Pyoderma Gangrenosum (PG)

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Condition for which IVIg use is in exceptional circumstances only

Specific Conditions	• Pyoderma Gangrenosum
Indication for IVIg Use	• Severe PG when immunosuppressant and biologic therapy is either ineffective or inappropriate due to unacceptable side effects • Relapse of PG in previously responding patients following a trial off Ig therapy
Level of Evidence	Insufficient data (Category 4a)
Description and Diagnostic Criteria	Pyoderma gangrenosum (PG) is a chronic inflammatory disease characterised by painful skin ulcerations with raised erythematous and undermined borders. The aetiology is 'not well understood but is generally considered to be an aberrant immune response characterised by a dermal neutrophilic infiltrate' (Patel et al, 2015) responding to immunosuppressant medication and sometimes presenting in patients treated with immune modifying medications such as Granulocyte - colony stimulating factor. The condition is recognised to occur more commonly in patients with immune mediated diseases including inflammatory bowel disease, inflammatory arthritis, and haematological diseases (myelodysplastic syndrome, multiple myeloma, polycythaemia vera, leukaemia). A clinical diagnosis of exclusion is required as there are no clear serologic or histological criteria. Traditional wound care including compression may be helpful. While trauma from surgery may exacerbate ulceration debridement and skin grafting may be options once evidence of any activity has resolved. The persistence of an ulcer does not indicate non-responsiveness to immunosuppressant medications given that they will take time to heal following successful suppression of the aberrant pathogenic immune response. Ig should be reserved for severe cases when treatment with combinations of immunosuppressants and also biological agents has been either ineffective or unable to be tolerated due to severity of side effects or contraindications. The safety profile of Ig means that it is useful when additional efficacy is required, without increasing levels of immunosuppression. Nevertheless, given the expense of Ig careful consideration should be given when considering its usage.
Justification for Evidence Category	Ig therapy is regarded as adjuvant treatment and is considered third or fourth line treatment, after alternative therapies have been unsuccessful in achieving improvement or remission. While Ig has been proven to be effective in small case series (Patel et al, 2015 and Cummins et al, 2007) and case reports (Cafardi & Sami, 2014 and De Zwaan et al, 2009), ideally it is used to enhance the effect of existing treatment, rather than as monotherapy.
Diagnosis Requirements	A diagnosis must be made by an Immunologist or a Dermatologist.

Qualifying Criteria for IVIg Therapy	Severe PG when immunosuppressant and biologic therapy is either ineffective or inappropriate due to unacceptable side effects

This indication should be used for new patients and those that have never trialled off from Ig therapy. Please use the indication **Relapse of PG in previously responding patients following a trial off Ig therapy** for responding patients who have relapsed after weaning from Ig therapy.

- Severe PG with large or persistent ulceration causing significant impact on quality of life

AND

- Unresponsive to a trial of oral corticosteroid therapy for at least six weeks

  OR
- Corticosteroid therapy is contraindicated or has resulted in unacceptable side effects or significant toxicity

AND

- Unresponsive to a trial of immunosuppressant therapy in combination with prednisolone for at least eight weeks

  OR
- Immunosuppressant medication is contraindicated or has resulted in unacceptable side effects or significant toxicity

AND

- Unresponsive to a trial of biologic therapy for at least three months

  OR
- Biologic therapy is contraindicated or has resulted in unacceptable side effects or significant toxicity or is unavailable

Review by a Dermatologist or an Immunologist is required after three months of treatment (induction plus two maintenance cycles) to determine whether the patient has responded. If no response is demonstrated after this time, Ig therapy should be abandoned. For patients on maintenance therapy, six monthly review is required.

A trial off therapy should be considered when disease activity is controlled by evidence of signs of healing/improvement in all ulcers. Treatment should be substituted with a combination of oral corticosteroids and an immunosuppressive steroid sparing agent at appropriate doses or biologic therapy (unless contraindicated) until ulcers have healed. Ig should be re-instituted if recurrence of disease activity occurs in spite of these measures.

