

CLINICAL REPORT

Analysis of High-dose Intravenous Immunoglobulin Therapy in 16 Patients with Refractory Autoimmune Blistering Skin Disease: High Efficacy and No Serious Adverse Events

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High-dose intravenous immunoglobulin (IVIG) therapy is used in patients with severe autoimmune blistering diseases that are refractory to standard immunosuppressive therapy. To determine the efficacy and frequency of adverse events of IVIG therapy, we retrospectively analysed data for 16 patients with pemphigus vulgaris, pemphigus foliaceus, paraneoplastic pemphigus, bullous pemphigoid and paraneoplastic bullous pemphigoid. Frequency of adverse reactions and efficacy of IVIG were analysed over time with a scoring system for every 6 months of IVIG therapy. Headache (43.8%) and fatigue (43.8%) were the most common side-effects recorded; serious adverse reactions did not occur. There was good overall efficacy, as measured by clinical response rates using a clinical score, as well as indicated by a mean reduction of 75.8% in the starting steroid dose. Key words: high-dose intravenous immunoglobulin therapy; autoimmune mucocutaneous blistering disease; pemphigus vulgaris; pemphigus foliaceus; bullous pemphigoid.

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High-dose intravenous immunoglobulins (IVIG) have immunomodulatory capacity and have been shown to be effective in treating severe autoimmune disease (1–5). In dermatology, autoimmune blistering diseases and connective tissue diseases, including dermatomyositis (6) and lupus erythematoses (6, 7), are the main diseases treated with IVIG after failure of standard immunosuppressive therapy.

Autoimmune mucocutaneous blistering diseases, including pemphigus vulgaris (PV) and bullous pemphigoid (BP), are rare, potentially life-threatening diseases. Standard treatment consists of a combination regimen of corticosteroids and different immunosuppressive agents, including methotrexate, azathioprine, mycophenolate mofetil, cyclosporine and dapsone (8).

However, some patients fail to respond to standard therapy or show relapses under immunosuppressive combination regimens. For these patients, high-dose IVIG are used to control disease activity (2, 6).

Even though IVIG therapy is considered to be effective and safe in treating autoimmune blistering diseases (9), clear evidence for the therapeutic effect of IVIG besides case reports and case series is missing. The paucity of randomized controlled trials on IVIG therapy can partially be explained by the high costs of IVIG (10). In addition, autoimmune blistering diseases are rare, thus recruitment for larger study cohorts is difficult.

There are only a few published double-blind placebo-controlled randomized trials for the use of IVIG in pemphigus that show the efficacy of IVIG in PV and pemphigus foliaceus (PF). One Japanese study showed a reduction in disease severity and autoantibody titres as measured by enzyme-linked immunoassay (ELISA) in patients who received a single dose of IVIG (11). The second study showed a reduction in autoantibody titres and improvement in subjective disease scores after a single cycle of IVIG (12).

In the present study we retrospectively analysed patient data for a relatively large cohort of 16 patients with severe or refractory autoimmune blistering diseases under IVIG therapy. We investigated the efficacy and frequency of adverse events during a 24-month period and conclude that IVIG therapy is efficient and safe for refractory autoimmune blistering diseases.

MATERIALS AND METHODS

Patients

We retrospectively investigated data for 16 patients who received treatment with high-dose IVIG for severe autoimmune blistering diseases at the Department of Dermatology, University of Heidelberg, between January 2004 and July 2011. Eligibility criteria were: (i) diagnosis of PV, PF, paraneoplastic pemphigus (Pn P), BP or paraneoplastic bullous pemphigoid (PnBP); (ii) refractory or relapsing disease under immunosuppressive combination therapy with at least 2 immunosuppressive drugs; and (iii) IVIG therapy for at least 6 full cycles between January 2004 and July 2011. Refractory disease was defined as time without control of disease activity under a given immunosuppressive combination therapy. Relapsing disease was defined as appearance of ≥ 3 new lesions/month, which do not heal spontaneously within one week, or by the extension of established lesions in a patient who has achieved disease control in accordance with the consensus definitions (16). Sixteen patients were eligible according to the above-mentioned criteria (10 patients with PV, 3 with PF, 1 with Pn P, 1 with BP, and 1 with PnBP).

The following data were retrospectively retrieved from patient records for analysis: gender, height, weight, age at diagnosis,

immunosuppressive therapy before IVIG, time from diagnosis to start of IVIG therapy, duration of IVIG therapy, number of IVIG cycles and cumulative dose of IVIG. The study was approved by the local ethics committee (S-188/2010).

