IVIg Therapy of Pemphigus and Pemphigoid

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University of California Irvine
What is IVIg?

IVIg = intravenous immunoglobulin

- Contains the pooled, polyvalent, IgG antibody extracted from the plasma of over 1000 blood donors

- Contains <2.5% IgA

- Mainly used as treatment in three major categories:
  - immune deficiencies
  - autoimmune diseases
  - acute infections

- Can be used in pregnancy
How is IVIg therapy given?

- Intravenously over several hours, gradually increasing the rate of infusion up to 200 ml/h.

- Daily for 2-5 days. Usually @400 mg/kg/day up to 2 g/kg per month = one cycle.

- Cycles can be repeated in 2-4 weeks, depending on circumstances (IgG half-life is 3-4 weeks).

- Multiple cycles are usually required: from 3-5 to 30-50 and more.

- Very expensive: ~$10,000 for one cycle.
Impact of cost of IVIg on treatment

- Need to obtain clearance from insurance company before treatment can be given.
- Insurance company may not allow it, or may restrict frequency or duration of treatment.
Comparison of cost of immune globulin intravenous therapy to conventional immunosuppressive therapy in treating patients with autoimmune mucocutaneous blistering diseases

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b Department of Oral Medicine, Harvard School of Dental Medicine, United States
c Center for Blistering Diseases, Department of Medicine, New England Baptist Hospital, United States

Abstract

Autoimmune mucocutaneous blistering diseases (AMBD) are a group of potentially fatal diseases that affect the skin and mucous membranes. AMBD have different target antigens as well as variable clinical presentation, course, and prognosis. The mainstay of conventional immunosuppressive therapy (CIST) for AMBD is long-term high-dose systemic corticosteroids and immunosuppressive agents. Such therapy has proven effective in many patients; however, in some patients, the disease continues to progress with significant sequelae such as blindness, loss of voice, anal, and vaginal stenosis which causes poor quality of life. Furthermore, the CIST may have some serious side effects including opportunistic infections which may cause death.

Immune globulin intravenous (IGIV) therapy has been reportedly used in the management of patients with AMBD refractory to CIST. IGIV has shown to be more clinically beneficial than CIST by bringing about long-term clinical remission and less recurrence. The high cost of the IGIV is of concern to patients, physicians, and insurance companies.

In this report, we compare the cost of IGIV to that of CIST in treating a cohort of 15 mucous membrane pemphigoid (MMP), 10 ocular cicatricial pemphigoid (OCP), 15 bullous pemphigoid (BP), and 32 pemphigus vulgaris (PV) patients.

In each cohort of patients, CIST had significant side effects, many of which were hazardous and required prolonged and frequent hospitalizations. Some of these side effects were severe enough to require discontinuation of the treatment. We consider the total cost of CIST to be the actual cost of the drug, plus the cost of management of the side effects produced by CIST. In the same patient cohort, no significant side effects to IGIV were observed. None of the IGIV treated patients required physician visits, laboratory tests, or hospitalizations specifically related to IGIV therapy. Hence, the total cost of the IGIV therapy is the actual cost of the IGIV only. The mean total cost of treatment of IGIV therapy is statistically significantly less than that of CIST during the entire course of the disease and on an annual basis.

In conclusion, IGIV therapy is a safe, clinically beneficial, and a cost effective alternative treatment in patients with AMBD, non-responsive to CIST.
Comparison of cost of conventional immunosuppressive therapy (CIST) with IVIg therapy in patients with mucous membrane pemphigoid (MMP), ocular cicatricial pemphigoid (OCP), bullous pemphigoid (BP) and pemphigus vulgaris (PV).