Relapse of PG in previously responding patients following a trial off Ig therapy

This indication should be used for responding PG patients who have relapsed within six months of commencement of a trial off immunoglobulin therapy. For new patients and those that have never trialled off from Ig therapy, please use the indication **Severe PG when immunosuppressant and biologic therapy is either ineffective or inappropriate due to unacceptable side effects.**

- Worsening in at least four of the following measures since cessation of Ig therapy in the majority of ulcers in a previously responding patient
    - Increase in the depth of violaceous colour at ulcer edge
    - increase in size
    - increase in depth
    - increase in undermining of edges
    - increase in slough
    - reduction in granulation tissue

AND

- Since cessation of Ig therapy, disease persists despite treatment with corticosteroids and at least one immunosuppressant or biological agent

  OR
- Corticosteroids and/or immunosuppressant and/or biologic agents are contraindicated or resulted in unacceptable side effects or significant toxicity

Review by a Dermatologist or an Immunologist is required by three months of treatment (induction plus two maintenance cycles) to determine whether the patient has responded. If no response is demonstrated after this time, Ig therapy should be abandoned. For patients on maintenance therapy, six monthly reviews are required.

A trial off therapy should be considered when disease activity is controlled by evidence of signs of healing/improvement in all ulcers. Treatment should be substituted with a combination of oral corticosteroids and an immunosuppressive steroid sparing agent at appropriate doses or biologic therapy (unless contraindicated) until ulcers have healed. Ig should be re-instituted if recurrence of disease activity occurs in spite of these measures.

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

Review Criteria for Assessing the Effectiveness of IVIg Use	Severe PG when immunosuppressant and biologic therapy is either ineffective or inappropriate due to unacceptable side effects

Review by a Dermatologist or an Immunologist is required after three months of treatment (induction plus two maintenance cycles) to determine whether the patient has responded. If no response is demonstrated after this time, Ig therapy should be abandoned.

For stable patients on maintenance therapy, six monthly reviews are required.

A trial off therapy should be considered when disease activity is controlled by evidence of signs of healing/improvement in all ulcers. Treatment should be substituted with a combination of oral corticosteroids and an immunosuppressive steroid sparing agent at appropriate doses or biologic therapy (unless contraindicated) until ulcers have healed. Ig should be re-instituted if recurrence of disease activity occurs in spite of these measures.

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

- Improvement in at least four of the following six measures in the majority of ulcers compared to the qualifying assessment:
  - Reduction in the depth of violaceous colour at ulcer edge
  - reduction in size
  - reduction in depth
  - reduction in undermining of edges
  - reduction in slough
  - increase in granulation tissue

On review of a continuing authorisation period

- Further improvement or stabilisation in ulcer(s) compared to previous assessment

  AND

- Once disease activity is controlled by evidence of healing/ improvement in *all* ulcers, a trial of weaning/cessation of therapy should be considered or if not planned, a valid reason provided

Relapse of PG in previously responding patients following a trial off Ig therapy

Review by a Dermatologist or an Immunologist is required by three months of treatment (induction plus two maintenance cycles) to determine whether the patient has responded. If no response is demonstrated after this time, Ig therapy should be abandoned.

For stable patients on maintenance therapy, six monthly reviews are required.

A trial off therapy should be considered when disease activity is controlled by evidence of signs of healing/improvement in all ulcers. Treatment should be substituted with a combination of oral corticosteroids and an immunosuppressive steroid sparing agent at appropriate doses or biologic therapy (unless contraindicated) until ulcers have healed. Ig should be re-instituted if recurrence of disease activity occurs in spite of these measures.

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

- Improvement in at least four of the following six measures in the majority of ulcers compared to the qualifying assessment:
  - Reduction in the depth of violaceous colour at ulcer edge
  - reduction in size
  - reduction in depth
  - reduction in undermining of edges
  - reduction in slough
  - increase in granulation tissue

On review of a continuing authorisation period

- Further improvement in ulcer(s)

  AND

- Once disease activity is controlled by evidence of healing/ improvement in *all* ulcers, a trial of weaning/cessation of therapy should be considered or if not planned, a valid reason provided

Dose	Severe PG when immunosuppressant and biologic therapy is either ineffective or inappropriate due to unacceptable side effects • **Initial therapy dose** - 1-2 g/kg in divided dose over 3 days, each month for 3 months. • **Maintenance Dose** - 0.4 to 2 g/kg in single or divided doses monthly. 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. Relapse of PG in previously responding patients following a trial off Ig therapy • **Initial therapy** - 1-2 g/kg in divided dose over 3 days, each month for 3 months. • **Maintenance Dose** - 0.4 to 2 g/kg in single or divided doses monthly. 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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