

## **INTRAVENOUS IMMUNOGLOBULIN (IVIg) IN AUTOIMMUNE DISEASES – EXPANDING INDICATIONS AND INCREASING SPECIFICITY**

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### **SUMMARY**

Even though intravenous immunoglobulin (IVIg) was originally used for the correction of immunodeficiency states, in the recent years it is also used as an immunomodulating agent in several autoimmune diseases. The indications for IVIg use in autoimmunity progressively expand and might include for example systemic lupus erythematosus, autoimmune vasculitides, and antiphospholipid syndrome. However, as disease indications expand, IVIg should be used in specific situations that depend on both patients' variables (e.g. clinical manifestations) and on IVIg-related variables (e.g. concentration of specific anti-idiotypes).

### **INTRODUCTION**

IVIg are composed of immunoglobulins, mainly of the IgG isotype, produced from numerous donors. Whereas its first indication was various immunodeficiency states, it is currently an ac-

cepted treatment also for immune thrombocytopenic purpura, Kawasaki disease, Guillain-Barré syndrome, and polymyositis/dermatomyositis.

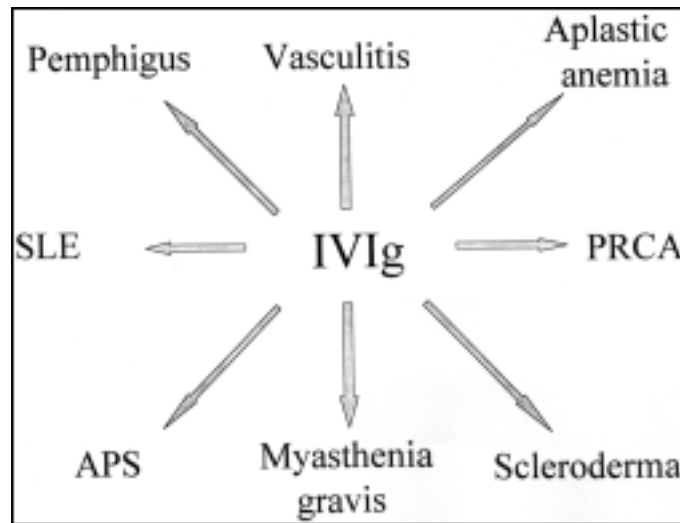
### **IVIg IN AUTOIMMUNE DISEASES – EXPANDING INDICATIONS**

In addition to the above-mentioned diseases, there are several reports of IVIg use in other autoimmune diseases. The persistent reports of clinical success in the treatment of autoimmune diseases with IVIg, combined with the understanding of the mechanisms of action of IVIg, result in expansion of the possible indications for its use as an immunomodulating agent (Figure 1).

#### **Literature review**

Herein we concentrate on the literature reports of IVIg in vasculitis and systemic lupus erythematosus (SLE).

The patients included in the case-series of IVIg in vasculitis had Wegener's granulomatosis, microscopic polyangiitis, rheumatoid vasculitis, parvovirus B19-associated polyarteritis nodosa, IgA nephropathy, and Henoch-Schönlein purpura. The largest case series of IVIg therapy in vasculitis included 26 patients: 14 with Wegener's granulomatosis, 11 with microscopic polyangiitis, and a patient with rheumatoid vasculitis (*Jayne and Lockwood, 1993*). The response rate to IVIg reported in this series was 100%, as in smaller case-series of 3-11 patients



**Figure 1:** Expanding indications for IVIg use in autoimmunity.

The indications for IVIg use in autoimmunity progressively expand. They currently include immune thrombocytopenic purpura, Kawasaki disease, polymyositis/dermatomyositis, and Guillain-Barré syndrome. IVIg may be a therapeutic option in several other autoimmune conditions.