<table>
<thead>
<tr>
<th></th>
<th>CIST</th>
<th>IGIV</th>
<th>Statistical analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total cost of care</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMP</td>
<td>$301,122</td>
<td>$134,400</td>
<td>$p &lt; 0.0005</td>
</tr>
<tr>
<td>BP</td>
<td>$184,708</td>
<td>$67,520</td>
<td>$p = 0.001</td>
</tr>
<tr>
<td>PV</td>
<td>$337,904</td>
<td>$176,100</td>
<td>$p = 0.005</td>
</tr>
<tr>
<td>OCP</td>
<td>$1,107,487</td>
<td>$194,080</td>
<td>$p = 0.005</td>
</tr>
<tr>
<td><strong>Annual cost of care</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMP</td>
<td>$168,518</td>
<td>$65,190</td>
<td>$p &lt; 0.05</td>
</tr>
<tr>
<td>BP</td>
<td>$78,229</td>
<td>$33,173</td>
<td>$p = 0.01</td>
</tr>
<tr>
<td>PV</td>
<td>$123,133</td>
<td>$76,249</td>
<td>$p = 0.01</td>
</tr>
<tr>
<td>OCP</td>
<td>$143,276</td>
<td>$84,923</td>
<td>$p = 0.014</td>
</tr>
</tbody>
</table>
Where is IVIg administered?

**In-hospital** – if extensive disease, very high steroid doses, or other serious medical problems.

**Infusion center** – an M.D. supervised setting.

**Home** – more convenient but needs medical supervision.
• Administer IVIg product at 400-500 mg/kg/day on 4-5 consecutive days up to the total dose of 2 g/kg/month times ? number of months.

• Premedicate patient with 25 mg Benadryl (diphenhydramine) and 500 mg Tylenol (acetaminophen) 15-30 min prior to starting the infusion.

• Place peripheral i.v. and maintain with 0.9% sodium chloride.

• Infusion Rate: start at 0.5 ml/kg/h, then increase by 15 ml/h every 15 min until target rate of 150-200 ml/h, as tolerated. Maximum rate is 200 ml/h.

• Observe vital signs prior to infusion. Blood pressure and pulse every 30 min until stable infusion rate, then every hour.

• Watch for signs of fluid overload, cardiovascular symptoms, allergic reactions, skin rash, fever, and moderate to severe headache.

• For adverse events, stop the infusion. Can restart the infusion at the same or lower rate if the symptoms subside.
Immediate side effects

- Headache, flushing, chills, fever, nausea, vomiting, dizziness, sweating, hypertension, feelings of tightness in the chest, back pain, and muscle aches. Related to infusion rate.

- Aseptic meningitis. More common with history of migraine.

- Thrombosis/stroke. Related to infusion rate + dose. More common if history of cardiac disease, stroke, myocardial infarction, thrombosis, old age, hypercoagulation, limited mobility.

- Anaphylaxis. If IgA deficient.

**Delayed side effects**

- Anemia—due to anti-AB antibodies (Type 0 = universal receiver)
- Cardiac insufficiency—due to fluid overload
- Renal insufficiency—due to immune complexes, sucrose
- Viral infection—less with detergent treatment or ultrafiltration
**Delayed side effects**

- **Anemia**—due to anti-ABO antibodies (Type 0 = universal receiver)
- **Cardiac insufficiency**—due to fluid overload
- **Renal insufficiency**—due to immune complexes, sucrose
- **Viral infection**—less with detergent treatment or ultrafiltration

In contrast to conventional immunosuppressive therapy:  
- no immune suppression  
- no ovarian/testicular suppression  
- no carcinogenicity
<table>
<thead>
<tr>
<th>VARIABLE</th>
<th>IMPACT</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgA content</td>
<td>Anaphylaxis, if patient is IgA deficient</td>
</tr>
<tr>
<td>Concentration</td>
<td>Fluid overload if dilute</td>
</tr>
<tr>
<td></td>
<td>Osmotic overload if concentrated</td>
</tr>
<tr>
<td>Sugar content</td>
<td>Sucrose – nephropathy</td>
</tr>
<tr>
<td>Administration rate</td>
<td>Slow – fewer side effects</td>
</tr>
<tr>
<td>Frequency</td>
<td>Fewer side effects if given over 4-5 d</td>
</tr>
</tbody>
</table>
# Commercially available IVIg products

