AWTTC
All Wales Therapeutics & Toxicology Centre
Canolfan Therapiwteg a Thocsicoleg Cymru Gyfan

One Wales Medicines Assessment Group (OWMAG)

Minutes of the Teams meeting held Monday 19 August 2024

Members in attendance
John Watkins, Consultant in Public Health, OWMAG Chair
Tim Banner, Clinical Director Pharmacy & Medicines Management, representative Cardiff and Vale
Sue Beach, Lead Clinical Development Pharmacist, deputy representative Hywel Dda
Anthony Cadogan, Deputy Chief Pharmacist, representative Velindre
Joe Castle, Operations Manager, ABPI Cymru Wales
Laurence Gray, Consultant Clinical Pharmacologist/AWPAG representative
Will Hardy, Research Fellow, Bangor University, Health Economist
Kathryn Howard, Head of Pharmacy, Royal Glamorgan Hospital, representative Cwm Taf Morgannwg
Malcolm Latham, Community Health Council, Lay representative
Craig Roberts, Assistant Director of Therapies and Health Science, deputy representative Aneurin Bevan

AWTTC
Clare Elliott, Senior Appraisal Scientist
David Haines, Medical Writer
Carolyn Hughes, Medical Writer
Laura Phillips, Admin Supervisor
Sara Pickett, Principal Health Economist
Gail Woodland, Senior Appraisal Pharmacist

Clinical experts
Dr Ricky Dylan Frazer, Consultant Clinical Oncologist, Velindre Cancer Centre
Dr Carey Macdonald-Smith, Associate Specialist Medical Oncologist, Betsi Cadwaladr

Patient organisation representative
Jackie Hodgetts, Melanoma Focus Helpline Support Manager & Nurse Clinician at the Christie Hospital in Manchester

List of Abbreviations:

ABPI	Association of the British Pharmaceutical Industry
AWTTC	All Wales Therapeutics and Toxicology Centre
ESR	Evidence Status Report
IPFR	Individual Patient Funding Request
NICE	National Institute for Health and Care Excellence

NMG	New Medicines Group
OWMAG	One Wales Medicines Assessment Group

1. Welcome and Introduction

The Chair opened the meeting and welcomed members.

2. Apologies

William King, Consultant in Public Health, representative Powys
Michael Thomas, Consultant in Public Health Medicine, representative Hywel Dda
Leo Pinto, Consultant in Public Health, representative Aneurin Bevan
Stuart Wynne Evans, Head of Medicines Governance and Optimising Medicines Value, representative Swansea Bay
Amy Jayham, Head of Pharmacy Operations, deputy representative Swansea Bay
Eilir Hughes, Assistant Medical Director, representative Betsi Cadwaladr

3. Declarations of Interests/Confidentiality

The Chair reminded members that all OWMAG proceedings are confidential and should not be disclosed outside of the meeting. Members were reminded that declarations of interest and confidentiality statements are signed by each member on an annual basis. The Chair invited any declarations of interest; there were none.

4. Reassessment 1

Infliximab for the treatment of immune checkpoint inhibitor induced grade 2-4 enterocolitis

Clare Elliott explained that this was a reassessment of a current One Wales recommendation to extend the indication covered. She presented an overview of the clinical background information pertinent to both assessments before presenting an overview of the key clinical effectiveness aspects of the infliximab evidence status report (ESR).

The Chair introduced the clinical experts, Dr Ricky Frazer, Consultant Clinical Oncologist and Lead for the Immunotherapy Toxicity Service for South East Wales, Velindre Cancer Centre and Dr Carey Macdonald-Smith, Associate Specialist Medical Oncologist and Immunotherapy Lead, Betsi Cadwaladr. The Chair described the role of the clinical expert as an invited observer of the OWMAG meeting to answer questions and input into discussions to enable members to gain a better understanding of the clinical context. The Chair highlighted that clinical experts were nominated by their specialist group or network and should not express personal opinion or promote the use of a medicine. The Chair invited any declarations of interest from the clinical experts; there were none.

