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Immune Checkpoint Inhibitor - induced Enterocolitis prescribing guideline

Background

Immune checkpoint inhibitors are a class of cancer treatment that have improved outcomes for cancer patients across various tumour groups. They work by antagonising inhibitory immune pathways, to boost immune-mediated antitumour responses. However, this often results in the activation of immune cells in non-cancer tissues causing off-target immune-mediated injury and organ dysfunction. Common sites of toxicity include the skin, gut, liver, and endocrine system. Consequently, it is now commonplace for oncologists to engage organ specialists to deliver optimal care for patients with different immune-related adverse events.

As a result, all immunotherapy-induced colitis cases are discussed with link gastroenterologists at surrounding trusts for their expertise. Management of the disease is then decided based on various patient and disease-related factors. If the pharmaceutical management is required, the treatment algorithm begins with high dose oral steroids, or intravenous steroids if oral formulation is not tolerated or treatment escalation is required due to severity of colitis (see Fig. 1).

What causes immunotherapy induced colitis?

The mechanism of action of the immunotherapies initiates an auto-immune response that is not specific to the cancer and therefore has led to a new series of immune-related adverse events with the potential to affect any organ system.

Diarrhoea is the second most common immune-related adverse event, after skin toxicities, and it is the most frequent reason for the interruption or permanent discontinuation of immune checkpoint inhibitor therapy.

The diarrhoea and gastrointestinal side effects of immunotherapy can be serious in nature and in so prompt recognition of gastrointestinal toxicity and, in many cases, rapid institution of anti-inflammatory or biologic therapy (or both) is required to reverse these complications.

The British Society of Gastroenterology (BGS) guidance on immune-checkpoint inhibitor induced enterocolitis defines this as diarrhoea associated with confirmed inflammation of the gastrointestinal tract (i.e. through macroscopic, histological, or biochemical means).

Management of immune checkpoint inhibitor - induced enterocolitis

Management algorithms recommend treatment with corticosteroids to treat diarrhoea in this patient cohort regardless of proven evidence of gastrointestinal inflammation.

Generally, treatment is based on the severity of the symptoms assessed through the international CTCAE criteria (Common Terminology Criteria for Adverse Events). This is a common tool utilised to stratify and manage adverse effects of many anti-cancer agents, however there are limitations with its use in colitis, and so management should be decided through the wider MDT with specialist gastroenterology input.

The current management algorithm for South West London is included in Fig. 1. This highlights the treatment algorithm funded by SW London ICB summarised below:

1. Infliximab to treat steroid-refractory colitis (to use up to 3 doses at 10mg per kg)
2. Vedolizumab to treat steroid-refractory colitis in patients unsuitable for infliximab (i.e. elderly or frail patients at high risk of infection), following gastrointestinal discussion and input.
3. Upadacitinib to treat infliximab/vedolizumab refractory colitis (after 3 doses), following gastrointestinal discussion and input.