Intravenous immunoglobulins therapy

Prior to initiation of IVIG therapy a complete physical examination and blood tests were performed, and contraindications, including IgA deficiency, were ruled out. Patients gave written informed consent to IVIG therapy. The majority of patients received Intratect® (Biotest Pharma GmbH, Dreieich, Germany), 2 patients (patient numbers 4 and 12) received Intraglobin® (Biotest Pharma GmbH) for <4 cycles at the beginning of the therapy and then were switched to Intratect® and one patient (patient number 6) received Intratect® at the beginning of his therapy and after relapse was switched to Privigen® (CSL Behring GmbH, Hattersheim am Main, Germany). High-dose IVIG were administered at a total dose of 2 g/kg body weight intravenously (i.v.) per cycle over 2 days. Some patients received the total dose per cycle fractionated over 3 or 4 days due to concomitant diseases. Patients received IVIG every 4 weeks, and prior to discontinuation of IVIG the time between cycles was extended to 5 or 6 weeks.

Tolerability of intravenous immunoglobulins therapy

Data on the following adverse events were retrospectively retrieved from patient records for analysis: headache, fatigue, back pain, increase/decrease in blood pressure, nausea, circulatory problems (vertigo/sweating), thoracic discomfort, blurred vision, skin symptoms (petechiae), allergic reactions (urticaria, anaphylaxis). Blood pressure was monitored before and every 60 min during administration of IVIG. Increase in blood pressure was defined as systolic pressure ≥ 180 mmHg, decreased blood pressure as systolic pressure < 100 mmHg.

Efficacy of intravenous immunoglobulins therapy

The following criteria were used to measure efficacy of IVIG therapy: changes in skin symptoms, changes in autoantibody titres, and tapering of steroid dose.

The treating physician documented clinical status after physical examination prior to administration of IVIG. Skin symptoms were recorded at each infusion cycle; the following 3 possible options regarding skin status (in comparison with the previous cycle) were considered to generate the efficacy score: 1) skin symptoms ameliorated, 2) skin symptoms unchanged, and 3) skin symptoms deteriorated.

According to our standard operating procedures, laboratory blood tests including anti-basement-membrane antibodies and anti-intercellular epidermal antibodies are routinely performed in patients on IVIG therapy. Blood is drawn before administration of IVIG, thus representing the situation at the end of the previous infusion cycle. Both types of auto-antibodies are determined by standardized indirect immunofluorescence, and results are given as titres. To measure efficacy of IVIG therapy we developed a score for each 6 months during the total period of 24 months:

- 1 (very good): no skin symptoms, autoantibody titre: no change or lower titre,
- 2 (good): skin symptoms ameliorated, autoantibody titre: no change or lower titre,
- 3 (satisfactory): skin symptoms unchanged, autoantibody titre: no change or higher titre,
- 4 (unsatisfactory): skin symptoms deteriorated, autoantibody titre: no change or higher titre.

The levels of autoantibodies against desmoglein (Dsg) 3 and Dsg 1 in patient sera were measured by specific ELISA, as described in the manufacturer's instructions (MESACUP, MBL, Nagoya, Japan).

Statistics

Data are shown in absolute numbers and percentage of indicated total entity. Values are given as means and standard deviations.

RESULTS

Patient characteristics are summarized in Table I. Of the 16 patients with autoimmune blistering diseases treated with IVIG, the majority had pemphigus, including PV, PF and Pn P, whereas only two patients had BP. The mean age at time of diagnosis was 50.4 years and the mean duration from diagnosis to initiation of IVIG therapy was 40.8 months. Patients had a mean of 2.9 immunosuppressive drugs prior to initiation of IVIG therapy (Table SI; available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1471>). By the end of the 24-month observational period of the present study most of the patients were still receiving IVIG. Until this cut-off the mean total number of cycles per patient was 38.6.

Table SII (available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1471>) details the immunosuppressive therapies prior to initiation of IVIG therapy, the reasons for starting IVIG, including non-response, relapse as defined in the consensus statement for pemphigus (13) and side-effects to immunosuppressive drugs for each patient.