The Chair opened general discussion relating to the clinical effectiveness of infliximab and invited OWMAG members to ask the clinical experts questions on the use of infliximab for the expanded indication being assessed. One query was about the proportion of patients who were able to resume their ICI cancer treatment after

their ICI-induced enterocolitis was successfully resolved through treatment with either infliximab or vedolizumab. Dr Frazer explained that about 90% of patients with grade 2 enterocolitis would be able to be rechallenged with ICIs after treatment with infliximab or vedolizumab compared to about 25% to 33% of patients with grade 3 enterocolitis and this is one of the reasons why treating patients with grade 2 before they progress to stage 3 disease is preferable. Dr Macdonald-Smith agreed with this and also added that refractory grade 2 patients are likely to receive steroids for longer than 12 weeks which means that rechallenge with an ICI is not possible; using infliximab or vedolizumab means that steroids can be discontinued quicker and therefore increases the likelihood of ICI-treatment rechallenge. The experts also confirmed that the majority of patients with grade 2 enterocolitis insufficiently responsive to corticosteroids would progress to stage 3 disease without alternative treatment options. They also highlighted a group of patients who, although responsive to higher doses of corticosteroids (i.e. 60-70 mg daily), have a re-flare of their enterocolitis as soon as reduction in steroid dosing (i.e. to 30-40 mg daily) is attempted and so require resumption of high dose steroids; this cycle of decreasing and increasing steroid dosing can go on for several weeks. Dr Macdonald-Smith stated that patients can only be rechallenged with ICIs if they are on less than 10 mg per day of steroids and the negative impact relapsing and remitting enterocolitis has on quality of life for these patients. Both clinical experts outlined the importance of the steroid-sparing potential of both infliximab and vedolizumab and highlighted the number of significant risks associated with prolonged steroid use in these patients including opportunistic infections which may need admittance to hospital for treatment, other side effects some of which may be irreversible and the impact on resources as patients on high-dose steroids need to remain under the care of immunotherapy toxicity clinics for longer for regular review, blood sugar monitoring and prophylaxis treatment.

Dr Frazer also provided more context as to why dose escalation of infliximab to 10 mg/kg would be a valuable option for some patients. In addition to those with very severe colitis who may respond better to a higher dose, he explained that there is a relationship between the effectiveness of infliximab and serum albumin levels, with infliximab less effective in patients with low albumin. Such patients have been observed to respond better to a higher dose of infliximab in clinical practice and this is also reflected in gastroenterology clinical guidelines for the treatment of chronic inflammatory bowel disease with infliximab. A group member queried whether the clinical experts had come across the development of infliximab antibodies in any patients they had treated. Both indicated that they hadn’t in their clinical experience of using infliximab although they acknowledged that this was a documented risk in the use of infliximab.

The group asked for comment on whether the number of patients requiring treatment for ICI-induced enterocolitis may change in the future as immunotherapy treatment options for cancer increase. Dr Macdonald-Smith agreed that more immunotherapy treatments are becoming available and a lot of patients receiving them are expected to go on to surgery and curative treatments, and so the management of side-effects

with infliximab and vedolizumab may be expected to increase. Dr Frazer agreed that an increase in use of these medicines would be expected although stated that the number of new indications for immunotherapy cancer treatments is starting to slow. However, he pointed out that enterocolitis is a predictable and well-known side effect of these treatments for a proportion of patients and that the management of these side effects is an important factor in being able to offer immunotherapy cancer treatments.

The clinical experts were asked how a patient with grade 2 enterocolitis was deemed to be unresponsive to corticosteroids in practice. The clinical experts indicated that these are patients whose diarrhoea has not responded and who are becoming more unwell despite being on steroids; additionally, if a colonoscopy or sigmoidoscopy show the presence of ulceration, 70% of such patients, even if grade 2 by CTCAE criteria, will not respond to steroids. Markers such as faecal calprotectin are also monitored to track progression of inflammation and response to steroids.

