A review of high-dose intravenous immunoglobulin (hdIVIg) in the treatment of the autoimmune blistering disorders

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Summary

High-dose intravenous immunoglobulin (hdIVIg) is being used increasingly for dermatological indications. Its mode of action is via a number of proposed mechanisms and it is not associated with the many side-effects of steroids and other immunosuppressive agents. The evidence for using hdIVIg in the treatment of autoimmune bullous disorders is based on uncontrolled trials and case reports. However, there are now 62 reported patients and this review aims to make a critical assessment of the current data. This has been obtained from a Medline search of the English literature from 1966 to 2000 for pemphigus vulgaris, pemphigus foliaceus, bullous pemphigoid, pemphigoid gestationis, cicatricial pemphigoid, epidermolysis bullosa acquisita and linear IgA disease. Taken together hdIVIg was effective in 81% of the patients with blistering disease. Patients appear to be more likely to respond when hdIVIg is used as adjunctive therapy (91% response rate) than as monotherapy (56% response rate). hdIVIg may offer a safe potential therapeutic avenue for resistant cases of the autoimmune bullous disorders but should be further assessed using double-blind placebo-controlled trials.

Introduction

The use of high dose intravenous immunoglobulin (hdIVIg) in resistant autoimmune blistering disease is increasing. It offers a potentially attractive therapeutic approach in this range of antibody-mediated conditions. Intravenous immunoglobulin (IVIg) is a blood product prepared by cold ethanol fractionation from the pooled plasma of 10 000–20 000 donors per batch.[1] Each product also undergoes additional viral inactivation procedures. The dose of IVIg used as replacement therapy for patients with primary antibody deficiency is 200 mg/kg every 2 weeks, however, when used to immunomodulate the dose is much higher, most frequently 2 g/kg per month.

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Side-effects of IVIg are generally mild and self-limiting, often occurring 30–60 min after the onset of the infusion. These include flushing, myalgia, headache, fever, chills, low backache, nausea or vomiting, chest tightness, wheezing, changes in blood pressure and tachycardia. Aseptic meningitis may occur,[2] and very rarely episodes of anaphylaxis, particularly in those IgA-deficient patients with anti-IgA antibodies. Adverse effects can be minimized by following the guidelines in the physicians checklist[3] but are generally easily managed by slowing or stopping the infusion, or by hydrocortisone and/or antihistamine premedication.[4]

The immunomodulatory mechanisms of hdIVIg are mediated via the Fc portion of IgG (which interacts with Fc receptors and complement) or the antigen binding sites, the variable regions of the antibody molecule $F(ab')_2$. There are six main nonexclusive mechanisms which have been proposed:[5] (i) functional blockade of Fc receptors on splenic macrophages; (ii) inhibition of complement-mediated damage; (iii) modulation of the production of cytokines and cytokine antagonists; (iv)

Table 1 HdIVIg in the autoimmune blistering diseases.

Disease	No. of patients	Demographics	Dose and frequency	Preparation	Additional treatment	Outcome	Response time	Duration	Reference
Pemphigus vulgaris	21	35–75 years 9 male, 12 female	0.4 g/kg per day for 5 days (16) 0.3 g/kg per day (4) 0.25 g/kg per day (1)	Sandoglobulin (10) Puimmun (1) and rest N/A	Adjunctive (18) Monotherapy (3)	Improved (17/18)* No change (2) Worse (1)	Days to 3 months N/A	Weeks to 3 months with a minority having very long remissions	9–17
Pemphigus foliaceous	1	37 years male	0.4 g/kg per day for 5 days	N/A	Prednisolone 80 mg/day Azathioprine 150 mg/day	Improved	Rapid	> 5 months	11
Bullous and Nodular pemphigoid	19	62–82 years 10 male, 9 female	0.4 g/kg per day for 5 days (17) 0.1 g/kg per day for 5 days (1) 0.3 g/kg per day for 5 days (1)	Veinoglobulin (11) Sandoglobulin (4) N/A (8)	Adjunctive (7) Monotherapy (12)	Improved (4/7)† Improved (8/12)	Rapid	2 weeks to 14 months	9,11, 15,18
Cicatricial pemphigoid	12	40–77 years 6 male 6 female	2–3 g/kg over 3 days 2–4 weekly	SNBTS and N/A (11)	All adjunctive	Improved	2–6 months	1–3 months	19,20
Epidermolysis bullosa acquisita	6	16–59 years 6 male	0.4 g/kg per day for 5 days, 2–6 weekly (4) 2 g/kg per day 2 weekly 40 mg/kg per day for 5 days 3–4 weekly × 4	Polyglobin Sandoglogulin (3) N/A (2)	Adjunctive (3) Monotherapy (3)	Improved (3) Improved (2/3)	Rapid to 4 months 1 week to many months	10 days to 4 months	15, 21–24, 28
Linear IgA disease	2	45 years male 50 years female	0.4 g/kg per day for 5 days, 2 g/kg over 3 days repeated 2 weekly	Sandoglobulin N/A	Methylpred 10 mg/day Pred and antibiotics 3 Monotherapy	Improved Improved 2/3 improved	Days Complete at 2 months	4 weeks 8 weeks	26 25
Pemphigoid gestationis	1	17 years female	0.4 g/kg per day 5 days, two cycles	Sandoglobulin 20 mg/day	Prednisolone	Improved	Rapid	5 weeks	27