The adverse events during IVIG therapy are listed in Table SIII (available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1471>). Adverse events were recorded in 87.5% of patients and in 56.3% of total infusion cycles. However, adverse events were mild, with no cases of severe side-effects, such as anaphylaxis, meningitis or embolic events including deep vein thrombosis, cardiac infarction or stroke. The most common adverse events were headache and fatigue (both in 43.8% of patients), followed by back pain (in 31.3% of patients) and changes in blood pressure (in 25% of patients either increase or decrease in blood pressure). In addition, we analysed changes in the prevalence of adverse events for every 6 months during the 24-month period in a given patient under IVIG therapy. However, there was no decrease or adaptation over time concerning any of the analysed side-effects (data not shown).

Headache, which was by far the most common adverse event, was treated with non-steroidal anti-inflammatory drugs (NSAIDs). In addition, patients were advised to

Table I. Patient characteristics

Disease (total No. of patients)	Sex M/F	Age at diag- nosis, years	IVIG cycles, <i>n</i>
Pemphigus vulgaris (<i>n</i> = 10), mean \pm SD	4/6	49.9 \pm 13.6	40.9 \pm 22.7
Paraneoplastic pemphigus (<i>n</i> = 1)	1/0	72	42
Pemphigus foliaceus (<i>n</i> = 3), mean \pm SD	1/2	38.7 \pm 11.9	29.7 \pm 22.4
Bullous pemphigoid (<i>n</i> = 1)	1/0	58	32
Paraneoplastic bullous pemphigoid (<i>n</i> = 1)	1/0	61	45
Overall (<i>n</i> = 16), mean \pm SD	8/8	50.4 \pm 14.1	38.6 \pm 20.0

IVIG: intravenous immunoglobulins.

ensure a fluid intake of 2–3 l/day. Using these measures, headaches were effectively treated in most patients. In patients with more severe headaches, preventive intake of NSAIDs helped to reduce the severity of headaches.

Fatigue as the second most common side-effect usually showed onset during/after the first day of infusion and lasted for several days. However, fatigue usually did not hinder patients in their everyday life, nor did it have a negative influence on their working life. There was no specific therapeutic measure applied to treat fatigue.

Increase in blood pressure occurred in all cases in patients with pre-existing elevated blood pressure and was effectively treated with standard antihypertensive drugs (calcium-channel blocker) without the need for any further intervention. Decreased blood pressure also occurred in patients displaying low blood pressure before IVIG therapy and was resolved by letting patients walk, indicating that immobilization during infusion was the main cause.

Thoracic discomfort was reported in one patient and immediately led to further evaluation. Cardiological examination did not reveal any pathological results; therefore no therapeutic intervention was necessary.

Blurred vision occurred in 2 patients, one of whom had a history of cytomegalovirus retinitis. He had previously reported blurred vision; however, the symptoms were aggravated during IVIG infusion. After changing the administration of infusion to 3 days, the symptoms disappeared. In the other patient blurred vision occurred during several cycles but did not last longer than the IVIG infusions themselves and was not accompanied by any pathological ocular changes.

As the only skin symptoms, only one patient reported petechiae after a single infusion cycle. These symptoms were not accompanied by any changes in blood counts, resolved spontaneously within one day without further treatment, and did not occur again thereafter. There was no case of allergic reaction or anaphylaxis in any of the analysed infusion cycles.

Efficacy of IVIG therapy was measured by development of clinical symptoms, autoantibody titres and degree of tapering of corticosteroids under continuous IVIG therapy. First we analysed the development of clinical skin symptoms during the full 24 months of IVIG therapy and found that in 62.5% of patients there was amelioration of skin symptoms, in 25% of patients there was no change, and 12.5% of patients showed an initial response, followed by relapse of disease under IVIG (Table II). In addition to the clinical symptoms, we analysed the degree of tapering corticosteroids, which was possible under continuous IVIG therapy. A mean dose reduction of 75.8% in the original steroid dose at initiation of IVIG therapy was achieved over the total period of 24 months (Table II).

The autoantibodies in sera of patients with PV correlate better with disease activity than patients with BP.

Table II. Efficacy of intravenous immunoglobulins (IVIG) in the first 24 months of treatment

Disease (n)	Skin symptoms, n (%)			Dose reduction of corticosteroid (% initial dose) Mean \pm SD
	Amelioration under IVIG	No change	Relapse under IVIG	
PV (10)	5 (50)	3 (30)	2 (20)	76.0 \pm 13.7
Pn P (1)		1 (100)		85.0
PF (3)	3 (100)			74.7 \pm 27.7
BP (1)	1 (100)			62.5
Pn BP (1)	1 (100)			81.3
Overall (16)	10 (62.5)	4 (25)	2 (12.5)	75.8 \pm 15.3

Dsg 3 is the major auto-antigen in PV and Dsg 1 for PF. Fig. 1 shows the reduction in autoantibody titres in a subgroup of patients with PV and PF, where results were available before and during therapy, the first data-point represents the amount of autoantibody before initiation of IVIG and the second one under IVIG treatment, both as measured by specific ELISA.

