28 February 2020

Hazel Moore
Editor
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Dear Ms Moore,

RE: SHPA FEEDBACK ON THERAPEUTIC GUIDELINES: GASTROINTESTINAL

The Society of Hospital Pharmacists of Australia is the national professional organisation for more than 5,000 pharmacists, pharmacists in training, pharmacy technicians and associates working across Australia's health system. SHPA is committed to facilitating the safe and effective use of medicines, which is the core business of pharmacists, especially in hospitals.

SHPA is grateful for the opportunity to provide comments regarding Therapeutic Guidelines: Gastrointestinal, ahead of its revision for the next edition. This guideline is an essential reference for our members and our feedback has been informed by the SHPA's General Medicine, Surgery and Perioperative Medicine, Critical Care, Infectious Diseases, Women's and Newborn Health, Paediatrics and Neonatal, Medicines Information and Medical Specialties Speciality Practice Groups.

Gastric disorders

SHPA recommends inclusion of the appropriate duration of time prior to initiating second line therapy for the treatment of *H. pylori*, post failure of initial therapy.

SHPA notes that high levels of clarithromycin resistance in Australia were reported in a 2018 systematic review and meta-analysis in WHO region[1] and therefore suggest an investigation into the current resistance patterns to clarithromycin in Australia and necessary changes to the TG's recommendations accordingly. A means of reducing resistance may include consideration to prior clarithromycin use when choosing appropriate therapy. In response to concerns about resistance, some prescribers are moving to a two-week course of the first line therapy. Members would like further information on evidence for this regimen compared with a sequential or quadruple treatment course.

SHPA members recommend a discussion on the management of gastrointestinal bleeds in anticoagulated patients, commenting on the reduced risk of gastrointestinal bleeding with apixaban. This information is unlikely to fit in the Nonsteroidal Anti-inflammatory Drug (NSAID) induced ulcers section of the guidelines.

Functional gastrointestinal disorders

SHPA members indicate that there seems to be some confusion around the role of erythromycin in the treatment of gastroparesis. Information on this in the current version of the guidelines is inconclusive. More clarity is sought on this topic in the revised version of the guidelines, including safety concerns and considerations of usage and further information such as dosage and duration of treatment.

Small bowel disorders

SHPA recommends further clarity regarding the use of antibiotics in small bowel disorders. The current statement *"Antibiotics used in clinical practice include amoxicillin+clavulanate, cephalosporins,doxycycline, metronidazole and norfloxacin"* does not offer much guidance to clinicians. It is recommended that either a statement noting that evidence supporting their role is limited or an order of first/second/third line therapy is included in the revised version of the guidelines.

Inflammatory bowel disease (IBD)

Overview

SHPA notes that the link in the overview referring to consumer information leaflets on the Gastroenterological Society of Australia's website, needs to be updated to: https://www.gesa.org.au/resources/inflammatory-bowel-disease-ibd/

Introduction of immunomodulatory drugs used in IBD

SHPA recommends including newer agents in the list of immunomodulatory drugs used in IBD and associated guidance such as, golimumab, adalimumab, ustekinumab and possibly tofacitinib which is coming soon.

Pre-treatment screening and vaccination

Some members have indicated that it is protocol in their health service to also screen for human immunodeficiency viruses (HIV) serology, hepatitis C serology and cytomegalovirus (CMV) serology. SHPA recommends consideration is given to the relevance of these serologies prior to initiation of treatment.

SHPA suggests adding human papillomavirus (HPV) vaccination to the list of vaccinations given at the point of diagnosis of IBD.

Monitoring

SHPA recommends newer medicines to be added to the list such as golimumab and adalimumab to tumour necrosis factor (TNF) inhibitor agents.

Some members have noted that tacrolimus (oral/rectal formulation) is occasionally used for IBD. SHPA recommends review of evidence for this and relevance for inclusion in this section.

Monitoring of azathioprine and mercaptopurine

SHPA has been informed that in practice, thioguanine is at times offered as a treatment option to patients who have experienced pancreatitis.