<table>
<thead>
<tr>
<th>Consideration</th>
<th>Gammagard Liquid 10% &amp; Gammaked</th>
<th>Gamunex-C 10%</th>
<th>Privigen 10%</th>
<th>Flebogamma 10% DIF</th>
<th>Octagam 5%</th>
<th>Carimune NF</th>
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</thead>
<tbody>
<tr>
<td><strong>Manufacturer</strong></td>
<td>Baxter Healthcare</td>
<td>Grifols (Talecris)</td>
<td>CSL Behring</td>
<td>Grifols</td>
<td>Octapharma USA</td>
<td>CSL Behring</td>
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<tr>
<td><strong>Concentration</strong></td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>10%</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>liquid</td>
<td>liquid</td>
<td>liquid</td>
<td>liquid</td>
<td>liquid</td>
<td>lyophilized</td>
</tr>
<tr>
<td><strong>Sodium Content</strong></td>
<td>trace</td>
<td>not detectable</td>
<td>trace</td>
<td>trace</td>
<td>not detectable</td>
<td>0.9%</td>
</tr>
<tr>
<td><strong>Stabilizer</strong></td>
<td>glycine</td>
<td>glycine</td>
<td>proline</td>
<td>sorbitol</td>
<td>maltose</td>
<td>sucrose</td>
</tr>
<tr>
<td><strong>Osmolality/Osmolarity</strong></td>
<td>240–300 mOsm/kg</td>
<td>258 mOsm/kg</td>
<td>240–440 mOsm/kg</td>
<td>240–370 mOsm/kg</td>
<td>310–380 mOsm/kg</td>
<td>690 mOsm/kg</td>
</tr>
<tr>
<td><strong>IgA Content</strong></td>
<td>37 mcg/mL</td>
<td>46 mcg/mL</td>
<td>&lt;25 mcg/mL</td>
<td>&lt;6 mcg/mL</td>
<td>&lt;200 mcg/mL</td>
<td>&gt;720 mcg/mL</td>
</tr>
<tr>
<td><strong>pH</strong></td>
<td>4.6–5.1</td>
<td>4–4.5</td>
<td>4.6–5</td>
<td>5.5</td>
<td>5.1–6</td>
<td>6.4–6.8</td>
</tr>
<tr>
<td><strong>Supply Size (Grams)</strong></td>
<td>30, 20, 10, 5, 2.5, 1</td>
<td>20, 10, 5, 2.5, 1</td>
<td>20, 10, 5</td>
<td>20, 10, 5</td>
<td>25, 10, 5, 2.5, 1</td>
<td>12, 6, 3</td>
</tr>
<tr>
<td><strong>Shelf Life</strong></td>
<td>24 months at room temp; 36 months refrigerated</td>
<td>6 months at room temp</td>
<td>36 months at room temp</td>
<td>24 months at room temp</td>
<td>24 months at room temp</td>
<td>24 months at room temp</td>
</tr>
</tbody>
</table>
Not All Intravenous Immunoglobulin Preparations are Equally Well Tolerated

Laurence FELDMeyer¹, Christian BENDEN², Sarah R. HAILE³, Annette BOEHLER², Rudolf SPEICH⁵, Lars E. FRENCH¹ and Günther F.L. HOFBAUER¹
¹Department of Dermatology, ²Division of Pulmonary Medicine, and ³Biostatistics Unit, Institute for Social and Preventive Medicine, University Hospital Zürich, Switzerland

Numbers of patients and adverse events

<table>
<thead>
<tr>
<th>IVIG preparation</th>
<th>Patients treated, $n$</th>
<th>Adverse events, $n$ (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Redimune NF Liquid®</td>
<td>28</td>
<td>14 (100)</td>
</tr>
<tr>
<td>Octagam®</td>
<td>26</td>
<td>0 (0)</td>
</tr>
</tbody>
</table>
IVIg in Autoimmune Blistering Diseases
A randomized double-blind trial of intravenous immunoglobulin for pemphigus

Masayuki Amagai, MD,a Shigaku Ikeda, MD,b Hiroshi Shimizu, MD,f Hajime Izuka, MD,a Katumi Hanada, MD,f Setsuya Aiba, MD, Fumio Kameko, MD, Seiichi Izaki, MD, Kunihiko Tamaki, MD, Zenro Ikezawa, MD,b Masahiro Takigawa, MD, Mariko Seishima, MD, Toshihiro Tamaka, MD, Yoshiki Miyachi, MD,b Ichiro Katayama, MD,f Yuji Horiguchi, MD,f Sachiko Miyagawa, MD,f Fukumi Furukawa, MD,f Keiji Iwatsuki, MD,f Michihiro Hide, MD, Yoshiki Tokura, MD,f Masutaka Furue, MD, Takashi Hashimoto, MD, Hiroshi Ito, MD, Yukihito Fujimura, MD, Takeji Nishikawa, MD, Hideoki Ogawa, MD,f and Koji Hashimoto, MD,f for the Pemphigus Study Group

