Abstract Immune thrombocytopenic purpura (ITP) is characterized by immune-mediated platelet destruction. The modulating effect of intravenous immune globulin (IVIg) was first recognized in ITP treatment and IVIg is currently considered a second-line (first-line in selected conditions) therapy for ITP according to American Society of Hematology guidelines.

Three acute ITP patients (mean age 63.3 ± 14.4 years; M:F = 1:2) with severe thrombocytopenia and bleeding symptoms have been observed. After the failure of high doses of intravenous corticosteroids and platelet transfusions in controlling bleeding symptoms, a single infusion cycle of IVIg was used as add-on therapy (0.4 mg/kg/day for 5 days). Circulating platelet counts and presence of bleeding symptoms were estimated. An increase of circulating platelet counts associated to complete symptom resolution was promptly obtained in all three patients. The mean platelet count increased from 6x10^3/μl at baseline to 184x10^3/μl by the 12th day, but with different time dynamics, the slowest (12 days) being observed in patient 1 versus 6 and 9 days in patients 2 and 3, respectively. Although IVIg efficacy has been largely demonstrated in ITP treatment, its main mechanism of action can not be easily determined, however, it may include its capacity to revert the steroid-resistant state in these three patients.

I. INTRODUCTION

IMMUNE thrombocytopenic purpura (ITP) is characterized by immune-mediated platelet destruction with consequent reduction of platelet count (<100x10^3/μl) and variable bleeding degree [1]. The destruction of circulating platelets is mediated by autoantibodies directed against glycoprotein IIb/IIIa (GP IIb/IIIa) and GP Ib/IX, which induce Fcγ receptor (FcγR)-mediated spleen clearance. However, the pathogenic mechanism seems more complex, by also including complement and T lymphocyte activation as well as insufficient platelet production [2].

Degree and risk of bleeding are highly variable and influence clinical aspects and therapy. The clinical picture ranges, in fact, from lack of hemorrhages to frequently recurrent bleeding. Only in patients with <10x10^3/μl platelets, spontaneous bleeding and severe, potentially life-threatening, symptoms may occur. The primitive ITP could be classified, according to symptom duration, in transient (<3 months), persistent (3-12 months) or chronic (>12 months) thrombocytopenias.

The ITP management mainly consists of corticosteroid use. In unresponsive patients or when a rapid rise in platelet count is needed in order to control bleeding, intravenous immune globulin (IVIg) is actually employed [3]. The immune-modulating effect of IVIg was, in fact, first recognized in ITP treatment [4] and thereafter largely demonstrated [5-11], thus ITP is included among the Food and Drug Administration (FDA) and European Medicines Agency (EMA) IVIg indications. Splenectomy or other immunosuppressive treatments are reserved to refractory patients [3].

This study describes three corticosteroid unresponsive acute ITP cases, in whom IVIg addition seemed to revert corticosteroid-resistant state.

II. PATIENTS AND METHODS

Three patients with acute ITP (mean age 63.3 ± 14.4 years; M:F = 1:2) have been observed at the Clinical Immunology Unit, S. Andrea University Hospital, Sapienza, University of Rome. At disease presentation patients had severe thrombocytopenia (mean platelet count 6x10^3/μl) and bleeding symptoms, such as purpura, hematomas and gingival bleeding.

Three years before the acute ITP episode observed by us, the patient 1 had already received an ITP diagnosis, whereas patients 2 and 3 were at the disease onset.

After the failure of high doses intravenous corticosteroids (methylprednisolone, mean dose 1 mg/Kg) and platelet transfusions in controlling bleeding symptoms, a single infusion cycle of IVIg was used as add-on therapy (0.4 mg/kg/day for 5 days). The treatment was monitored by evaluating circulating platelet count and the presence of bleeding, according to American Society of Hematology guidelines [11]. In particular, a complete response (CR) is defined as platelet count ≥100x10^3/μl measured on 2 occasions >7 days apart and absence of bleeding.

III. RESULTS

A satisfactory response was obtained in all three patients, characterized by symptom resolution and platelet count...
increase (Fig.1). The mean platelet count increased from $6 \times 10^3/\mu l$ at baseline to $184 \times 10^3/\mu l$ at the 12th day after IVIg infusion. A different time dynamics of the platelet count increase up to the requested level to define a CR ($\geq 100 \times 10^3/\mu l$), ranging from 6 and 9 days for patients 2 and 3, to 12 days for patient 1 has been observed (Fig.2).

IV. CONCLUSIONS

IVIg is an effective treatment for ITP when other therapy had failed. IVIg efficacy has been, in fact, largely demonstrated, although its multiple mechanisms of action have not been completely elucidated [12, 13]. The possible mechanisms of action by which IVIg could increase the number of circulating platelets and control bleeding symptoms, are several and probably synergic. One of the most relevant effects is to reduce the splenic destruction of opsonized platelets through competitive inhibition of the FcγRs in spleen [14, 15], increase the inhibitory FcγRIIb expression [16, 17] or different mechanisms [18]. The saturation of the neonatal receptor (FcRn) that reduces autoantibody titer by increasing their clearance [19], as well as the complement inhibition [20] could play an important role. The activation of anti-idiotype network could also be effective in ITP. In fact, in IVIg preparation anti-idiotype antibodies, able to recognize GPIIb/IIIa [21] and potentially capable of inhibiting their action, are present. Moreover, the modulating effect of IVIg on B lymphocytes, T lymphocytes, and the recently characterized effect on dendritic cells (DC), mediated by the sialic acid [22], may participate in the beneficial IVIg effect on this disease.

Interesting is also the IVIg capacity to revert corticosteroid-resistant state through glucocorticoid receptor modulation [23], described for the first time in asthmatic patients [24]; however, also in rheumatoid arthritis, systemic lupus erythematosus, ulcerative colitis and transplant rejection, states of glucocorticoid-resistance or insensitivity have been reported [25]. In the three acute ITP cases here described, this latter mechanism could actually be hypothesized, having IVIg been used as an add-on therapy after corticosteroid failure. Such a mechanism may provide a biological interpretation to the observation that IVIg plus oral corticosteroids induces a more rapid and sustained response in ITP than high dose methylprednisolone (HDMP) infusion followed by oral prednisone, IVIg or HDMP alone [10], as reported by Godeau et al in 2002. Thus, IVIg efficacy in ITP could also be mediated by its ability to revert corticosteroid insensitivity even though it is never been hypothesized before, to the best of our knowledge, in this context.

IVIg is a precious and harmless therapeutic tool in acute ITP, able to promptly reconstitute the platelet count at levels of absolute safety. The recently identified IVIg capacity to revert the corticosteroid-resistant state through the glucocorticoid receptor modulation provides a biological plausibility to the observed synergic activity of corticosteroids and IVIg in ITP.

Figure 2. Platelet counts in three patients after Intravenous Immune Globulin administration.
REFERENCES


