Epidermolysis bullosa acquisita

Condition for which Ig use is in exceptional circumstances only

Specific Conditions	• Epidermolysis bullosa acquisita
Indication for Ig Use	• Persistent severe EBA refractory to conventional immunosuppressive therapy • Treatment of an ongoing flare of EBA disease in responding patients who have ceased Ig therapy
Level of Evidence	Insufficient data (Category 4a)
Description and Diagnostic Criteria	Epidermolysis bullosa acquisita (EBA) is a rare, potentially severe life-threatening disease which has no cure. This subepidermal blistering disorder of the skin and mucous membranes primarily affects adults but has been described in a few children. Although the majority of patients may have mild disease with blistering over trauma prone areas, there have been cases of severe widespread disease that remains refractory to conventional therapies. The end stage results of severe disease include ocular disease with conjunctival scarring and blindness, mucosal disease with oesophageal strictures and scarring fibrosis of the skin with alopecia, nail loss and mitten like deformities of the hands. EBA is an autoimmune disease characterised by the production of antibodies against type VII collagen resulting in immune-mediated disruption of the anchoring fibrils that connect the basement membrane to dermal structures and the clinical development of blistering. Diagnosis of EBA is based on history, full skin examination, and skin biopsies. There is limited data on treatment options for EBA and optimal approach to treatment has not been established. Suggested initial treatment is with colchicine or dapsone (Grade 2C). If treatment is not effective, these agents may be used simultaneously. EBA that is refractory to the above requires more aggressive therapy. Agents that may have efficacy for refractory EBA include immunosuppressants, intravenous immunoglobulin and rituximab.
Justification for Evidence Category	Intravenous immunoglobulin (IVIg) may be an option in severe disease. Multiple case reports suggest that the periodic administration of IVIg alone or in combination with other agents is also effective for improving the clinical manifestations of epidermolysis bullosa acquisita (EBA). In a 2011 review of published reports, 14 of 15 patients, mostly with severe widespread refractory disease, given IVIg as monotherapy or in conjunction with other therapies achieved clinical improvement (Gurcan et al, 2011). Multiple cycles of IVIg were typically given; each cycle usually consisted of a total of 1.5-2 g/kg of IVIg given over the course of 3-5 days. Thirteen of 15 patients remained on IVIg for maintenance treatment. A more recent retrospective case series demonstrated similar clinical response rates, but suggested IVIg may induce a more sustained remission (Ahmed et al, 2012). Ten patients, all nonresponsive to conventional treatments, were started on 2 g/kg/cycle of IVIg for a mean of 23 cycles over 39 months. All 10 demonstrated clinical response and were able to completely withdraw their previous therapy; no recurrence was observed during a mean follow-up period of 54 months after cessation of treatment.
Diagnosis Requirements	A diagnosis must be made by an Immunologist or a Dermatologist.

Qualifying Criteria for Ig Therapy

Persistent severe EBA refractory to conventional immunosuppressive therapy

Rituximab has been shown to be effective in the treatment of epidermolysis bullosa acquisita (EBA). A course of rituximab should be considered for the patient if not already trialled, unless strongly contraindicated.

- Persistent severe EBA disease confirmed by biopsy and/or immunofluorescence including ophthalmological and/or mucosal sites

AND

- Persistent disease despite standard treatment with colchicine and dapsone and at least two other immunosuppressant agents

  OR

- Corticosteroid and/or immunosuppressant therapy is contraindicated or has resulted in unacceptable side effects or significant toxicity

Treatment of an ongoing flare of EBA disease in responding patients who have ceased Ig therapy

Rituximab has been shown to be effective in the treatment of epidermolysis bullosa acquisita (EBA). A course of rituximab should be considered for the patient if not already trialled, unless strongly contraindicated.

- Ongoing flare of mucosal or ophthalmic EBA disease in patients with EBA disease confirmed by biopsy and/or immunofluorescence including ophthalmological and/or mucosal site

  AND

- Reduction in severity and/or the number of lesions was demonstrated in response to initial Ig therapy

  AND

- At least one immunosuppressant medication is to be given concurrently

IVIg should be used for 4 months (induction and 3 maintenance cycles) before determining whether the patient has responded. If the patient has not responded after this time, Ig therapy should be abandoned. Review is required by a dermatologist or immunologist after the first 4 months of treatment to confirm response, and 6 monthly thereafter.

Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Review Criteria for Assessing the Effectiveness of Ig Use

Persistent severe EBA refractory to conventional immunosuppressive therapy

Review is not mandated for this indication however the following criteria may be useful in assessing the effectiveness of Ig therapy.

- Reduction in number of blisters/erosions and improved healing compared to the level at the qualifying assessment

Treatment of an ongoing flare of EBA disease in responding patients who have ceased Ig therapy

IVIg should be used for 4 months (induction and 3 maintenance cycles) before determining whether the patient has responded. If the patient has not responded after this time, Ig therapy should be abandoned.

Review is required by a dermatologist or immunologist after the first 4 months of treatment to confirm response, and 6 monthly thereafter.

Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Clinical effectiveness of Ig therapy can be assessed by:

On review of the initial authorisation period

- Reduction in severity and number of erosions or blisters and improved healing compared to the level at the qualifying assessment

AND

- At least one immunosuppressant medication is given concurrently

On review of a continuing authorisation period

For stable patients on maintenance treatment, review by a dermatologist or immunologist is required 6 monthly.

Consideration should be given to a trial-off immunoglobulin (Ig) therapy once the patient has achieved stabilised disease or clinical remission.

Clinical effectiveness of Ig therapy can be assessed by:

- Reduction in the number of erosions or blisters and improved healing compared to the previous review

  AND
- There is remaining activity or stable disease requiring further treatment

  AND
- Immunosuppressant medication is given concurrently

  AND
- A trial-off Ig therapy is planned or, if not planned, a reason is provided

Dose

Persistent severe EBA refractory to conventional immunosuppressive therapy

- **Initial therapy (IVIg)** - 1.5-2 g/kg over 3 to 5 days, monthly for 3 months.

  Treatment should be for no longer than 3 months initially after which time a clinical response should be demonstrated, and the patient trialled off therapy. If the patient has not responded within this time, Ig therapy should be abandoned. If disease flares following cessation in responding patients, a request for low dose maintenance therapy can be made.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

Treatment of an ongoing flare of EBA disease in responding patients who have ceased Ig therapy

- **Induction Dose (IVIg)** - 1.5-2 g/kg over 3 to 5 days.
- **Maintenance Dose (IVIg)** - 0.4 g/kg given 4-6 weekly.

The aim should be to use the lowest dose possible that achieves the appropriate clinical outcome for each patient.

Refer to the current product information sheet for further information on dose, administration and contraindications.

Bibliography

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