APS = Antiphospholipid syndrome

PRCA = Pure red cell aplasia

SLE = Systemic lupus erythematosus

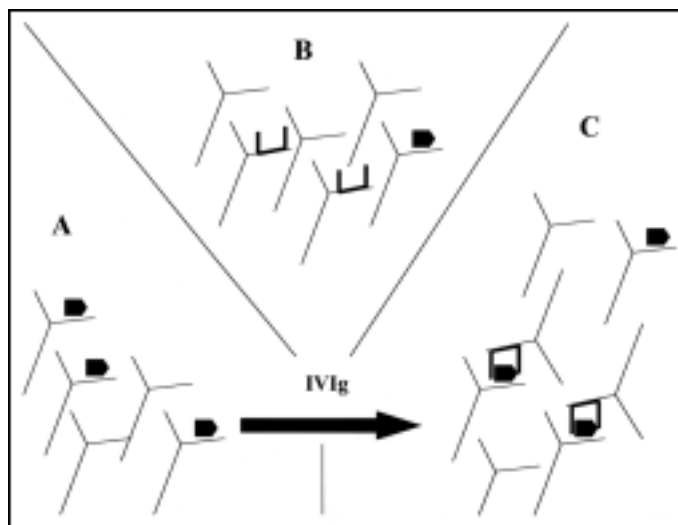
(Finkel et al., 1994; Jayne et al., 1991; Jayne and Lockwood, 1996; Rostoker et al., 1994). However, in other series of 9-15 patients with anti-neutrophil cytoplasmic antibody (ANCA)-associated systemic vasculitides, the response rate was only 40-55% (Richter et al., 1993; 1995).

The various clinical manifestations of SLE that were reported to be successfully treated by IVIg in case-reports include: autoimmune haemolytic anaemia (Marmont, 1983; Roldan et al., 1994), thrombocytopenia (Roldan et al., 1994; Ruiz-Valverde et al., 1994; Lseprit et al., 1996), pancytopenia (Akashi et al., 1990), pleural effusion (Ben-Chetrit et al., 1991), pericarditis (Hjortkjoer Petersen et al., 1990), nephritis (Akashi et al., 1990; Oliet et al., 1992; Winder et al., 1993; Welch et al., 1995), pure red cell aplasia (Ilan and Naparstek, 1993), secondary antiphospholipid syndrome with cerebral infarction (Strufelt et al.,

1990), end-stage renal disease (Becker et al., 1995), pneumonitis and encephalitis (Winder et al., 1993), polyradiculoneuropathy (Lesprit et al., 1996), acquired factor VIII inhibitors (Lafferty et al., 1997), and cardiogenic shock (Disla et al., 1993). There are also few case series of IVIg use in SLE patients (Corvetta et al., 1989; De Pita et al., 1997; Francioni et al., 1994; Lin et al., 1989; Maier et al., 1990; Schroeder et al., 1996) in which the response rate to IVIg therapy ranged from 33% (3 of 9) to 100% (5 of 5), while the 2 largest series included 12 patients each.

### Personal experience

We have recently concluded a clinical study in which we treated patients with various autoimmune diseases with IVIg. These diseases included: SLE, vasculitis, immune thrombocytopenic purpura, Guillain-Barré syndrome, polymyositis/dermatomyositis, haematologica



**Figure 2:** Anti-idiotypic activity of IVIg.

- 1st- The plasma of patients with autoimmune diseases (e.g. SLE) contains pathogenic idiotypes that are either absent in healthy subjects or are found in decreased concentrations.
- 2nd- IVIg, a plasma pool from numerous donors, contains many idiotypes and anti-idiotypes.
- 3rd- Anti-idiotypes within IVIg preparations bind pathogenic idiotypes in the patient's plasma and neutralise them, concomitant with clinical improvement. IVIg restores the normal balance between idiotypes and anti-idiotypes found in normal subjects.

autoimmune diseases (e.g. autoimmune haemolytic anaemia, pure red cell aplasia, aplastic anaemia, Evan's syndrome), and pemphigus vulgaris. We have treated 10 patients having vasculitis (2 with Wegener's granulomatosis, 2 with Churg-Strauss vasculitis, 2 with livedo vasculitis, and 4 with other systemic vasculitides) with 1-6 courses of IVIg to which 6 patients had a beneficial response (Levy et al., 1999). The clinical

manifestations of several SLE patients treated by us with IVIg are myelofibrosis (Aharon et al., 1997), psychosis (Tomer et al., 1992), a patient with cytopenia, nephritis and serositis (Aharon et al., 1994), pleural effusion (Sherer et al., 1999a), myocardial dysfunction (Sherer et al., 1999b), and neuropsychiatric lupus (Sherer et al., 1999c).