SHPA members have noted that protocols for blood count monitoring when initiating thiopurine in their own practice, has been fortnightly rather than weekly with dose adjustments until target does is achieved. Once target dose is reached, full blood examination (FBE)/liver function tests (LFT's) and metabolites testing occurs 4-6 weeks later in order to check levels. Members have also highlighted that recent evidence proves that whilst slow up-titration is not necessary, it often improves tolerability and compliance.

Whilst macrocytosis and lymphopenia are common effects of these drugs and do not require cessation of therapy, there are certain times when myelosuppression is severe enough to warrant cessation. SHPA suggests adding guidance on this in the revised version of the guidelines.

SHPA members suggest that cervical cancer screening for women is to be completed along with a skin cancer check to detect early cancer.

Members have noted that the following sentence reads as though 6-MMP is an active metabolite, however it is inactive but related to hepatotoxicity. SHPA recommends rephrasing this sentence to reflect the true properties of 6-MMP: *'Azathioprine and mercaptopurine are thiopurine drugs that are metabolised to a number of inactive products and to active 6-thioguanine nucleotides (6-TGNs) and 6-methylmercaptopurine (6-MMP).'*

With regards to thiopurine methyltransferase (TPMT), SHPA recommends noting that these medicines can be used in patients with intermediate activity, often at reduced doses and that they are generally avoided in patients with low or undetectable activity.

Whilst low-dose allopurinol is sometimes added to the thiopurine to optimise therapy in patients who preferentially metabolise thiopurines to 6-MMP, SHPA members believe it is important to note that combination therapy should result in a dose reduction of thiopurine to a quarter or a third of the dose prior to the addition of allopurinol.

SHPA members have noted that it may be useful to include a statement indicating that the close monitoring of full blood examination (FBE)/liver function tests (LFTs) and metabolites testing, with the use of aminosalicylates can be safely used in combination with thiopurines despite interaction, as many patients are being advised to stop one of these treatments when they are prescribed together.

Ulcerative colitis (UC)

Members are seeking clarity on the appropriate dosage regimen for budesonide multimatrix system (MMX) used in the treatment of UC. Some members have noted that the regimen in practice is 9mg once daily for 4-8 weeks, and if weaning is required then reduced to 9mg every alternate day.

SHPA recommends including adalimumab and golimumab as treatment options under moderate to severe chronically active or frequently relapsing UC and also under UC maintenance therapy.

SHPA members would appreciate a discussion on the appropriateness of use of tacrolimus suppositories in patients refractory to standard therapy of proctitis, noting that this formulation in currently practice is requiring homemade preparations or the assistance of compounding pharmacies.

SHPA suggests highlighting that combination therapy with infliximab and another immunomodulatory drug is more effective than infliximab monotherapy as it increases infliximab levels and reduces the rates of auto-antibody formation as indicated in the SONIC study[2].

SHPA members have noted that the role and efficacy of methotrexate in IBD is limited, with benefits only seen in combination therapy used to reduce immunogenicity associated with concomitant use of infliximab as discussed in the *British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults*[3]. It is at times used in patients with arthralgia extra-intestinal manifestation or concurrent arthritis diagnosis, but otherwise no indication in UC.

If the optimal dosage regimen for infliximab used in acute severe colitis has been determined, SHPA members would appreciate the inclusion of this information in the revised version of the guidelines. Whilst higher doses such as 10mg/kg are commonly used in practice, evidence has not yet proven benefit of this versus 5mg/kg doses[4].

SHPA members note that specialist centres may dose more frequently than standard regimen in conjunction with monitoring of drug levels e.g. infliximab higher doses and/or given 6-weekly or 4-weekly, vedolizumab 4-weekly and adalimumab higher doses – up to 80mg weekly. Members have also highlighted that at times higher doses are used as re-induction when loss of response has occurred due to subtherapeutic drug levels.

Members have identified the need for a discussion on the role of tofacitinib in patients who have failed standard biological therapy for the treatment of moderate-severe UC. Comments on the role of tofacitinib induction and maintained therapy and the use of dose escalation to recapture repose in patients who have initially responded to tofacitinib but have subsequently lost response, would be a valuable addition to the revised guidelines.