The impact of progression from grade 2 to grade 3 enterocolitis on hospitalisation rates was queried by the group. Both clinical experts agreed that, due to the availability of infliximab and vedolizumab for grade 3 enterocolitis, increasingly most patients can be managed in day units as symptom response (especially for infliximab) is usually within 24 hours. Patients who are typically admitted for grade 3 are on high dose steroids and will be scoped and then screened for latent viral infections before commencing on infliximab. Some patients may be admitted to hospital for supportive therapies such as rehydration.

It was queried whether any future licensed treatments for ICI-induced enterocolitis have been identified through horizon-scanning or other information routes. AWTTC and the clinical experts confirmed that they weren’t aware of any potential new licensed treatments in the pipeline.

Finally, the group asked for clarification on access via local agreements to infliximab for grade 2 enterocolitis. It was confirmed by the clinical experts that these were only in some health board areas and were not formally established routes of access.

Sara Pickett presented an overview of the key aspects of the infliximab health economics. She confirmed that no published cost-effectiveness evidence was available for infliximab for the extended indication and presented the results of a cost consequence analysis undertaken by AWTTC. The conclusion of this was that there was insufficient evidence to inform a decision on cost-effectiveness. The Chair opened discussion on cost-effectiveness and noted that the longer-term impact of a patient being able to resume their cancer treatment and thus increasing the possibility of durable outcomes was not captured in the cost consequence analysis. This was confirmed by Sara who also acknowledged that the statements made earlier by the clinical experts in that the vast majority of patients with grade 2 enterocolitis treated with infliximab would be rechallenged with ICIs and that nearly all patients with grade 2 unresponsive to steroids would progress to stage 3 would

also have an impact on the threshold analysis presented. Will Hardy, OWMAG health economist, asked the clinical experts whether the quality of life decrements used in the cost consequence analysis and derived from patients with ulcerative colitis (UC) and Crohn's disease (CD) were an appropriate proxy to use for patients with ICI-induced enterocolitis. Both clinical experts agreed that it was important to differentiate ICI-induced colitis, which is acute and reversible, from UC and CD, which are chronic and lifelong and thought that the likely expected gain in benefits would be higher for patients with ICI-induced enterocolitis.

The Chair invited Clare Elliott to present the budget impact estimates; no issues relating to this were raised by the group. Clare then presented key aspects of patient impact and experience highlighting the impact of enterocolitis and also high dose/long term use of steroids on patient quality of life.

The Chair introduced the patient organisation representative Jackie Hodgetts, Melanoma Focus Helpline Support Manager and a Nurse Clinician at the Christie Hospital in Manchester. The Chair described the role of the patient organisation representative to attend meetings and observe proceedings, answer questions and input into discussion to give a better understanding from a patient and carer perspective. The Chair invited any declarations of interest from the patient organisation representative; there were none.

The Chair invited the patient organisation representative to give an overview of the patient and carer perspective. Jackie explained that grade 2 enterocolitis can have a significant impact on quality of life with patients generally unable to work and being sleep deprived as the diarrhoea tends to happen in the early hours of the morning. Patients often have malnutrition and chronic dehydration and experience chronic weight loss and lethargy; although these wouldn't necessarily require admission to hospital, they have a detrimental impact on the performance status of a patient. Additionally, long-term steroid use can lead to adrenal insufficiency in a proportion of patients which requires specialist referral to endocrinology for long term management. Elderly patients also have problems mobilising again after long term steroid use. Jackie emphasised the importance of being able to resolve enterocolitis quickly so that patients can resume ICI treatment promptly as it can't be restarted if the break in treatment is longer than 12 weeks.