*Three patients in the group reported by Harman *et al.*[15] experienced transient benefit from hdIVIg with subsequent courses being less effective. †There are two treatment failures reported by Godard *et al.*[18] in the adjunctive group both of whom received doses of IVIg < 0.4 g/kg per day for 5d and were also on low dose prednisolone.

neutralization of circulating autoantibodies by anti-idiotypic antibodies in IVIg; (v) neutralization of pathogens involved in the aetiology of the autoimmune disease; (vi) blockade of Fas receptors by anti-Fas antibodies present in IVIg.[6] Other immunologically active substances present in IVIg e.g. HLA Class II, soluble CD4, and IFN-γ have also been suggested to play a role.[7]

Pemphigus vulgaris and pemphigus foliaceus

In pemphigus circulating IgG autoantibodies have been shown to be pathogenic. The target antigen in pemphigus vulgaris is desmoglein 3, a 130-kDa cadherin expressed on basal keratinocytes. In pemphigus foliaceous the target antigen is desmoglein 1.[8] Twenty-one patients with pemphigus vulgaris and one with pemphigus foliaceus have been treated with high dose IVIg: overall 18 of the 22 patients improved, three failed to respond and one progressed (Table 1). There are no controlled studies thus making interpretation extremely difficult; however, looking more closely at the reports, a number of patterns emerge in the responders.[9–17] All patients except one treated with 2 g/kg/month of IVIg divided usually into five doses of 0.4 g/kg responded rapidly and produced clinical benefits lasting weeks to months allowing a reduction in other therapies. The patient who failed to respond to 2 g/kg/month given adjunctively subsequently died of sepsis.[14] One case report described using a slightly lower dose of 0.4 g/kg per day for 3 days per month took 4 months to respond, but yielded a long-lasting effect. All responders used hdIVIg treatment as an adjunctive therapy. Of the four treatment failures three received hdIVIg alone and were deemed to have failed if no response was observed after 5 days, they were then commenced on conventional therapy of prednisolone and azathioprine resulting in a complete remission of disease in all patients.[9] The interpretation of these responses is difficult because none received an adequate therapeutic trial and indeed it is unclear whether the prior hdIVIg enhanced the effect of prednisolone and azathioprine. Reductions in

second line therapies were achieved in the majority of the responders and decreases in autoantibody titre are reported in 10 patients. Monotherapy in the three patients was unsuccessful in all. Three responders had only transient improvement with the benefit from the third and fourth courses of hdIVIg being marginal.[15] Although the reports are suggestive of benefit using adjunctive hdIVIg, a randomized controlled trial of adjunctive hdIVIg vs. conventional therapy is required in resistant pemphigus.

Bullous pemphigoid

Bullous pemphigoid (BP) is characterized by the linear deposition of IgG and C3 at the epidermal basement membrane, the targets being a 180-kDa BPAg2 and a 230-kDa BPAg1 within hemidesmosomes.[8] Nineteen patients treated with hdIVIg have now been reported, one uncontrolled study of 11 patients and eight case reports, a response to hdIVIg was noted in 12 patients (63%).[9,11,15,18] Interpretation of the data is complicated by its heterogeneity. Of the seven nonresponders, four had monotherapy and two receiving adjunctive therapy had doses of hdIVIg lower than 2 g/kg (0.1 g/kg per day and 0.3 g/kg per day for 5 days) and two had nodular type pemphigoid. There was a dramatic response in some of these patients to conventional therapy following hdIVIg. In the 12 responding patients eight were treated with monotherapy and had responses lasting on average 2 weeks with one long lasting response.[18] The remaining patients with adjunctive treatment had responses of 2–14 months duration. The time to response was generally rapid. Changes in autoantibody titres when reported did not correspond uniformly with clinical improvement.

