**Update on Applications of IVIg in Immunologically-related Dermatoses**

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### Introduction

IVIg has been used as an immunomodulator in various specialties and represents a novel therapy for immune dysfunction. Its use for immune-mediated dermatoses has increased rapidly in the last decade (or past decades), permitting a corresponding reduction of the immunosuppressive therapy and subsequent decrease in immunosuppressive drug-related adverse events.

A single donation of whole blood (450ml) yields approximately 15ml of plasma proteins, of which only 2-3ml is γ-globulin. Since the 1980s, IVIg has been produced by fractionation of pooled human plasma from 3,000 to 5,000 donors for each batch. Safety measures have been taken during the preparation regarding the source of plasma and standard of microbial inactivation procedures. The preparation currently used in HA hospitals is Intragam® P (CSL Limited, Australia). The plasma source is from the Hong Kong Red Cross Blood Transfusion Service. It contains maltose 10% as the sugar base. Each vial of Intragam® P (50ml) contains nearly 3g of IgG. There may be 'lot to lot' variations in purity, antibody activity and content of immunomodulatory proteins leading to differences in response to IVIg.

### Mechanisms of Immunomodulation

IVIg exerts several immunomodulating properties. The precise mode of action is still not clearly understood. IVIg seems to act on suppression of pathogenic antibody production, neutralisation of antibody and complement-mediated effects by anti-idiotypic antibodies, T-cell activation and Fas/Fas ligand interaction. Furthermore, the functional blockade of antibody Fc receptors on leukocytes, the modulation of cytokine profiles and increased T cell suppressor activity are other postulated mechanisms of action of IVIg.

### Dermatological Indications

The number of dermatological conditions having reported usefulness with IVIG is ever increasing. The majority of IVIg applications are "off-label" use given the scarcity of randomised controlled trials for most dermatologic entities. The general consensus is that it should be considered as a second line therapy. It is indicated when the conditions fail to respond and continue to progress despite the standard treatments or when there are significant side effects resulted from the conventional treatments or contraindications to the use of long-term immunosuppressive agents such as concomitant tuberculosis.

Benefits of IVIg have been proven in dermatomyositis resistant or partially responsive to conventional therapy as shown in randomised controlled trials with clearing of the rash, improvement of muscle strength and successful tapering of corticosteroid. Clinical and serologic improvements following IVIG were noted in different series of patients with systemic lupus erythematosus. The treatment of scleroderma with immunosuppressive therapy is difficult and the disease often shows a progressive course. Significant improvements of scleroderma including regression of dystrophic calcification have been observed with the use of IVIg on a monthly basis in some case reports. Kawasaki disease is one of the most well known indications to use IVlg in paediatric patients given within the first 10 days to prevent coronary anuerysms. The current recommended dose for Kawasaki disease is a single dose of 2g/kg over 8 to 12 hours in combination with aspirin.

There are ample publications on the use of IVlg in autoimmune mucocutaneous blistering diseases but the majority reporting favourable responses are uncontrolled series and anecdotal reports. The diseases include pemphigus vulgaris, pemphigus foliaceus, cicatricial pemphigoid, bullous pemphigoid, linear IgA disease and epidermolysis bullosa acquista. In general, this treatment appears to have greater efficacy as an adjunctive therapy than monotherapy. Some authors advocate the concurrent use of immunosuppressive agents to improve the effectiveness of IVlg therapy by inhibiting antibody synthesis to offset the rebound in autoantibody level that follows its depletion by IVlg. In a review of 21 patients with severe pemphigus, 81% showed clinical improvement and were able to reduce systemic immunosuppressants.

Stevens-Johnson syndrome (SJS) / toxic epidermal necrolysis (TEN) is a life threatening mucocutaneous reactions to drug characterised by extensive damage of epidermis, leading to blistering and erosions. The mortality, ranging from 16-30%, is due to sepsis and multiorgan failure following the loss of epidermis. Apoptosis owing to the up-regulation of death receptor ligand (FasL) on keratinocytes is the potential mechanism causing massive keratinocyte death in TEN. Naturally occurring anti-Fas antibodies in IVlg were found to be effective in inhibiting Fas-mediated keratinocyte apoptosis induced by FasL in vitro.
develop anti-IgA antibodies in Japanese population.27,28

Use of IVIg has been reported anecdotally in other dermatoses including systemic vasculitis, pyoderma gangrenosum, livedoid vasculopathy, drug hypersensitivity syndrome, nephrogenic fibrosing dermopathy, pretibial myxedema and scleromyxedema.31,32,21,24 There is insufficient evidence to recommend its use in atopic dermatitis and chronic idiopathic urticaria because of the heterogeneous mechanisms underlying these diseases.1 It remains a therapeutic option in patients with severe autoantibody-mediated chronic urticaria demonstrated by positive autologous interdermal serum test.2

Safety

IVIg therapy is generally well tolerated and its side effects are mostly mild and self-limiting. The incidence of adverse events reported is less than 5%.3 The safety profile of IVIg is more favourable than other immunosuppressive agents. The reported adverse effects include fever, chills, flushing, myalgia, nausea, headache, hypertension and hypotension.26 (Table 2) Development of cutaneous side effects is not uncommon and pompholyx, palpable purpura and generalised eczematous eruptions have been noted several days after IVIg.21 These are fortunately self-limiting and can be treated with topical steroid and emollients. Many of the acute side effects can be settled by slowing down or temporarily discontinuing the infusion. Intravenous hydrocortisone and antihistamine may be given if necessary.

