HEMATOLOGY

Brief report

Intravenous immunoglobulins in autoimmune cytopenias: an old tool with an alternative dosing schedule

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INTRODUCTION

Intravenous immunoglobulins (IVIG) have been used in the last 40 years for the treatment of various autoimmune disorders, including neurologic and hematologic diseases[1]. Their mechanism of action is pleiotropic and not yet fully understood. IVIG saturate Fc receptors (FcR) on spleen macrophages, inhibiting phagocytosis and antibody-dependent cell-mediated cytotoxicity, in particular, in antibody-mediated autoimmune cytopenias (AIC) such as immune thrombocytopenia (ITP). Moreover, IVIG increase autoantibody clearance by blocking neonatal FcR (FcRn), a natural mechanism that protects circulating antibodies from lysosomal degradation. In addition, anti-idiotype antibodies in IVIG preparations may interact with variable regions of natural or disease-associated autoantibodies, promoting their clearance. Finally, inhibition of complement-mediated damage and modulation of inflammatory cytokine patterns have been proposed as additional mechanisms[2]. IVIG are a well-recognized tool for rapidly increasing the platelet count and reducing bleeding in ITP during the acute phase. Although response rates are over 80%, they are generally of a short duration[3]. IVIG are less efficacious in autoimmune hemolytic anemia (AIHA); a 1993 study reported a pooled response rate of around 40%[4], while more recent retrospective evidence suggests a response to IVIG in severe AIHA flare ups comparable to that obtained with steroids alone in non-severe events[5].

High-dose IVIG (i.e., 2 g/kg over 2-5 days) are generally reserved for the acute phase of AIC due to their high cost, limited availability, and possible adverse effects, including fluid overload. An alternative lower dose schedule (i.e., 0.4 g/kg every 21-28 days) is used as replacement therapy to reduce the risk of infection in hypogammaglobulinemic patients affected by primary immunodeficiencies (ID) or ID secondary to oncohematologic conditions[6]. Little is known about the impact of IVIG at an alternative replacement-like dosage on AIC outcome. Here we report on a case series of AIC patients who received IVIG at an alternative replacement-like dose.

MATERIALS AND METHODS

We analyzed medical records from 2000 to the time of writing in a cohort of AIC subjects followed at two Italian reference centers in Milan, Italy. Only patients who had received more than 2 IVIG administrations with an alternative replacement-like dosing schedule (i.e., 0.3-0.5 g/kg/day every 15-28 days) were included in the analysis. AIC subjects diagnosed with primary ID or receiving IVIG for indications other than the treatment of AIC (e.g., as replacement therapy for secondary hypogammaglobulinemia due to previous

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immunosuppressive treatments) or at higher doses (i.e., 2 g/kg over 2-5 days) were excluded. For ITP, complete response (platelet count ≥100×10^9/L and absence of bleeding) and response (platelet count ≥30×10^9/L, at least 2-fold increase in baseline count, and absence of bleeding) were defined according to the International Working Group criteria[7]. For AIHA, the definitions of complete response (normalization of hemoglobin [Hb], no evidence of hemolysis, and absence of transfusions) and response (Hb increase >2 g/dL or normalization of Hb without biochemical resolution of hemolysis, and no transfusion for the previous 7 days) were those of the International Consensus Meeting criteria[8].

All patients gave their informed consent for publication of the data according to the principles of the Declaration of Helsinki.

RESULTS

The cohort included 486 adult AIC patients (250 AIHA, 208 ITP, 28 Evans' syndrome), with a median age of 53 years (range 19-92); median follow-up was 3.5 years (range 1-22). Five consecutive patients fulfilled the inclusion criteria: 4 females and 1 male, aged 57-69 years (**Table I**). ITP was the most represented AIC; 4 out of the 5 patients had an AIC secondary to chronic infection, autoimmune or lymphoproliferative disorders. All 5 patients had a history of long-lasting, multi-treated AIC, with a median of 4 therapy lines (range 4-8). All were responsive to standard high-dose IVIG, and presented various complications, mostly infections (4/5 patients, severe in 2). Four patients received 0.4 g/kg IVIG every 15-28 days, while Patient 2 received 0.3 g/kg for 1-2 days whenever the platelet count fell below 10-15×10^9/L. Overall, all patients achieved a response to the alternative replacement-like dosing IVIG schedule. In detail, ITP Patients 1 and 4 achieved a partial response and were able to gradually stop concomitant immunosuppressive therapies (IST). ITP Patient 2 showed a transient, but repeated response to IVIG. After the introduction of cyclosporin A, the frequency of IVIG cycles was dramatically reduced in this patient. In January 2022, she was enrolled on a study with a subcutaneous FcRn inhibitor, and rapidly achieved a complete response. Patients 3 and 5 started IVIG because of AIHA reactivation and hypogammaglobulinemia secondary to previous rituximab administration. They obtained a partial response (Hb around 11 g/dL with persistently altered markers of hemolysis) which allowed a dose reduction of concomitant IST. Notably, no infectious episodes were reported in any patient during IVIG treatment.