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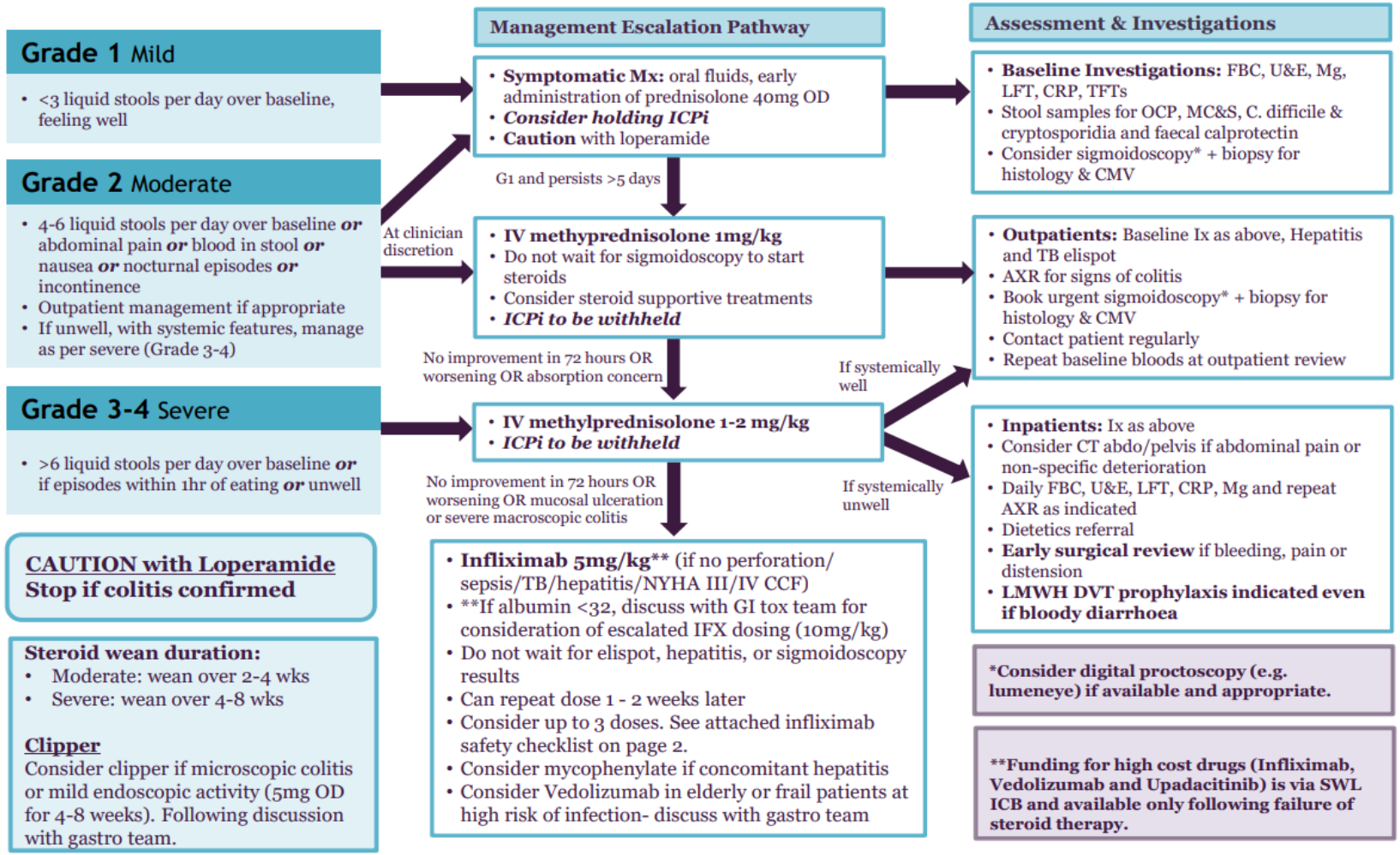

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INFLIXIMAB SAFETY CHECKLIST

Check prior to administration:

- **TB infection/exposure history and perform T spot test (if positive, referral to TB specialist as indicated); CXR (or CT) to exclude granulomas**
- **Baseline LFTs (if moderate derangement – seek advice prior to administration)**
- **Baseline Hepatitis B & C, HIV, VZV serology**
- **Check vaccination history: seek advice if live vaccine received in last 4 weeks**
- **Start PJP prophylaxis**

Key side effects for patient consent:

- Increased risk of infection for 6 months – including pneumonia, TB & HBV reactivation
- Hypersensitivity reaction
- Very small increased risk of malignancy (lymphoma)

Absolute* and relative contraindications:**

*Active severe infection/sepsis (including active TB)
*Bowel perforation
**Prior severe hypersensitivity
**Moderate to severe heart failure
**Past history of TB– need to D/W TB/respiratory team
**Demyelinating CNS disorders (risk of exacerbation)
**Pregnancy

Previous exposure increases risk of hypersensitivity reaction and pre-medication recommended

Monitoring and follow-up:

- Alert GP to use of infliximab in discharge summary
- Monitor for infections for 6 months following use
- Monitor for Hepatitis B reactivation if evidence of previous infection