Asplatic meningitis is occasionally observed and presents with headache, photophobia and nuchal rigidity. Haemolysis and neutropenia are potential haematological complications. There is a theoretical risk of infectious complications and patients should be warned of the remote risk of blood borne infections related to IVIg.26 Anaphylaxis has been reported due to the presence of anti-IgA antibodies in selective IgA deficiency (SlgAD) patients. IVIg contains trace amount of IgA. However, IgA level determination may not be feasible in emergency situation. Fortunately, the prevalence of selective IgA deficiency in Chinese population was 0.0024%, contrasting to incidence of 1 in 700 in Western population and 25% of SlgAD patients develop anti-IgA antibodies in Japanese population.27,28

Caution must also be taken when IVIg is administered to patients with renal impairment owing to the toxic effects to renal tubules, especially when sucrose-based preparation is used. Acute renal failure has been reported after IVIg therapy, particularly in elderly patients with renal impairment and dehydration.29

There are increasing number of reports of thrombotic complication after administering IVIg related to increase in blood viscosity.30 The risk seems to be greater when higher doses or rapid infusion rates are adopted.

Administration and Precautions

The optimum dose, duration and maintenance regime of IVIg have not been determined. The doses range from 1-3g/kg per cycle.32 Infusion is usually given over 4 to 6 hours as in-patients. For most chronic dermatologic indications, the current evidence supports the dose of 2g/kg per cycle administered over 2 to 5 days. The half-life of IVIg is approximately 4 weeks. An average of 4 to 6 monthly cycles are used in most studies if maintenance treatment is required.

Live vaccination, such as MMR, should be avoided 2 weeks before and 3 months after the IVIg administration because of the interference of the development of immune response.2 Baseline blood tests comprising complete blood count, liver and renal function tests should be checked. Measuring immunoglobulin levels is advised to screen for IgA deficiency especially in elective cases with pre-existing immunodeficiency. Rheumatoid factors and cryoglobulins should be checked if there are pre-existing purpuric rashes and arthralgia. There is increased risks of acute renal failure after IVIg infusion resulted from immunoprecipitation in the presence of cryoglobulinemia.33 The risk is particularly high in patients with B-cell lymphoma associated with raised serum IgM levels.34

Depending on the risk of thromboembolism and fluid status of the patients, particularly with cardiac or renal failure, IVIg infusion should be slow and not exceed 4ml/min to reduce the risk of fluid overload. Adequate hydration is desirable to minimise the renal toxicity. Close monitoring of the vital signs and body temperature is important, as untoward reactions are often apparent during the first hour of administration. Vital signs should be monitored every 15 minutes for 1 hour and then hourly. Complete blood count and renal function tests should be monitored following IVIg infusion.

Conclusion

Although the use of IVIg in treating dermatologic conditions seems promising, the effectiveness remains to be confirmed as the number of patients in most of the reported conditions is small. These largely uncontrolled and heterogeneous studies should be interpreted with caution in view of the likely reporting bias for favourable outcomes, differences in IVIg preparations, dosing schedules, severity of disease and prior use of immunosuppressive agents. Kawasaki disease, dermatomyositis and autoimmune blistering diseases have the greatest evidence for efficacy of IVIg. The perceived benefits of IVIg treatment should be balanced against the risk and the cost of therapy as opposed to the adverse effects of other systemic immunosuppressants. It should be considered on an individual basis, according to severity and relative contra-indication of other potential therapy.
It appears that IVIg is more useful as an adjuvant therapy or steroid sparing purposes, given the excellent overall tolerability. Despite some adverse events, the cost and inconvenience of hospital admission, IVIg represents a therapeutic option in patients with selected immune-mediated dermatoses.

### Table 1
**IVIg for dermatologic indications**

<table>
<thead>
<tr>
<th>Autoimmune bullous dermatoses</th>
<th>Rheumatological disorders</th>
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<tbody>
<tr>
<td>Pemphigus vulgaris and foliaceus</td>
<td>Dermatomyositis</td>
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<tr>
<td>Bullous pemphigoid</td>
<td>Scleroderma</td>
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<td>Cicatricial pemphigoid</td>
<td>Systemic lupus erythematosus</td>
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<tr>
<td>Epidermolysis bullosa acquista</td>
<td>Other dermatoses</td>
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<tr>
<td>Pemphigoid gestations</td>
<td>Chronic idiopathic urticaria</td>
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<tr>
<td>Linear IgA bullous dermatosis</td>
<td>Graft-versus-host disease</td>
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### Table 2
**Adverse effects of IVIg therapy**

- Fever, chills, flu-like symptoms
- Headache
- Aseptic meningitis
- Hypertension
- Hypotension or shock
- Transiently deranged liver or renal function tests
- Urticarial eruption
- Palpable purpura
- Generalised eczema
- Pompolyx

### References