Tokyo, Sapporo, Asahikawa, Hiroshim, Sendai, Fukushima, Kawagoe, Yokohama, Hamamatsu, Ogaki, Osaka, Osaka, Kashiwara, Waikam, Okayama, Hiroshima, Kitakyushu, Fukuoka, Kurume, Kumamoto, Yufu, Gifu, and Toon, Japan

Background: Pemphigus is a rare life-threatening intractable autoimmune blistering disease caused by IgG autoantibodies to desmogleins. It has been difficult to conduct a double-blind clinical study for pemphigus partly because, in a placebo group, appropriate treatment often must be provided when the disease flares.

Objective: A multicenter, randomized, placebo-controlled, double-blind trial was conducted to investigate the therapeutic effect of a single cycle of high-dose intravenous immunoglobulin (400, 200, or 0 mg/kg/d) administered over 5 consecutive days in patients relatively resistant to systemic steroids.

Methods: We evaluated efficacy with time to escape from the protocol as a novel primary end point, and pemphigus activity score, antidesmoglein enzyme-linked immunosorbent assay scores, and safety as secondary end points.

Results: We enrolled 61 patients with pemphigus vulgaris or pemphigus foliaceus who did not respond to prednisolone (≥20 mg/d). Time to escape from the protocol was significantly prolonged in the 400-mg group compared with the placebo group (P < .001), and a dose-response relationship among the 3 treatment groups was observed (P < .001). Disease activity and enzyme-linked immunosorbent assay scores were significantly lower in the 400-mg group than in the other groups (P < .05 on day 43, P < .01 on day 85). There was no significant difference in the safety end point among the 3 treatment groups.

Limitation: Prednisolone at 20 mg/d or more may not be high enough to define steroid resistance.

Conclusion: Intravenous immunoglobulin (400 mg/kg/d for 5 d) in a single cycle is an effective and safe treatment for patients with pemphigus who are relatively resistant to systemic steroids. Time to escape from the protocol is a useful indicator for evaluation in randomized, placebo-controlled, double-blind studies of rare and serious diseases. (J Am Acad Dermatol 2009;60:595-603.)
Pemphigoids:

Intravenous Immunoglobulin Therapy in Patients with Multiple Mucosal Involvement in Mucous Membrane Pemphigoid

Naveed Sami,*† Kallash C. Bhol,† and A. Razzaque Ahmed∗†‡

*Center for Blistering Diseases, New England Baptist Hospital; †Department of Oral Medicine, Harvard School of Dental Medicine; and ‡Department of Dermatology, Harvard Medical School, Boston, Massachusetts 02115


Treatment of oral pemphigoid with intravenous immunoglobulin as monotherapy. Long-term follow-up: influence of treatment on antibody titres to human α6 integrin

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A randomized double-blind trial of intravenous immunoglobulin for bullous pemphigoid

Masayuki Amagai,1,2* Shinagawa Ikeda,2,3 Takashi Hashimoto,2 Masato Mizuashi,4 Akihiro Fujisawa,5 Hironobu Inoue,5 Yasushi Matsuzaki,6 Mikio Ohtsuka,6 Hiroshi Fujinami,6 Junichi Furuta,7 Osamu Tago,8 Jun Yamagami,9 Akiko Tanikawa,9 Hidashi Uehara,10 Akimichi Morita,10 Gen Nakanishi,10 Mamori Tani,1,2,10 Yumi Aoyama,1,2,10 Eichi Makino,1,2 Masahiko Muto,1,2 Motomu Manabe,2 Takayuki Konno1,2 Satoru Murata1, Koichi Izaki1,2,10 Hideaki Watanabe1,2 Yukie Yamaguchi1,2 Setsuko Matsukura,11 Mariko Seishima,12 Koji Habe,12 Yuichi Yoshida,12 Saka Kaneko13,14 Hajime Shindo13,14 Kimiko Nakajima13,14 Takuro Kanekura13,14 Kenzo Tahashi13,14,15 Yasuo Kitaizumi13,14, Koiti Hashimoto,13 for the Bullous Pemphigoid Study Group