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Special Situations	Management Approach
Persistent diarrhoea in absence of endoscopic or histological inflammation	• Consider ileocolonoscopy (with biopsies + CMV) • Consider OGD especially if upper GI symptoms • Faecal elastase • Coeliac serology • Change PPI to H2 antagonist • If remains on steroids, start calcium/Vit D supplementation
Recurrent Sx on steroid wean	• Instigate investigations for persistent diarrhoea (above) if not already performed; consider malabsorptive process if on oral steroids. • Recurrence of diarrhoea - escalate steroids to lowest effective dose and wean more slowly or consider infliximab.
Refractory to infliximab/ vedolizumab	• Discuss with GI toxicity team and consider mycophenolate mofetil (preferred choice if concomitant hepatitis), calcineurin inhibitors or Upadacitinib** with appropriate patient counselling and monitoring • Consider bowel rest (i.e. no oral intake) with TPN support or FMT– anecdotally these have been helpful in some cases.
Microscopic inflammation (i.e. endoscopy normal)	• For microscopic inflammation or mild endoscopic activity, start clipper (beclomethasone dipropionate) 5mg OD for 4-8 weeks. If features of collagenous colitis (on histology), start budesonide 9mg OD for 8 weeks then stop, alongside fast taper of systemic corticosteroids. • In event of relapse- a further 8- week course of topical corticosteroids can be administered with a slower taper for the last 4 weeks.
IO + targeted therapy/chemotherapy	• When immunotherapy is given in combination or in sequence with other SACT consider the contributory impact of the other drug to the aetiology and severity of the diarrhoea

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- **Red flag symptoms for pathological diarrhoea**
  - nocturnal diarrhoea, new incontinence, fever, weakness, tachycardia, blood or mucous in stool, abdominal pain, food avoidance
- **Red flag investigation results**
  - AXR – colitis can be associated with an empty colon; distended large bowel, thumb printing
  - Elevated CRP/white cell count
- **Suggested modified diet for moderate symptoms**
  - bananas, rice, pasta
  - avoid fiber and minimise lactose-containing foods
- **Sigmoidoscopy preparation – discuss with Endoscopist if unsure**
  - Mild/moderate: phosphate enema
  - Severe: no prep (perforation risk)
- **Infection control issues:**
  - 'Diarrhoea' is defined by Bristol chart Type 7, or any incontinence
  - Acute diarrhoea –isolation is indicated for minimum 48 hours whilst awaiting faecal culture/PCR results (exclude Salmonella/Shigella/Campylobacter/C. difficile/norovirus/rotavirus/ova/parasites)
  - Issues are 1) potential for infection of others with pathogen and 2) multi-drug resistant organisms (eg VRE) which are excreted in larger volumes with diarrhoea
  - Cultures take >48hrs for faecal M/C/S & C.Diff. toxin
  - On weekends the cultures are not commenced until Monday, therefore results will take >48hrs
  - For patients being transferred from other hospitals, ideally faecal M/C/S, C diff toxin, viral PCR and culture for multi-drug resistant organisms can be performed prior to transfer to enable decision on isolation requirements on arrival at Trust.

Fig. 1: Management of immune checkpoint-inhibitor (ICPi) induced enterocolitis

Duration and dose of treatments

Infliximab – 5mg per kg at 0, 2 and 6 weeks (see Fig. 1 for dosing information if albumin is less than 32grams per Litre).

A single dose of 5 mg per kg might be sufficient to allow full resolution of symptoms, although up to 35% of patients might need a second dose because of symptomatic relapse or incomplete response, which should be administered within 2 weeks.

Some patients require additional doses, with the decision to administer further doses usually made based on the presence of ongoing symptoms. The value of repeat dosing, or the completion of standard induction regimens in patients with rapid symptom resolution, has not been established. This might be a particularly important issue in patients with high-risk endoscopic features, and especially in those with deep mucosal ulceration.

Vedolizumab – 300mg at 0, 2 and 6 weeks

Upadacitinib – 45mg prolonged-release tablet once daily for 8 weeks

References

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- UNPUBLISHED Case series (attached to proposal): Ibraheim, H. et al. Upadacitinib in refractory immune checkpoint inhibitor-induced colitis.

Document History

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