To analyse the efficacy of IVIG therapy in more detail we developed a score, which combines clinical changes in skin symptoms as well as changes in autoantibody titres. We applied this score for each half-year period within the total time-frame of 24 months. The majority of patients had a very good score (43.8%, 75%, 61.5% and 58.3%, respectively) in all of the 4 half-year periods, indicating a constant therapeutic effect of IVIG over time (Table SIV; available from <http://www.medicaljournals.se/acta/content/?doi=10.2340/00015555-1471>). The mean efficacy score over the total time of 24 months was 1.6, thus confirming the therapeutic effect of IVIG in severe autoimmune blistering diseases.

DISCUSSION

The cohort of patients treated with IVIG consists of patients with severe autoimmune blistering diseases who were either resistant to, or experienced relapse under, conventional immunosuppressive therapy. The long duration of 40.8 months from diagnosis to initiation of IVIG reflects the difficulties in controlling disease activity and underlines disease severity in this cohort of patients. In addition, the mean number of 2.9 immunosuppressive drugs outlines the need for double or even triple combination regimens during the course of disease before initiation of IVIG therapy.

The adverse events reported in our cohort of patients during the total period of 24 months of IVIG therapy were all mild to moderate. No severe adverse events were recorded, emphasizing the accepted fact that IVIG is a relatively safe therapy (3, 14). The results of our study with only mild to moderate adverse events, such as headache and fatigue, being by far the most common side-effects, are in line with another observational study analysing side-effects of IVIG therapy (14). Most of the other adverse events appeared either only during a

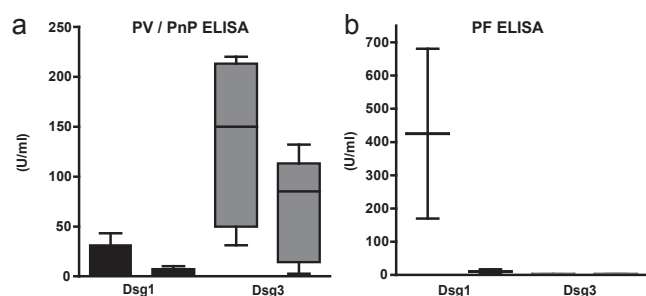


Fig. 1. Levels of desmoglein 1 (Dsg 1) and 3 (Dsg 3) autoantibodies in sera of patients with (a) pemphigus vulgaris (PV) and paraneoplastic pemphigus (PnP) and (b) pemphigus foliaceus (PF). The first data-point represents the level of autoantibody before initiation of intravenous immunoglobulins (IVIG), the second during IVIG therapy. Data are shown as means \pm standard deviations (SD) in U/ml as determined by specific enzyme-linked immunoassay (ELISA) ($n=7$ for PV; $n=2$ for PF).

single cycle or disappeared without further intervention (petechiae and thoracic discomfort both in one patient) or can be related to a concomitant disease (e.g. blurred vision in a patient with known cytomegalovirus retinitis).

Once initiated, the majority (62.5%) of patients showed amelioration under IVIG therapy and this effect was consistent during all 4 half-year periods analysed (Table SIV). Remarkably, at the same time tapering of steroids up to a mean reduction of 75.8% in starting dose was possible without relapse in most patients. However, 4 patients only showed stable disease with no change in skin symptoms. One patient had PnP with underlying refractory malignant lymphoma, which made it impossible to control disease activity. The other 3 patients had severe recalcitrant disease, which did not show improvement under therapy. Two patients experienced a relapse during IVIG therapy; in both cases the combination of IVIG with rituximab, which was reported as an effective regimen for patients with relapsing disease under IVIG therapy (15), finally achieved remission.

In summary, this study showed, for a cohort of 16 patients with refractory autoimmune blistering disease, that the administration of high-dose IVIG can clear clinical symptoms and result in constant amelioration over time, while tapering of corticosteroids is possible at the same time. This high efficacy of IVIG is not hampered by severe side-effects, as is often the case for other effective treatment regimens, such as chemotherapy.

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