### **IVIg IN AUTOIMMUNE DISEASES – INCREASING SPECIFICITY**

The impressive clinical reports of beneficial response to IVIg in various autoimmune diseases strongly suggest that IVIg might be the treatment of choice in some of these cases. However, as the disease-indications for IVIg use would expand, it might be beneficial in these diseases in specific situations rather than in every case. Hence, future clinical research of IVIg should concen-

trate on identifying the patients sub-populations that would benefit most from IVIg, based on clinical presentation, laboratory parameters, response to other therapeutic modalities, or a combination of these. Examples for these variables include our preliminary data of IVIg in SLE that discloses that 8 of 9 patients with fever and arthritis had a beneficial response to IVIg. In addition,

the various laboratory parameters measured in the case-series of IVIg in SLE (*Corvetta et al.*, 1989; *De Pita et al.*, 1997; *Francioni et al.*, 1994; *Lin et al.*, 1989; *Maier et al.*, 1990; *Schroeder et al.*, 1996) emphasise that in general, IVIg therapy led to decreased anti-ds-DNA antibody levels, increased C3, C4 and total complement haemolytic activity, and no change in antinuclear antibody level, antibodies to RNP, Sm, and SSA/SSB. Finally, it has been claimed that patients with immune thrombocytopenic purpura who have good or excellent responses to IVIg are likely to similarly respond to splenectomy, as the spleen is a major site of macrophages with Fc receptors and platelet destruction (*Law et al.*, 1997). This exemplifies the need for larger patient-series in order to determine who are the best candidates to IVIg therapy.

Patient selection for IVIg therapy is however only one aspect of increased specificity in IVIg therapy. Apart from the patient's characteristics, the specificity can be increased by modification of IVIg preparations. Examples for the mechanisms of action of IVIg include regulation of the idiotypic network, enhanced suppressor activity, Fc receptor blockade, complement regulation, and T-cell regulation (*Ballou*, 1996). Idiotypic network modulation is involved both in the pathogenesis and the treatment of various autoimmune diseases. There is a strong evidence for the

presence of anti-idiotypes in IVIg preparations. For example, IVIg was shown to have anti-idiotypic activity both to anti-DNA and anti-cardiolipin antibodies, and in an animal model IVIg infusion succeeded in decreasing and ameliorating of experimental SLE and antiphospholipid syndrome, and resulted in a decrease of the respective antibodies to within normal levels (*Bakimer et al.*, 1993; *Krause et al.*, 1995). As emphasised in Figure 2, the anti-idiotypes within IVIg preparations bind pathogenic idiotypes in the patient's plasma (which is deficient in anti-idiotypes) and reverse the imbalance between idiotypes and anti-idiotypes which is followed by clinical improvement. Since the vast majority of the IVIg preparations contain polyclonal IgG rather than anti-idiotypes to pathogenic autoantibodies, it is natural to speculate that use of isolated anti-idiotypes will result in a superior effect than that of IVIg. Therefore, the specificity of IVIg therapy might also be increased by the formation of super-IVIg: IVIg preparation that contains increased concentration of anti-idiotypes to pathogenic idiotypes. Moreover, as different patients having the same disease can have different pathogenic idiotypes, as occurs in SLE, future immunotherapy with IVIg might be patient-specific with preparation of a cocktail of IVIg enriched with anti-idiotypes to the very same idiotypes found in every patient's plasma.

## CONCLUSION

Nowadays IVIg is an immunomodulating agent used for the treatment of a few autoimmune diseases. However, the indications for IVIg use progressively expand. Since patients respond differently to IVIg, and currently there is no reliable way to predict who would benefit from this treatment, an effort should be carried out in order to predict

who might enjoy from IVIg. The means of increased specificity of IVIg therapy should include both patient-related variables (clinical manifestations, laboratory parameters, response to other therapeutic modalities) and drug-related characteristics such as specific idiotypes' concentration within IVIg.

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