CLINICAL PRACTICE GUIDELINE: Emergency Department

Thyroid-Associated Orbitopathy

Disclaimer: This Clinical Practice Guideline ('CPG') was written for use in The Royal Victorian Eye and Ear Hospital Emergency Department. It should be used under the guidance of an Eye registrar or an ENT registrar. If clinical advice is required, please contact the Eye and Ear Admitting Officer for assistance: EYE: +61 3 9929 8033; ENT: +61 3 9929 8032. Links to internal Eye and Ear documents cannot be accessed from the website CPG.

Description:

Thyroid-associated Orbitopathy (TO) affects 25% of patients with Graves' hyperthyroidism. One in 20 of these patients will have moderate-severe active disease that will require medical intervention to reduce both TO activity and its severity.

To date, intravenous corticosteroid has been the mainstay of treatment for moderate-severe active TO.

This guideline has been developed as a clinical decision making framework for medical staff based on current evidence for corticosteroid and immunotherapy in the treatment of TO.

How to Assess:

Active, Mild TO

Definition:

- Mild soft tissue involvement (lid oedema, erythema, chemosis, conjunctival injection)
- Minimal proptosis (20-22mm)
- Minimal double vision and extra-ocular muscle enlargement

Management:

- Supportive treatment
  - Ocular lubricants
  - Advice on head elevation at night.
- Selenium supplementation
  - 200 micrograms per day over 6 months.
    The role of selenium is to help with periocular soft tissue swelling. It acts as an anti-oxidant to reduce local orbital oxidative stress but does not reduce proptosis.
- Smoking status
  - Smokers are advised to quit smoking, getting advice from general practitioner about Quit smoking program.
- Euthyroid status
  - Check the patient's baseline thyroid function test and TSH receptor antibody level.
  - Refer back to endocrinologist if not euthyroid.

Active, Moderate-Severe TO

Definition
VISA inflammatory index score of ≥4/10 or CAS >3/7 for ≤6 months, with *at least one* of the following:

- Moderate to marked soft tissue involvement
  - lid oedema
  - lid erythema
  - chemosis
  - conjunctival injection
- Extra-ocular muscle involvement with limitation of vertical or horizontal duction to <30 degree from primary position.
- Intermittent or constant diplopia in primary position.
- Proptosis ≥3mm above general population upper limits i.e. Caucasian ≥25mm, East Asian≥21mm, where moderate proptosis is 23-25mm, severe proptosis ≥26mm.

Assessment
Use TED Assessment and Follow Up form for objective measurements to include 4 aspects:

- Visual acuity
- Inflammation index score
- Extra-ocular muscle movement & strabismus
- Appearance

Management

- First Line
  Intravenous methylprednisolone (IVMP)
  - 500mg weekly for 6 weeks
  - Followed by 250mg weekly for 6 weeks as per EUGOGO recommendation if responding to this treatment.

  IVMP protocol applies:
  - Baseline blood sugar level (BSL)
  - Blood pressure (BP)
  - Electrolytes (U&E)
  - Liver function test (LFT)
  - Full blood examination (FBE)

  With each IVMP infusion check
  - BP,
  - BSL and
  - Bloods for FBE, LFT, U&E

  Gastroprotection with proton pump inhibitor e.g. omeprazole 20mg daily with each infusion.
  Assess for IVMP efficacy and side effects at:

- 4 weeks
- 8 weeks and
- 12 weeks

- Assess Response
  Response is defined by:
  - Inflammation index score reduction by 2 points
  - Proptosis reduction by 2mm
  - EOM and strabismus improvement by 15 degree (which is graded by corneal light reflex at pupil 0 degree, edge of pupil 15 degree, mid-iris 30 degree, limbus 45 degree)
  - Reduction of lid retraction by 2mm.
- After 3 IVMP infusions:
  - Responder
    - Continue on IVMP
  - Minimal Responder & Partial Responder
    - Refer to Ocular Rheumatology Clinic (EORC) by completing an Internal Referral form (Drs Timothy Godfrey, Julian Bosco, Michelle Papondony, Laura Ross) for commencement of mycophenolate 2g daily dose for 6 months as second line;
    - Continue IVMP until 12 weeks course is completed.
    - Rheumatologist would consider gastroprotection, vitamin D, bisphosphonate and pneumocystis prophylaxis (resprim 800/160mg tab Mon/Wed/Fri) in combination immunotherapy according to individual patient medical assessment.
- Investigations prior to combination immunotherapy:
  - Quantiferon,
  - Hepatitis B/C serology including Hep B core AB, +/- HIV
  - Strongyloides serology if at risk
  - TSH Receptor antibody
  - Consider also baseline CXR and consider DEXA (Bone density).
- Medical recommendations to prevent steroid-induced osteoporosis:
  - Optimize calcium intake (1,000–1,200 mg/day)
  - Vitamin D intake (600–800 IU/day)
  - Lifestyle modifications including balanced diet, maintaining weight in the recommended range, smoking cessation, regular weight-bearing or resistance training exercise, limiting alcohol intake to 1–2 alcoholic beverages/day.

  This is recommended for all patients continuing on corticosteroids for an extended period.

  For further information on steroid-induced osteoporosis guideline, refer to Buckley, L. *et al.* 2017 American College of Rheumatology Guideline for the

Prevention and Treatment of Glucocorticoid-Induced Osteoporosis. *Arthritis Rheumatol* 69, 1521–1537 (2017)

- At 12 weeks review

  Decide if adjuvant radiotherapy is needed; This is indicated for ongoing active, severe disease, especially with motility restriction.

- Reactivation

  Reactivation after cessation of corticosteroid cases are referred to EORC for commencement of mycophenolate as steroid sparing agent.

  [Refer to Diagram 1]

Dysthyroid Optic Neuropathy (DON)

Definition

Confirmed by clinical findings of the following, often in the setting of active disease:

- reduced colour vision
- reduced visual acuity
- with or without relative afferent pupillary defect depending on the degree of symmetry of bilateral apical crowding
- with or without optic discs swelling
- corresponding visual field changes

Assessment

Same as for active, moderate-Severe TO

Evaluate to exclude other causes of reduced vision such as cataract, macular pathology, retinopathy, optic neuropathy and neuro-ophthalmic causes.

Management

- First Line
  IV methylprednisolone
  - 1g daily 3 doses
- At 2 Weeks
  Assess response of treatment to:
  - visual acuity
  - colour vision
  - disc changes
  - inflammatory index score
  - ocular motility
  - proptosis

  Good Responder
  - Continue on 500mg weekly IVMP for 6-8 weeks (8g max.)

Partial Responder

- With good visual acuity (better than 6/12) are referred to radiation oncology centre for low dose 20 Gray orbital radiation and ongoing IVMP for the synergistic effect, reassessed 4 weekly for response.

Clinical Deterioration and Non-Responder

- List for orbital decompression

Refractory Cases

Definition

DON cases failing to improve with IVMP, orbital decompression and orbital radiotherapy.

This definition is more stringent than any of the clinical studies, due to consideration of costing of rituximab and tocilizumab, which has been used in active, severe cases not responsive to IVMP and in multiple studies for both drugs before onset of DON.

Management

- Refer to Ocular Rheumatology Clinic for immune therapy infusion assessment – please complete an Internal Referral form
    - As for choosing between rituximab or tocilizumab, rituximab has the advantage of a short course of 2 infusions over 2 weeks as compare to tocilizumab of 4 infusions over 4 months. Rituximab use was reported in multiple refractory DON cases, while tocilizumab efficacy has been reported in one DON case within a clinical trial. Therefore for this guideline, rituximab is chosen as first line for refractory cases. When teprotumumab costing and access is clearer, guideline will be reviewed.
- Streamline application to drug therapy committee for:
    1. SASB approval
    2. Roche for compassionate stock.
- Pharmacy to contact the Ocular Rheumatology Clinic consultants upon approval of biologics, who would arrange for St Vincent's Hospital medical admission (day infusion) through the rheumatology registrar, for the date to initiate treatment.