DISCUSSION

To our knowledge, this is the first case series describing the use of IVIG at a low alternative replacement-like dosing schedule for treating AIC. The improvement in cytopenia, which was persistent in 4 out of 5 patients, suggests a long-lasting, immunomodulatory effect of IVIG at lower doses which may be attributed to the ability of IVIG to modulate B and T lymphocytes[2], the derangement of which is part of the complex pathogenesis of AIC[9,10]. In contrast, the effect of standard high-dose IVIG is of short duration, which is probably related to phagocyte inhibition via FcR blockage. Indeed, intravenous and subcutaneous immunoglobulin replacement therapy in primary ID (common variable immunodeficiency) has been shown to have a positive impact on associated autoimmune cytopenias[11]. In addition, 4 out of the 5 patients described had an associated condition characterized by immune dysregulation, and 2 subjects showed therapy-related hypogammaglobulinemia. Immunoglobulins given at an alternative replacement dose may have addressed these immunological alterations, similar to their effect in primary ID.

The small number of patients and the heterogeneous AIC included in this case series do not allow definitive conclusions to be drawn. Moreover, concomitant immunosuppressive treatments may have contributed to the response observed after IVIG. However, the timing of response following IVIG administration, along with IST discontinuation in some patients (Patients 1 and 4), suggest a positive impact of IVIG on the AIC outcome. Interestingly, Patient 2, who was responsive only to low-dose IVIG for any length of time (albeit temporarily), showed a dramatic response to an FcRn inhibitor, whose selective mechanism of action is reported to be among the various therapeutic effects of IVIG in ITP[2,12].

The impact of IVIG in AIHA Patients 3 and 5 is even more complex to establish, because the concomitant treatment with recombinant erythropoietin (rhEPO) may have had a synergistic effect. Given this, IVIG + rhEPO treatment in these two patients warranted a partial response in

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Table I - *Patients with autoimmune cytopenias treated with an alternative replacement dosing schedule of intravenous immunoglobulins*

