Graves ophthalmopathy

Version: 3.0

Published: 20 October 2018

Condition for which IVIg use is in exceptional circumstances only

Specific Conditions	• Graves ophthalmopathy
Indication for IVIg Use	• Severe Graves ophthalmopathy disease where immunosuppressant treatments have failed or are contraindicated
Level of Evidence	Evidence of probable benefit – more research needed (Category 2a)
Description and Diagnostic Criteria	Graves ophthalmopathy (GO) is an inflammatory disorder of the eye occurring in association with autoimmune thyroid disease which can result in adverse visual outcome in few severe cases. The most severe complications include corneal ulcerations, globe subluxation and dystrophic optic neuropathy. Evidence based guidelines of the European Group on Graves' Ophthalmopathy (EUGOGO) by Bartalena et al (2016) advocate high dose glucocorticoids, preferably intravenous as first line therapy for moderate-to-severe and active GO. For second line therapy, the guidelines recommend shared decision making with a second course of intravenous glucocorticoids, oral glucocorticoids combined with orbital radiotherapy or cyclosporine, or rituximab. Orbital decompression surgery, or squint or eyelid surgery are recommended for patients when GO has been managed conservatively and inactivated by immunosuppressive treatment. IVIg is considered third line therapy if active GO persists after treatment with glucocorticoid and other therapies, preferably in the setting of multi-disciplinary care with co-ordination between Ophthalmology, Immunology and Endocrinology. Rituximab should be considered ahead of IVIg, unless the risk of dysthyroid optic neuropathy is high, as rituximab can precipitate this complication.
Justification for Evidence Category	A randomised trial (Kahaly G et al, 1996) studied 19 patients with active Graves ophthalmopathy (GO), treated with a 20 week course of oral prednisolone starting at 100 mg daily for one week, and tapering by 5 mg/week, and 21 patients with 1g IVIg/kg body weight for two consecutive days every three weeks, repeated six times. The proportion of responders was similar in both groups: 12/19, 63 percent in the prednisolone arm and 13/21, 62 percent in the IVIg arm. In that study, responders to treatment in both groups showed similar moderate improvements in proptosis, and reductions of exophthalmos and soft tissue involvement. The authors' discussion of their results, mirrored in the EUGOGO guidelines, refers to the high cost and potential risks as limiting factors for the use of IVIg.
Diagnosis Requirements	A diagnosis must be made by an Immunologist, Ophthalmologist or an Endocrinologist.

Qualifying Criteria for IVIg Therapy	Rituximab has been shown to be effective in the treatment of Graves ophthalmopathy. A course of rituximab should be considered for the patient if not already trialled, unless contraindicated. • Persistent and severe ophthalmic disease AND • Unresponsive to intravenous steroid treatment OR • Steroid treatment is contraindicated or has resulted in unacceptable side effects or significant toxicity AND • A trial of rituximab has failed to demonstrate a response, three months following the last dose OR • Rituximab is contraindicated or unavailable AND • A trial of at least two alternative treatments has been undertaken Review by an ophthalmologist, endocrinologist or immunologist is required within three months of treatment to determine whether the patient has responded, and six monthly thereafter. If no response has been demonstrated by three months, IVIg therapy should be abandoned. For stable patients on maintenance treatment, review by an ophthalmologist, endocrinologist or immunologist is required every six months. Documentation of clinical effectiveness is necessary for continuation of IVIg therapy.

Review Criteria for Assessing the Effectiveness of IVIg Use	Review by an opthalmologist, endocrinologist or immunologist is required within three months of treatment to determine whether the patient has responded, and six monthly thereafter. If no response has been demonstrated by three months, IVIg therapy should be abandoned. For stable patients on maintenance treatment, review by an ophthalmologist, endocrinologist or immunologist is required every six months. 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 the severity and level of activity of eye disease compared to the qualifying assessment AND • A reduction in dose is planned or if not planned, a valid reason is provided **On review of a continuing authorisation period** • Further improvement in severity or stabilisation of eye disease AND • A trial of weaning/cessation of Ig therapy are considered annually for patients who are clinically stable or a valid reason provided as to why a trial is not being planned or is contraindicated at this time Rituximab has been shown to be effective in the treatment of Graves ophthalmopathy. A course of rituximab should be reconsidered for this patient if not already trialled, unless contraindicated.
Dose	• **Induction Dose** - 1 to 2g/kg over 2 days. • **Maintenance Dose** - 0.4 to 2g/kg in single or divided doses monthly. A maximum dose of 2g/Kg may be given in any 4 week period. This might be by divided doses more frequently than 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