[Refer to Diagram 2]

Evidence Table

Author(s)	Title	Source	Level of Evidence (I – VII)
Kahaly, G. J., et al.	Randomized, single blind trial of intravenous versus oral steroid monotherapy in Graves' orbitopathy	Clin Endocrinol Metab 2005; 90(9): 5234-5240	II
Marcocci, C., et al.	Comparison of the effectiveness and tolerability of intravenous or oral glucocorticoids associated with orbital radiotherapy in the management of severe Graves' ophthalmopathy: results of a prospective, single-blind, randomized study	Clin Endocrinol Metab 2001; 86(8): 3562-3567	II
Bartalena, L., et al.	Efficacy and safety of three different cumulative doses of intravenous methylprednisolone for moderate to severe and active Graves' orbitopathy	J Clin Endocrinol Metab 2012; 97(12): 4454-4463	II
Mourits, M. P., et al.	Radiotherapy for Graves' orbitopathy: randomised placebo-controlled study	Lancet 2000; 355(9214): 1505-1509	II
Ye, X., et al	Efficacy and safety of mycophenolate mofetil in patients with active moderate-to-severe Graves' orbitopathy	Clin Endocrinol (Oxf) 2017; 86(2): 247-255	II
Kahaly, G. J., et al.	Mycophenolate plus methylprednisolone versus methylprednisolone alone in active, moderate-to-severe Graves' orbitopathy (MINGO): a randomised, observer-masked, multicentre trial	Lancet Diabetes Endocrinol 2018; 6(4): 287-298	II
Khanna, D., et al.	Rituximab treatment of patients with severe, corticosteroid-resistant thyroid-associated ophthalmopathy	Ophthalmology 2010; 117(1): 133-139 e132	IV
Salvi, M., et al.	Efficacy of B-cell targeted therapy with rituximab in patients with active moderate	J Clin Endocrinol Metab 2015; 100(2): 422-431	V

	to severe Graves' orbitopathy: a randomized controlled study		
Perez-Moreiras, J. V., et al	Treatment of active corticosteroid-resistant graves' orbitopathy	Ophthalmic Plast Reconstr Surg 2014; 30(2): 162-167	IV
Perez-Moreiras, J. V., et al.	Efficacy of Tocilizumab in Patients With Moderate-to-Severe Corticosteroid-Resistant Graves Orbitopathy: A Randomized Clinical Trial	Am J Ophthalmol 2018; 195: 181-190	II
Smith, T. J., et al.	Teprotumumab for Thyroid-Associated Ophthalmopathy	N Engl J Med 2017; 376(18): 1748-1761	II
Douglas, R. S., et al.	Teprotumumab for the Treatment of Active Thyroid Eye Disease	N Engl J Med 2020; 382(4): 341-352	II

The Hierarchy of Evidence

The Hierarchy of evidence is based on summaries from the National Health and Medical Research Council (2009), the Oxford Centre for Evidence-based Medicine Levels of Evidence (2011) and Melynk and Fineout-Overholt (2011).

I) Evidence obtained from a systematic review of all relevant randomised control trials.

II) Evidence obtained from at least one well designed randomised control trial.

III) Evidence obtained from well-designed controlled trials without randomisation.

IV) Evidence obtained from well-designed cohort studies, case control studies, interrupted time series with a control group, historically controlled studies, interrupted time series without a control group or with case series.

V) Evidence obtained from systematic reviews of descriptive and qualitative studies.

VI) Evidence obtained from single descriptive and qualitative studies.

VII) Expert opinion from clinician, authorities and/or reports of expert committees or based on physiology.