Patient	Age (years), sex	AIC type	Associated conditions	Year of diagnosis	IgA/G/M at baseline	Previous treatments	Complications (year)	Start of replacement-like IVIG	IVIG schedule; n administrations (last)	PLT/Hb count and concomitant treatments at IVIG start	Outcome	Safety
#1	64, M	ITP	Chronic HCV infection (eradicated in 2018)	1978	Within normal ranges	Steroids, high-dose IVIG, splenectomy, rituximab, dapsone, PLT pool transfusions	Multiple osteoporotic vertebral fractures (2006), CMV reactivation (Jul 2006)	Jul 2006	0.4 g/kg every 17-21 days; 25 (Aug 2007)	PLT 10×10^9/L; prednisone 15 mg/day, dapsone 100 mg/day	Stabilization of PLT 20-30×10^9/L without transfusions; prednisone tapered to 5 mg/day and then discontinued in Mar 2010 due to achievement of CR; dapsone discontinued in Sep 2010 for persistent CR	IVIG well tolerated. No infectious complications
#2	69, F	ITP	Sjogren's syndrome	2003	Low IgM	Steroids, high-dose IVIG, splenectomy, azathioprine, danazol	Acute myocardial infarction (2010), muco-cutaneous bleeding	Apr 2009	0.3 g/kg/day for 1-2 days "on demand" for PLT<15×10^9/L; 142 (Jul 2019)	Prednisone 5 mg/day + eltrombopag 75 mg/day since 2011	Only transient PLT increase (zenith 60-120×10^9/L) lasting 1- 2 months after each IVIG administration. In May 2019 started CyA 2 mg/kg/day with reduction of IVIG need. ASA restarted. In January 2022 FcRn inhibitor started, obtaining CR	IVIG well tolerated. No infectious complications
#3	62, F	ES (wAIHA and AIN)	Sjogren's syndrome	2008	Hypogamma after rituximab	Steroids, high-dose IVIG, azathioprine, rituximab, MMF	Influenza A pneumonia (Jan 2019), PJ+Aspergillus+CMV pneumonia complicated by AKI and pulmonary embolism (Jul 2019)	Oct 2019	0.4 g/kg every 28 days; 34 (ongoing)	Hb 10 g/dL, ANC 0.3×10^9/L); prednisone 25 mg/day, MMF 1.5 g/day	Stable response (Hb 11 g/dL, LDH 3.5×ULN); added rhEPO 40,000 IU/7-10 days since Dec 2020; prednisone tapered to 5 mg/day, MMF tapered to 1 g/day	IVIG well tolerated. No infectious complications
#4	57, F	ITP	-	2004	Within normal ranges	Steroids, high-dose IVIG, splenectomy, azathioprine, eltrombopag, romiplostim, rituximab, danazol	Spontaneous cerebellar hemorrhage, menometrorrhagia, pneumonia (Oct 2019), multiple osteoporotic fractures, bilateral cataract	May 2020	0.5 g/kg every 21-28 days; 32 (ongoing)	PLT 15×10^9/L; prednisone 25 mg/day	PLT count progressively raised to 40-60×10^9/L; prednisone discontinued in June 2020 due to persistent response	IVIG well tolerated. No infectious/ hemorrhagic complications
#5	62, F	cAIHA	Marginal zone B-NHL (concomitant diagnosis)	2013	Hypogamma after rituximab	Steroids, high-dose IVIG, RBC transfusions, rituximab+CTX (for NHL, CR), rhEPO	Pneumonia (2018), PJ+CMV pneumonia (Mar 2019)	Nov 2020	0.4 g/kg every 28 days; 21 (ongoing)	Hb 8 g/dL; prednisone 37.5 mg/day, rHEPO 40,000 IU/week	Hb raised to 11-12 g/dL, LDH persistently >2×ULN; prednisone tapered and discontinued in Aug 2021 due to persistent response	IVIG well tolerated. No infectious complications

AIC: autoimmune cytopenias; IVIG: intravenous immunoglobulin; Ig: immunoglobulin; PLT: platelets; Hb: hemoglobin; ITP: immune thrombocytopenia; HCV: hepatitis C virus; CMV: cytomegalovirus; CR: complete response; CyA: cyclosporine A; ASA: acetylsalicylic acid; FcRn: neonatal Fc receptor; ES: Evans' syndrome; wAIHA: warm-type autoimmune hemolytic anemia; AIN: autoimmune neutropenia; MMF: mofetil mycophenolate; PJ: Pneumocystis jirovecii; AKI: acute kidney injury; ANC: absolute neutrophil count; LDH: lactate dehydrogenase; ULN: upper limit of normal; rhEPO: recombinant human erythropoietin; cAIHA: cold-type autoimmune hemolytic anemia; B-NHL: B-cell non-Hodgkin lymphoma; RBC: red blood cells; CTX: cyclophosphamide.

two difficult-to-treat subjects. Because of the previous life-threatening infections in both of them, and the concomitant autoimmune neutropenia in Patient 3, it was considered too risky for them to be given rituximab again; moreover, Patient 5 could not be enrolled on clinical trials with small molecules because of her history of non-Hodgkin lymphoma (even though this was in complete remission).

The overall clinical benefit was not only the improvement in cytopenia, but also an "immunosuppressant-sparing" effect; in fact, 2 patients reduced and 2 discontinued concomitant IST. Along with the well-known anti-infection effect of IVIG, this approach may also help reduce the risk of infection in an often heavily immunosuppressed population[13].

Finally, use of an alternative replacement-like dosage instead of the classic treatment schedules for ITP or other autoimmune diseases may have cost-saving benefits. On the other hand, the decision to use them for longer (e.g., Patient 2 received 142 IVIG administrations) needs to be considered from a pharmacoeconomic point of view.

CONCLUSIONS

Alternative replacement-like dosing of IVIG appears effective and safe in treating AIC. Use of IVIG could be suggested in heavily treated patients previously responsive to high-dose IVIG who have no other therapeutic options or who cannot be enrolled on clinical trials. Moreover, the reduction in immunosuppression consequent to IVIG use is desirable in this patient setting.

AUTHORSHIP CONTRIBUTIONS

All Authors followed patients, collected and analyzed the data, wrote the manuscript, and critically revised it for important intellectual content.

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The Authors declare no conflicts of interest.

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