Intravenous Immunoglobulin (IVIg) in Dermatology

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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

Skin diseases treated with IVIg

Autoimmune connective tissue disorders
- *Cutaneous lupus erythematosus
- *Dermatomyositis
- Mixed connective tissue disease
- Nephrogenic fibrosing dermopathy
- Scleroderma (Systemic sclerosis)

Autoimmune mucocutaneous blistering diseases
- *Bullous pemphigoid
- *Epidermolysis bullosa acquisita
- Lichen planus pemphigoides
- Linear IgA bullous disease
- *Mucous membrane (Cicatricial) pemphigoid
- Paraneoplastic autoimmune multiorgan syndrome (Paraneoplastic pemphigus)
- Pemphigoid (Herpes) gestationis
- *Pemphigus foliaceus
- *Pemphigus vulgaris

Disclosure:
I do not have any relevant relationships with industry.
### Vascular disorders
- Anti-neutrophil cytoplasmic autoantibody (ANCA) positive vasculitides:
  - Microscopic polyangiitis
  - Wegener's granulomatosis
- Behçet's disease
- Churg–Strauss syndrome
- Cutaneous polyarteritis nodosa
- Degos' disease
- Leukocytoclastic vasculitis
- Livedoid vasculopathy

### Drug-induced disorders
- Anticonvulsant hypersensitivity syndrome
- Erythema multiforme
- Kaposi sarcoma due to immunosuppression
- Methotrexate-induced acral erythema
- Stevens–Johnson syndrome
- Toxic epidermal necrolysis (Lyell's syndrome)

### Skin infectious and infection-related diseases
- Lyme disease
- Measles
- Necrotizing fasciitis
- Rubella
- Staphylococcal scalded skin syndrome (SSSS; Ritter's disease)
- Streptococcal toxic shock syndrome (STSS)
- Varicella

### Miscellaneous dermatoses
- Alopecia universalis
- Atopic dermatitis
- Calcinosi cutis
- Chronic urticaria:
  - Angioedema with hypereosinophilia
  - Autoimmune urticaria
  - Chronic idiopathic urticaria
  - Delayed pressure urticaria
  - Solar urticaria
- Graft-versus-host disease
- Hyper-IgE syndrome
- Kawasaki's syndrome
- Necrobiosis lipoidica diabeticae
- POEMS syndrome: polyneuropathy, organomegaly, endocrinopathy, monoclonal gammopathy, and skin changes
- Polymorphous light eruption
- Pretibial myxedema
- Psoriasis
- Pyoderma gangrenosum
- Scleromyxedema
- Wiskott–Aldrich syndrome

### 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.

### Impact of cost of IVIg on treatment

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>IVIg</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>
</tbody>
</table>
| OCP      | $143,276 | $84,923  | p = 0.014           

**Where is IVIg administered?**

- **In-hospital** – if extensive disease, very high steroid doses, or other serious medical problems.
- **Infusion center** – best setting.
- **Home** – more convenient but needs medical supervision.
Generic IVIg infusion protocol

- 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 6 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.
- If 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-ABO antibodies
- 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
What affects the safety of IVIg therapy?

<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 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>

IVIg in Autoimmune Connective Tissue Diseases

Not All Intravenous Immunoglobulin Preparations are Equally Well Tolerated

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>Redimmune 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>

Dermatomyositis:

Effects of intravenous immunoglobulin therapy in Japanese patients with polymyositis and dermatomyositis resistant to corticosteroids: a randomized double-blind placebo-controlled trial

High-Dose Intravenous Immunoglobulin Exerts Its Beneficial Effect in Patients with Dermatomyositis by Blocking Endomysial Deposition of Activated Complement Fragments

Transparency Note: All images are from the document itself.
A controlled trial of high-dose intravenous immune globulin infusions as treatment for dermatomyositis

MAURICE C. DALLAS, M.D., ISRAEL ILIA, M.D., JAMES M. DAMROSE, Ph.D., SINNER A. SOLOMAN, M.D., DANIEL D. STEIN, M.D., CARLOS OTERO, M.D., STEVEN T. DEMPSEY, D.O., and JOHN MCCOY, R.N.

Abstract: Dermatomyositis is a clinically distinct myopathy characterized by rash and a complement-mediated microangiopathy that results in the destruction of muscle fibers. In some patients the condition is associated with antibodies against the target of therapy and causes severe physical disabilities.

Methods: We conducted a double-blind, placebo-controlled study of 15 patients (age 18 to 55 years) with biopsy-proved, treatment-resistant dermatomyositis. The patients continued to receive prednisone (mean daily dose: 25 mg) and were randomly assigned to receive one infusion of immune globulin (2 g per kilogram of body weight) or placebo per month for three months, with the option of crossing over to the alternative therapy for three more months. Clinical response was judged by an evaluation of changes in the rash, changes in muscle symptoms, and improvements in muscle strength.

Results: The eight patients assigned to immune globulin had a significant improvement in scores of muscle strength (P = 0.005), whereas the seven patients assigned to placebo did not. With crossovers, a total of 15 patients received immune globulin. Of these, nine with severe disabilities had a major improvement to nearly normal function. Their mean muscle-strength scores increased from 35 to 84.7, and their neuromuscular symptoms and signs disappeared in four patients. In one patient, the rash improved, and he had no change in his condition. Of 11 clinically healed patients, none had major improvement, 5 had mild improvement, 5 had no change in their condition, and 1 had worsening of their condition. Repeated biopsies in five patients of muscles whose strength improved to nearly normal showed an increase in muscle fiber diameter (P < 0.05), an increase in the number and a decrease in the diameter of capillaries (P < 0.01), no evidence of complement deposits on capillaries, and a reduction in the expression of intercellular adhesion molecule-1 and major histocompatibility complex class I antigens.