Objective: A multicenter, randomized, placebo-controlled, double-blind trial was conducted to investigate the therapeutic effect of high-dose intravenous immunoglobulin (IVIG; 400 mg/kg/day for 5 days) in BP patients who showed no symptomatic improvement with prednisolone (≥0.4 mg/kg/day) administered.

Methods: We evaluated the efficacy using the disease activity score on day15 (DA15) as a primary endpoint, and changes in the DA5 over time, the anti-BP180 antibody titer, and safety for a period of 57 days as secondary endpoints.

Results: We enrolled 56 patients in this study. The DA15 was 12.5 points lower in the IVIG group than in the placebo group (p = 0.089). The mean DA5 of the IVIG group was constantly lower than that of the placebo group throughout the course of observation, and a post hoc analysis of covariance revealed a significant difference (p = 0.041). Furthermore, when analyzed only in severe cases (DA5 ≥ 40), the DA5 differed significantly (p = 0.046). The anti-BP180 antibody titers showed no difference between the two groups.

Conclusion: IVIG provides a beneficial therapeutic outcome for patients with BP who are resistant to steroid therapy.
Epidermolysis bullosa acquisita: High-dose intravenous immunoglobulins for the treatment of autoimmune mucocutaneous blistering diseases: Evaluation of its use in 19 cases

Sonia Segura, MD, Pilar Iranzo, MD, Isabel Martinez-de Pablo, MD, Jose Manuel Mascaro, Jr, MD, Merce Alsina, MD, Josep Herrero, MD, and Carmen Herrero, MD Barcelona, Spain

Epidermolysis bullosa acquisita: treatment with intravenous immunoglobulins

K. Gougliotou,† D. Exadaktylou,† K. Aroni,† E. Rallis,† E. Nicolaidou,† H. Paraskevakou,† A. D Katsambas* Departments of †Dermatology and ‡Pathology, University of Athens, A. Sygros Hospital, Athens, Greece. *Corresponding author, S. I. Drogoumi Str. Kerastris 161 21, Athens, Greece, tel. (0030 21) 7210 839, fax: +7211 122; E-mail: katsambas@compulink.gr

Treatment of epidermolysis bullosa acquisita with intravenous immunoglobulin in patients non-responsive to conventional therapy: clinical outcome and post-treatment long-term follow-up

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*Correspondence: A. Razzaque Ahmed. E-mail: aramanuscript@msn.com

Abstract

**Background** Epidermolysis bullosa acquisita (EBA) is a chronic subepidermal blistering disease that is caused by antibodies binding to type VII collagen within anchoring fibrils. It is rare disease with an incidence of 0.25 cases per 1 000 000 population.

**Objective** The objective of this study is to report the treatment outcomes with intravenous immunoglobulin (IVig) therapy in 10 patients with severe and widespread EBA non-responsive to conventional therapy.

**Methods** Patients were treated according to a protocol published in a Consensus Statement to treat autoimmune mucocutaneous blistering diseases, including EBA with IVig. A dose of 2 g/kg/cycle was used.

**Results** Ten patients: four males and six females, all were North American Caucasian. The age at onset varied from 37 to 75 years (mean 57.4). A satisfactory clinical response was observed in all 10 patients. The patients received 16–31 cycles (mean 23.1) of IVig over a period of 30–52 months (mean 38.8). Once IVig was initiated, earlier drugs (prednisone, dapson e others) were gradually withdrawn over a 5–9 month period (mean 7.2). Thereafter, IVig was used as monotherapy. No serious side-effects were observed. The follow-up period since discontinuation of IVig varied from 29 to 123 months (mean 53.9). During this follow-up period, recurrence of disease was not observed.