Cicatricial pemphigoid

Cicatricial pemphigoid is an uncommon autoimmune blistering disease of skin and mucosal surfaces in which blistering is followed by scarring. Conjunctival scarring may lead to blindness. Two reports describe a total of 12 patients[19,20] all of whom responded to adjunctive hdIVIg. Ten patients with ocular involvement had all failed to respond to other extensive second line therapies[19] and antibodies to β4 integrin measured in one patient correlated with disease activity. In this study a dose of 2–3 g/kg 2 weekly was administered. The response time was always at least 2 months and often 3–4 months to reach maximal effect. The other two patients did not have ocular involvement and 2 g/kg per month was used with a gradual response over 3–4 months. The response time was substantially longer than that for BP.

Epidermolysis bullosa acquisita

Epidermolysis bullosa acquisita is a chronic severe bullous disease characterized by mechanically induced detachment of the epidermis from the dermis after minor trauma. Type VII collagen within the dermoepidermal junction appears to be the target antigen.[8] There are six case reports of the use of high dose IVIg to treat epidermolysis bullosa acquisita,[15,21–24] five of six patients improved following hdIVIg. Three patients received adjunctive therapy and all improved and were able to reduce other second line medication, while two of three given monotherapy improved. Response time varied from 1 week to many months and again autoantibody titres did not always reflect improvements in the disease. The duration of action of hdIVIg was up to 4 months and therefore repeated doses would be required to maintain the remission.

Linear IgA disease

Linear IgA disease is a blistering disease with heterogeneous clinical manifestations. There are two reports of adjunctive hdIVIg used in patients with linear IgA disease[25, 26] both of whom improved. The response time was rapid in one, and in the second was 6 weeks using a dose of 4 g/kg per month of hdIVIg. It was possible to reduce second line therapies in both patients and duration of effect was between 4 and 8 weeks. Autoantibody titres were reported in one patient and declined with therapy.

Pemphigoid gestationis

Pemphigoid gestationis is an autoimmune blistering disease specific to pregnancy which usually presents in the second or third trimester. There is a single report of pemphigoid gestationis responding to adjunctive hdIVIg[27] allowing prompt disease control and steroid withdrawal. Remission was maintained on cyclosporin as hdIVIg was effective for only 5 weeks and autoantibody titres fell after the first course only.

Discussion

Analysis of the 62 patients with autoimmune blistering disease who have been treated with hdIVIg to date is made difficult by the likely reporting bias for positive results and the fact that all are small uncontrolled series

or case reports. It is however, possible to draw some conclusions. HdIVIg is a well tolerated therapy with few side-effects, and there are no reports of exacerbation of disease whilst undergoing therapy. Side-effects can be minimized further by taking the precautions outlined in the checklist.[3] There was no clear difference in efficacy between the 3 day or 5 day treatment regimen and due both to lack of numbers and reporting failure it was not possible to determine any differences between immunoglobulin preparations. A long-lasting remission was reported only in a minority of patients. In those patients achieving a remission it was frequently possible to gradually extend the duration between cycles, reducing the overall IVIg requirement. The rate of response ranged from days to 6 months and it appears that cicatricial pemphigoid and epidermolysis bullosa acquisita may take longer to respond than the other blistering diseases. Taking all the reported cases of hdIVIg use in blistering disease together, efficacy was much greater when hdIVIg was used as adjunctive therapy with a response rate of 91% as compared with 56% when used as a monotherapy. Thus patients who have responded poorly or are suffering unacceptable side-effects from conventional therapy may make the best candidates for treatment with hdIVIg; however, a controlled study, perhaps most appropriately in pemphigus vulgaris, is needed to establish the evidence base for this promising form of therapy.

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Key points

- High dose intravenous immunoglobulin (hdIVIg) is being increasingly used to treat dermatological conditions.
- Evidence regarding hdIVIg in the blistering diseases is based on small uncontrolled series and case reports.
- HdIVIg is well tolerated and free of the side-effects of steroids and immunosuppressive agents.
- Efficacy was much greater when hdIVIg was used as adjunctive therapy with a response rate of 91% as compared with 56% when used as a monotherapy.
- Long lasting remission with hdIVIg was observed in a minority; however, dose reduction strategies were often successful.
- Cicatricial pemphigoid and epidermolysis bullosa acquisita may take longer to respond than the other blistering diseases.