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Diagram 1 – Treatment for Active, Moderate to Severe TO

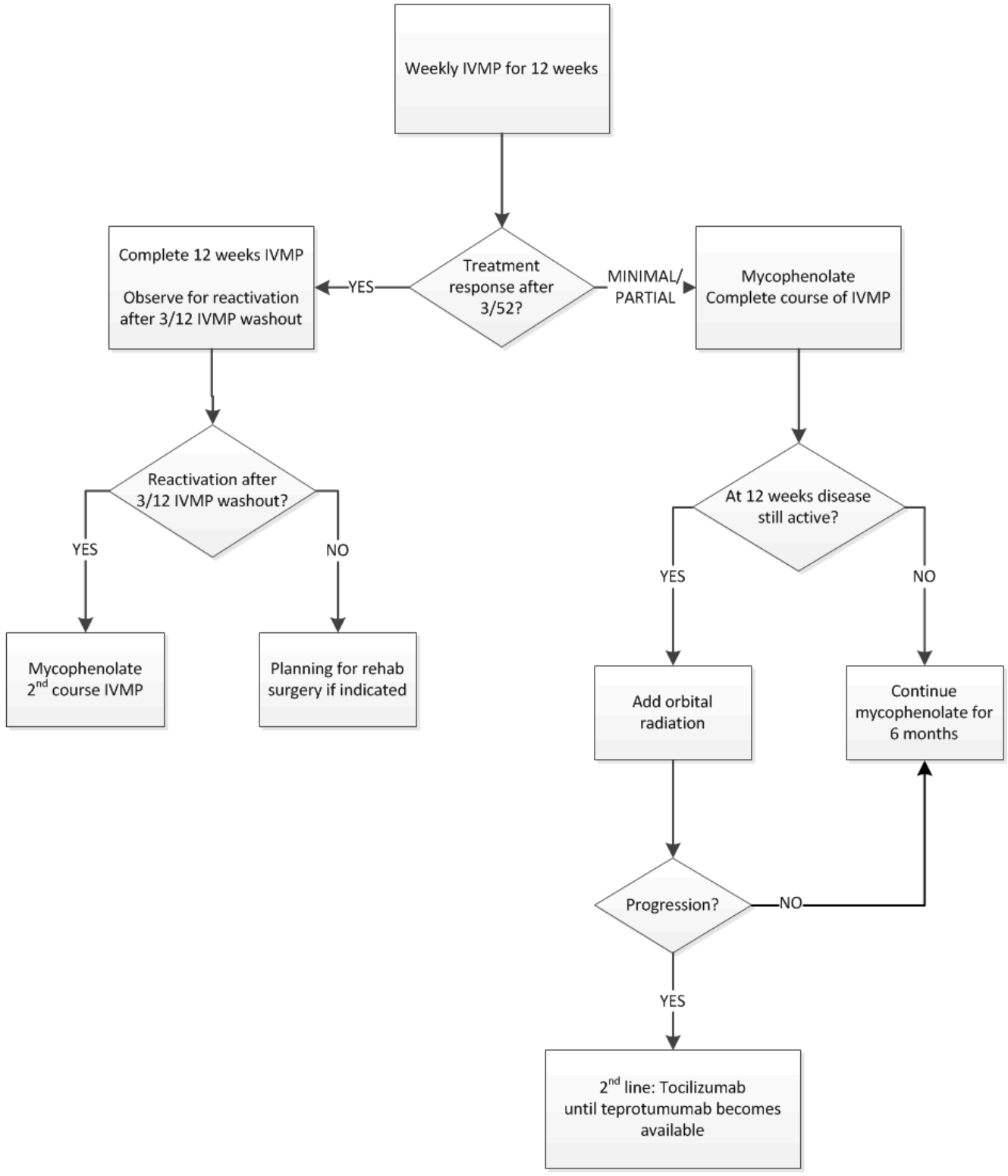

Diagram 2 – Treatment for Dysthyroid Optic Neuropathy