**Conclusion** The data suggest that IVig can produce a long-term sustained clinical remission in patients with EBA. In the patients, of this study concomitant therapy could be discontinued and IVig was used as monotherapy.
Analysis of High-dose Intravenous Immunoglobulin Therapy in 16 Patients with Refractory Autoimmune Blistering Skin Disease: High Efficacy and No Serious Adverse Events

Vera SEIDLING, Jochen H. O. HOFFMANN, Alexander H. ENK and Eva N. HADASCHIK
Department of Dermatology, University Hospital Heidelberg, Heidelberg, Germany

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.

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

Acta Derm Venereol 2013; 93: 346–349,
How does IVIg work in autoimmune skin diseases?
IVIG POOL

Anti-idiotypic effect of IVIG

Increased IL-10 production

Anti-inflammatory effects of IVIG sialylation

FcyRIIb upregulation

FcRN-mediated recycling of IgG

Nonspecific uptake

Recycling of bound IgG

Binding of FcRN to IgG at pH 6.0

Lysosomal degradation of unbound antibodies

Anti-apoptotic effect of FAS/FASL blockade

Blocking basement membrane zone autoantibodies

Blocking intercellular antibodies

Epidermis

BCR

Anergy

B Cell

FcyRIIb
Can IVIg be made to work better?
Effect IVIg on levels of pemphigus (intercellular; IC) and total IgG antibodies

![Graph showing the effect of IVIg on levels of pemphigus antibodies and total IgG over time.](image-url)

Bystryn, 2004
Influence of intravenous immunoglobulin therapy on serum levels of anti-β4 antibodies in ocular cicatricial pemphigoid

A correlation with disease activity

A preliminary study

Erik Leiko¹, Kailash Bhol¹, C. Stephen Foster¹ and A. Razzaque Ahmed¹

Figure 3. Correlation between disease activity and serum levels of antibodies to β4-integrin in patients with OCP during a consecutive 12 month period. Left hand Y axis demonstrates mean serum titers of anti-β4-integrin antibodies (solid line). Right hand Y axis demonstrates mean disease activity (dash line). “0” represents baseline levels prior to initiation of IVIg therapy. A decline in disease activity parallels a decline in titers of anti-β4 antibodies.
How does IVIg selectively lower autoantibody levels?

Normal degradation and removal from the body of all kinds of IgG antibodies after IVIg infusion results in a **selective decrease of relative titer of pathogenic antibodies**, because:

- The level of normal antibodies is maintained by those present in the IVIg preparation.
Feedback mechanism maintains individual antibodies at a constant serum level.
Therapeutic implications of mechanism of IVIg action

- Feedback mechanism maintains individual antibodies at a constant serum level.
- Rapid decrease in autoantibodies will trigger new autoantibody synthesis and a “rebound” in their serum level.
**Therapeutic implications of mechanism of IVIg action**

- Feedback mechanism maintains individual antibodies at a constant serum level.

- Rapid decrease in autoantibodies will trigger new autoantibody synthesis and a “rebound” in their serum level.

- “Rebound” can be prevented by cytotoxic drugs.
Can IVlg effectiveness be improved by co-administration of a cytotoxic drug?
PREVENTION OF ANTIBODY REBOUND WITH CYCLOPHOSPHAMIDE

% change in antibody levels

☆ with cyclo
➕ no cyclo

Bystryn, 2004
Effect of cytotoxic drug on IVlg induced decrease in IC Ab

IC IgG level (% change from baseline)

Baseline 1 2

Weeks from Initiation of IVlg

- Cytoxan (n=12)
- Imuran (n=3)
- Inadequate Rx (n=2)

Bystryn, 2004
### Effect of IVIg vs. IVIg plus cyclophosphamide in pemphigus.