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Intravenous Immunoglobulin (IVig) for Therapy-Resistant Cutaneous Lupus Erythematosus (LE)

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Intravenous Immunoglobulin for Recalcitrant Subacute Cutaneous Lupus Erythematosus

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Intravenous Immunoglobulin in the Treatment of Recalcitrant Subacute Cutaneous Lupus Erythematosus: A Possible Alternative

D. H. C. L. F. R. J. T. von B. ROEDEER

Intravenous Immunoglobulin in Lupus Panniculitis

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IVlg in Autoimmune Blistering Diseases
Epidermolysis bullosa acquisita:

**High-dose intravenous immunoglobulin for the treatment of autoimmune mucocutaneous blistering diseases: Evaluation of its use in 19 cases**


**Abstract**

The authors aimed to evaluate the potential of high-dose intravenous immunoglobulin (IVIG) as a therapeutic option for patients with severe autoimmune mucocutaneous blistering diseases, in particular epidermolysis bullosa acquisita (EBA), which is characterized by chronic skin blistering, pain, and scarring.

**Conclusion**

In conclusion, high-dose IVIG appears to be a promising treatment option for patients with severe autoimmune mucocutaneous blistering diseases, including EBA. Further studies are needed to confirm these findings and to assess the long-term effects of IVIG therapy in these patients.

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


**Patient characteristics**

<table>
<thead>
<tr>
<th>Disease (total No. of patients)</th>
<th>Sex</th>
<th>Age at diagnosis (years)</th>
<th>TIVG dose (mg/kg)</th>
<th>Treatment outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pemphigus vulgaris (n = 10)</td>
<td>5</td>
<td>49.9 ± 19.6</td>
<td>49.4 ± 19.2</td>
<td>72</td>
</tr>
<tr>
<td>Pemphigus foliaceus (n = 3)</td>
<td>3</td>
<td>38.7 ± 17.2</td>
<td>29.7 ± 22.4</td>
<td>58</td>
</tr>
<tr>
<td>Bullous pemphigoid (n = 1)</td>
<td>1</td>
<td>61 ± 45</td>
<td>58 ± 45</td>
<td>58</td>
</tr>
<tr>
<td>Overall (n = 16)</td>
<td>8</td>
<td>50.4 ± 18.1</td>
<td>38.4 ± 26.0</td>
<td>58</td>
</tr>
</tbody>
</table>

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**References**


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**Pemphigus:**

**A randomized double-blind trial of intravenous immunoglobulin for pemphigus**


**Objective**

The aim of this study was to evaluate the efficacy and safety of high-dose IVIG treatment in patients with pemphigus.

**Conclusion**

High-dose IVIG appears to be a promising treatment option for patients with severe autoimmune mucocutaneous blistering diseases, including EBA. Further studies are needed to confirm these findings and to assess the long-term effects of IVIG therapy in these patients.

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**Pemphigoid:**

**Intravenous immunoglobulin therapy for patients with bullous pemphigoid unresponsive to conventional immunosuppressive treatment**


**Objective**

The aim of this study was to evaluate the efficacy and safety of high-dose IVIG treatment in patients with bullous pemphigoid.

**Conclusion**

High-dose IVIG appears to be a promising treatment option for patients with severe autoimmune mucocutaneous blistering diseases, including EBA. Further studies are needed to confirm these findings and to assess the long-term effects of IVIG therapy in these patients.
How does IVlg work in autoimmune skin diseases?

Inhibition of keratinocyte apoptosis by blockade of Fas by anti-Fas antibody present in IVlg

Anti-Inflammatory effect of IVlg sialylation

Effect IVlg on levels of pemphigus (intercellular; IC) and total IgG antibodies

Bystryn, 2004
How does IVIg selectively lower autoantibody levels?

Normal degradation and removal from the body 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.
Pemphigus pathophysiology: an update

- Autoimmunity in pemphigus is directed against multiple organ-specific and non-organ specific proteins, some of which are also targeted in other types of autoimmune diseases.

- Anti-Dsg 3 antibody is pathogenic in a sense that it is an indispensable element within the multifactorial pathophysiological mechanism of pemphigus, which is yet to be understood.

Can IVIg be made to work better?

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

Therapeutic implications of mechanism of IVIg action
**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 IVIG effectiveness be improved by co-administration of a cytotoxic drug?**

**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.

**Table: Effect of IVIG vs. IVIG plus cyclophosphamide in pemphigus.**

<table>
<thead>
<tr>
<th></th>
<th>Anti-Dog 1</th>
<th>Anti-Dog 2</th>
<th>Prednisone dose (%)</th>
<th>Disease severity (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IVIG</td>
<td>4</td>
<td>74</td>
<td>55</td>
<td>47</td>
</tr>
<tr>
<td>IVIG + cyclophosphamide</td>
<td>3</td>
<td>72</td>
<td>55</td>
<td>47</td>
</tr>
</tbody>
</table>

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


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.