Bartalena, L, Baldeschi, L, Boboridis, K, et al 2016, 'The 2016 European Thyroid Association/European Group on Graves' Orbitopathy', *European Thyroid Journal*, vol. 5, pp. 9-26. http://www.karger.com/Article/PDF/443828

Bartalena, L, Tanda, ML, Medea, A, et al 2002, 'Novel approaches to the management of Graves Ophthalmology', *Hormones*, vol. 1, no. 2, pp. 76-90. http://www.hormones.gr/pdf/1116273756.pdf

Bartalena, L, Baldeschi, L, Dickinson, A, et al 2008, 'Consensus statement of the European Group on Graves' Orbitopathy (EUGOGO) on management of GO', *Thyroid*, vol. 18, no. 3, pp. 333–346. https://www.ncbi.nlm.nih.gov/pubmed/18299459

Baschieri, L, Antonelli, A, Nardi, S, et al 1997, 'Intravenous immunoglobulin versus corticosteroid in treatment of Graves'

ophthalmopathy', *Thyroid*, vol. 7, no. 4, pp. 579–585. https://www.ncbi.nlm.nih.gov/pubmed/9292946

Kahaly, G, Pitz, S, Muller-Forell, W et al 1996, 'Randomised trial of intravenous immunoglobulins versus prednisolone in Graves ophthalmology', *Clinical and Experimental Immunology*, vol. 106, no. 2, pp. 197-202. https://www.ncbi.nlm.nih.gov/pubmed/8918563

Khanna, D, Chong, KK, Afifyan, NE, et al 2010, 'Rituximab treatment of patients with severe, corticosteroid-resistant thyroid- associated ophthalmopathy', *Ophthalmology*, vol. 117:133, –pp. 152. https://www.ncbi.nlm.nih.gov/pubmed/19818507

Ontario Regional Blood Coordinating Network, 2016, 'Ontario Intravenous Immune Globulin (IVIG) Utilization Management Guidelines, Version 3.0. [online]. Available from: http://transfusionontario.org/en/.

Salvi, M, Vannucchi, G,Currò N, Campi, I, Covelli, D, Dazzi, D, et al 2015, 'Efficacy of B-Cell Targeted Therapy With Rituximab in Patients With Active Moderate to Severe Graves' Orbitopathy: A Randomized Controlled Study', *Journal of Clinical Endocrinology & Metabolism*, vol. 100, no. 2, pp. 422–431. https://www.ncbi.nlm.nih.gov/pubmed/25494967

Stan, MN, Garrity, JA & Bahn, RS 2012, 'The evaluation and treatment of graves ophthalmopathy', *Medical Clinics of North America*, vol. 96, no. 2, pp. 311-28. https://www.ncbi.nlm.nih.gov/pubmed/22443978

Stiebel-Kalish, H, Robenshtok, E, Hasanreisoglu, M, et al 2009, 'Treatment Modalities for Graves' Ophthalmopathy', *Journal of Clinical Endocrinology & Metabolism*, vol. 94, no. 8, pp. 2708-2716. https://www.ncbi.nlm.nih.gov/pubmed/19491222

Strianese, D, Iuliano, A, Ferrara, M, et al 2014, 'Methotrexate for the treatment of Thyroid Eye Disease', *Journal of Ophthalmology*, 2014. https://www.ncbi.nlm.nih.gov/pubmed/24678411

Tagami, T, Tanaka, K, Sugawa, H, et al 1996, 'High-dose intravenous steroid pulse therapy in thyroid associated ophthalmopathy', *Endocrinology Journal*, vol. 43, no. 6, pp. 689–99. https://www.ncbi.nlm.nih.gov/pubmed/9075609

UK Department of Health, 2011, 'Clinical Guidelines for Immunoglobulin Use: Second Edition Update', Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/216671/dh_131107.pdf

Wiersinga, W, 2016, 'Advances in treatment of active, moderate-to-severe Graves' ophthalmopathy', *The Lancet Diabetes & Endocrinology*, vol. 5, no. 9, pp. 134-142. http://www.thelancet.com/journals/landia/article/PIIS2213-8587(16)30046-8/fulltext

Generated on: 31 March 2019