Crohn Disease

SHPA recommends consistent phrasing is used within this section in relation to when antibiotics should be used i.e. *'confirmed infection'* or *'transmural complications (e.g. abscess, complex fistula).'*

SHPA members recommend adding ustekinumab for induction and maintenance therapy of Crohn disease along with infliximab.

For maintenance with biologic agents, SHPA suggests including a similar phrase to that used in UC regarding the combination therapy with infliximab (and to some extent adalimumab) with another immunomodulatory drug, explaining that it may be required and as mentioned above, is more effective as proven in the SONIC study.

Also, as recommended above, SHPA recommends noting in the UC maintenance therapy section, that specialist centres may dose more frequently than standard regimen in conjunction with monitoring of drug levels e.g. infliximab higher doses and/or given 6-weekly or 4-weekly, vedolizumab 4-weekly and adalimumab weekly.

SHPA members believe it is important to include a brief discussion on the role of biosimilars highlighting that biosimilar products used should be documented and not interchanged unless approved by the prescriber.

Current recommendations are for the use of either metronidazole or ciprofloxacin in the treatment of active perianal Crohn disease. SHPA members advise that treatment regimens using both metronidazole and ciprofloxacin in combination are being prescribed in practice and would like clarity on the appropriateness of this practice in the next edition.

Fertility and pregnancy

SHPA recommends reviewing the latest evidence regarding the use of vedolizumab in pregnancy for the revised guidelines and notes that tofacitinib is contraindicated in pregnancy.

SHPA members would appreciate a discussion on breastfeeding in IBD as this seems to be a common query they are faced with by both clinicians and patients.

General comments on IBD

SHPA members request consideration to be given to the appropriateness of including a new section on therapeutic drug monitoring. Whilst this is still an area of development in the IBD cohort, hospital pharmacists note its use is increasing and the role of proactive monitoring of drug levels (in particular TNF) is significant in the optimisation of patient clinical care.

Clostridium difficile (C.Difficle) is prominent in the management of IBD. SHPA members would value a discussion on the management of this infection to be included in the updated version of the guidelines.

Iron deficiency

SHPA recommends adding new intravenous iron product – ferric derisomaltose (Monofer) to the list of iron supplements. Advantages of this product is that it can fully replace iron stores (higher doses as with polymaltose) in one single infusion.

Preparation for gastrointestinal procedures

SHPA suggests including a suggested dosing regimen for lavage solutions.

SHPA members request a discussion indicating when it is recommended to restart non-vitamin K antagonist oral anticoagulants (NOACs) and other blood thinning agents such as clopidogrel post gastrointestinal procedures.
SHPA suggests referring clinicians to the existing section for the management of patients with diabetes, when reading the 'other regular medications' section.

SHPA members request the inclusion of recommendations for the periprocedural management of type 2 diabetes in the special situations section of the guidelines.

SHPA recommends reformatting information on withholding of medicines to include a table of medication, risk of bleed and associated recommendation.

Whilst we acknowledge that there may be slight variations between practices, SHPA members believe it would be useful to include a guide of a standard bowel preparation dose.

We hope this feedback is valuable and thank you again for the opportunity to provide it. If you have any queries, please do not hesitate to contact Johanna de Wever, General Manager, Advocacy and Leadership on jdewever@shpa.org.au.

Yours sincerely,

Kristin Michaels

Chief Executive

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[1] Savoldi A et al. *Prevalence of Antibiotic Resistance in Helicobacter pylori: a systematic review and meta-analysis in WHO regions.* Gastroenterology. 2018; 155: 1372-1382)
[2] Colombel JF et al. *Infliximab, azathioprine, or combination therapy for Crohn's Disease.* NEJM 2010; 362: 1383-1395
[3] Lamb et al. *British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults;* GUT sept 2019
[4] Choy et al. *Systematic Review and Meta-analysis: Optimal Salvage Therapy in Acute Severe Ulcerative Colitis*, IBD July 2019

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