG led to better effectiveness than IVIG and eventually allowed us to stretch the intervals between the applications without complications. As this is a single-patient observation, it could be speculated, that a spontaneous partial recovery of platelet counts occurred independently from the therapy trial with SCIG. However, an accidental interruption of SCIG led to a consequent drop of the platelet counts, accompanied by a bleeding event. Therefore, a spontaneous remission, occurring coincidentally while under SCIG therapy, appears to be an unlikely explanation for the favorable dynamics of the platelet counts in this case.

The role of CMV as trigger of ITP, and a potential attenuation of CMV-mediated effects in the absence of other CMV-related clinical symptoms by IgG replacement therapy are possible, but difficult to assess in this patient. Of note, plasma was repeatedly tested negative for CMV at and after the onset of ITP, and urine was positive, but first tested after prolonged glucocorticosteroid treatment period (Fig. 1a). Later, after MMF was terminated because increased CMV copy numbers were detected, CMV remained negative in the blood, followed by negativity in the urine. This is likely to be attributable to the combination of a physiologically improved adaptive immunity, antiviral therapy, and, potentially, also the IVIG and SCIG treatment. In patients with CMV-related thrombocytopenia or CMV-mediated secondary ITP, preceding or ongoing symptoms of viral infection and a response to antiviral therapy were noted [9]. In contrast, in the present patient, cITP persisted despite successful CMV-directed treatment, continuous CMV-negativity over 3 years; and the course of clinical and laboratory parameters did not suggest an active viral infection, probably arguing against a merely CMV-mediated thrombocytopenia held in check by IVIG/SCIG.

The cost-effectiveness of the subcutaneous IgG treatment approach was highlighted by Iuliano et al. (2014), at least for patients with repetitive, chronic need for therapeutic interventions [4]. Because SCIG can be administered at home without the need of hospitalization and because of smaller needed volumes and better tolerability, we consider this a patient-friendly, alternative, treatment option that should be evaluated in IVIG-responders who require repetitive treatment for cITP in future.

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Authors' Contribution AK and MGS designed the study. AK, DK, HL, MB, and MGS cared for the patient and collected data. AK and DK analyzed the data. MM gave relevant advice in patient care and the discussion of the data. DK drafted the manuscript and the figures.

Compliance with Ethical Standards

Ethics Statement Written informed consent was obtained from the participant's next of kin for the publication of this patient report, which was conducted according to the Declaration of Helsinki.

Conflict of Interest The authors declared that they have no conflict of interest.

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