<table>
<thead>
<tr>
<th></th>
<th># pts</th>
<th>Anti-Dsg 1</th>
<th></th>
<th>Anti-Dsg 3</th>
<th>Prednisone dose (%)</th>
<th>Disease severity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>IgG1 (%)</td>
<td>IgG4 (%)</td>
<td>IgG1 (%)</td>
<td>IgG4 (%)</td>
<td></td>
</tr>
<tr>
<td>IVIg</td>
<td>4</td>
<td>−34</td>
<td>−33</td>
<td>−27</td>
<td>−66</td>
<td>−7</td>
</tr>
<tr>
<td>IVIg + cyclophosphamide</td>
<td>3</td>
<td>−71</td>
<td>−72</td>
<td>−55</td>
<td>−47</td>
<td>−21</td>
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Patients unresponsive to conventional therapy were randomized to receive IVIg 500 mg/kg/day for 4 days every 2 weeks, for a total of four cycles with or without oral cyclophosphamide 50 mg three times a day.
Comparison of effects of IVIg administered with and without an immunosuppressive drug on serum levels of pemphigoid IgG (A) and IgG4 (B) autoantibody levels.
Treatment of Pemphigus Vulgaris with Rituximab and Intravenous Immune Globulin


ABSTRACT

BACKGROUND
Pemphigus vulgaris is a potentially fatal autoimmune mucocutaneous blistering disease. Conventional therapy consists of high-dose corticosteroids, immunosuppressive agents, and intravenous immune globulin.

METHODS
We studied patients with refractory pemphigus vulgaris involving 30% or more of their body-surface area, three or more mucosal sites, or both who had inadequate responses to conventional therapy and intravenous immune globulin. We treated the patients with two cycles of rituximab (375 mg per square meter of body-surface area) once weekly for 3 weeks and intravenous immune globulin (2 g per kilogram of body weight) in the fourth week. This induction therapy was followed by a monthly infusion of rituximab and intravenous immune globulin for 4 consecutive months. Titers of serum antibodies against keratinocytes and numbers of peripheral-blood B cells were monitored.

RESULTS
Of 11 patients, 9 had rapid resolution of lesions and a clinical remission lasting 22 to 37 months (mean, 31.1). All immunosuppressive therapy, including prednisone, could be discontinued before ending rituximab treatment in all patients. Two patients were treated with rituximab only during recurrences and had sustained remissions. Titers of IgG4 antikeratinocyte antibodies correlated with disease activity. Peripheral-blood B cells became undetectable shortly after initiating rituximab therapy but subsequently returned to normal values. Side effects that have been associated with rituximab were not observed, nor were infections.

CONCLUSIONS
The combination of rituximab and intravenous immune globulin is effective in patients with refractory pemphigus vulgaris.
Long-Term Remissions of Severe Pemphigus After Rituximab Therapy Are Associated with Prolonged Failure of Desmoglein B Cell Response

Natacha Colliou, Damien Picard, Frédérique Caillot, Sébastien Calbo, Stéphanie Le Corre, Annick Lim, Brigitte Lemercier, Brigitte Le Mauff, Maud Maho-Vaillant, Serge Jacquot, Christophe Bedane, Philippe Bernard, Frédéric Caux, Catherine Prost, Emmanuel Delaporte, Marie-Sylvie Doutrc, Brigitte Dreno, Nathalie Franck, Saskia Ingen-Housz-Oro, Olivier Chosidow, Christine Pauwels, Catherine Picard, Jean-Claude Roujeau, Michèle Sigal, Emmanuelle Tancrede-Bohin, Isabelle Templier, Rüdiger Eming, Michael Hertl, Michel D'Incarn, Pascal Joly, Philippe Musette


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PV: Pemphigus vulgaris, PNP: Pemphigus pemphigoides, PF: Pemphigus foliaceus
CROT: Complete remission off treatment, CRMT: Complete remission on minimal therapy, IR: Incomplete remission
Gender: M: male and F: female
CRD: Cardiovascular disease
* Dose of prednisone (mg/day) at the time of death
+ this patient was considered in IR despite corticosteroids withdrawal since he still received immunosuppressant (mycophenolate mofetil)
+ relapses were treated with topical corticosteroids alone

Disease course after rituximab treatment

Months

RTX: Rituximab infusion  +: Relapse  ×: Corticosteroids withdrawal
Summary

• IVIg is a safe and effective drug to induce and maintain a prolonged clinical remission

• it can rapidly and effectively control mucocutaneous autoimmune diseases unresponsive to conventional therapy

• it has a corticosteroid-sparing effect

• its early use is of significant benefit in patients who may experience life-threatening complications from corticosteroids and immunosuppression

• IVIg works better if given together with a cytotoxic drug like Rituxan, Cytoxan, CellCept or Imuran