The Chair opened discussion on the patient and public perspective. The lay representative, Malcolm Latham, commented on the possibility of patients be able to achieve remission from their cancer if their cancer treatments can be restarted after their enterocolitis has been resolved and so highlighted the real benefit treatment with infliximab would bring to these patients. He also highlighted the comparative low cost of this treatment per patient.

The Chair invited discussion on any outstanding wider societal and health and social care issues. No questions were raised.

5. Reassessment 2

Vedolizumab for the treatment of immune checkpoint inhibitor induced grade 2-4 enterocolitis

Clare Elliott presented key aspects specific to the vedolizumab evidence status report. She explained that this was a reassessment of a current One Wales recommendation to extend the indication covered.

The Chair reminded members that, although both medicines are for very similar indications they are separate considerations and that they are judged on their individual merit.

The Chair invited the clinical experts, Dr Ricky Frazer and Dr Carey Macdonald-Smith for any additional comment on the clinical effectiveness to that already discussed and specific to vedolizumab. Both agreed that because of its gut specific immunosuppressive effects, vedolizumab tends to be better tolerated than infliximab especially in elderly patients but that the arguments for vedolizumab were similar to those for infliximab. No further questions on clinical effectiveness were raised.

Sara Pickett presented an overview of the key aspects of the vedolizumab health economics. She confirmed that there were no studies on cost effectiveness and a cost consequence analysis undertaken by AWTTC. The conclusion of this was that there was insufficient evidence to inform a decision on cost-effectiveness.

The Chair invited Clare Elliott to present the budget impact estimates; no issues relating to this were raised by the group. Clare then presented key aspects of patient impact and experience which were the same as for the infliximab reassessment.

The Chair opened discussion on the patient and public perspective. The patient organisation representative and lay representative highlighted that the arguments for vedolizumab were similar to those for infliximab and no additional points were raised.

The Chair asked the clinical experts and patient organisation representative if there were any additional points they wished to make, there were none. The clinical experts and patient organisation representative were thanked and left the meeting.

The Chair asked the group if there were any outstanding issues that required discussion before the vote was opened for the infliximab reassessment. The OWMAG recommendation to go to the All Wales Medicines Strategy Group (AWMSG) for endorsement was agreed:

Date of advice: Monday 19 August 2024

Using the agreed starting and stopping criteria infliximab can be made available within NHS Wales for the treatment of:

- immune checkpoint inhibitor (ICI) induced grade 2-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids
- ICI-induced grade 2–4 enterocolitis in patients who are corticosteroid-dependent requiring multiple challenges with corticosteroids
- ICI-induced grade 2-4 enterocolitis in patients requiring dose escalation to 10 mg/kg when there has been an inadequate response to standard 5 mg/kg dosing

Infliximab should be prescribed on the basis of lowest acquisition cost.

The Chair asked the group if there were any outstanding issues that required discussion before the vote was opened for the vedolizumab reassessment. The group noted that for grade 2 enterocolitis, vedolizumab is the preferred treatment option over infliximab in ESMO guidelines. The group noted the difference in cost of the two treatments and discussed the lack of data on the comparative benefits of each versus cost and agreed that vedolizumab and infliximab should be placed at the same point in the pathway as options for the treatment of grade 2 enterocolitis. The vote was opened for the vedolizumab reassessment and the OWMAG recommendation to go to the All Wales Medicines Strategy Group (AWMSG) for endorsement was agreed:

Date of advice: Monday 19 August 2024

Using the agreed starting and stopping criteria vedolizumab can be made available within NHS Wales:

- for the treatment of immune checkpoint inhibitor (ICI) induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids and infliximab or when infliximab is unsuitable
- for the treatment of ICI-induced grade 3–4 enterocolitis in patients who are corticosteroid-dependent requiring multiple challenges with corticosteroids when symptoms have not responded to infliximab or when infliximab is unsuitable
- as an option for the treatment of ICI-induced grade 2 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids or in patients who are corticosteroid-dependent requiring multiple challenges with corticosteroids

The Chair thanked the group and closed the meeting at 11.30.