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 20 March 2023

Members in attendance:
Andrew Champion, Assistant Director, Evidence Evaluation, representative WHSSC, Deputy OWMAG Chair
Timothy Banner, Clinical Director Pharmacy and Medicines Management, representative Cardiff and Vale
Alan Clatworthy, Clinical Effectiveness and Formulary Pharmacist, representative Swansea Bay
Joe Ferris, Operations Manager, ABPI Cymru Wales
Teena Grenier, Medicines Governance Lead, representative Betsi Cadwaladr
Kathryn Howard, Head of Pharmacy, Royal Glamorgan Hospital, representative Cwm Taf Morgannwg
Malcolm Latham, Community Health Council, Lay representative
Berni Sewell, Senior Lecturer, Health Economist, Swansea University
Jonathan Simms, Clinical Director of Pharmacy, representative Aneurin Bevan
Michael Thomas, Consultant in Public Health, representative Hywel Dda

AWTTC:
Clare Elliott, Senior Appraisal Scientist
David Haines, Medical Writer
Gail Woodland, Senior Appraisal Pharmacist
Laura Phillips, Admin Supervisor
Rosie Spears, Senior Appraisal Scientist

Clinical expert:
Dr Marguerite Hill, Consultant in Neurology, Swansea Bay UHB

Observer(s):
Sara Pickett, AWTTC Health Economist

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
WHSSC	Welsh Health Specialised Services Committee

1. Welcome and Introduction
The Chair opened the meeting and welcomed members.

2. Apologies
John Watkins, Consultant in Public Health, OWMAG Chair
William King, Consultant in Public Health, representative Powys

Hywel Pullen, Assistant Director of Finance, Cardiff and Vale, representative Finance Directors
James Coulson, Clinical Pharmacologist, Cardiff and Vale
Richard Hain, Consultant in Paediatric Palliative care, representative Cardiff and Vale
Bethan Tranter, Chief Pharmacist, representative AWPAG/Velindre
Ian Campbell, Hospital Consultant CAV, representative NMG
Karen Samuels, AWTTC

3. Declaration 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. Endorsement

The Chair informed the group of endorsements received from Chief Executive Management Team since the last OWMAG meeting.

From the November 2022 meeting:

- Infliximab for immune checkpoint inhibitor induced (ICI) enterocolitis
- Vedolizumab for ICI induced enterocolitis

From the December 2022 meeting:

- Infliximab for refractory pulmonary sarcoidosis
- Vedolizumab for inflammatory bowel disease in children
- Ustekinumab for inflammatory bowel disease in children

5. Re-Assessment
Rituximab for the treatment of myasthenia gravis in adults

The Chair welcomed clinical expert, Dr Marguerite Hill, Consultant in neurology, Swansea Bay UHB. 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 provided an overview of the order of considerations for the meeting.

Clare Elliott presented an overview of the key aspects of the rituximab evidence status report.

The Chair invited the clinical expert, Dr Marguerite Hill, to give an overview of the disease and experience of using rituximab as a first line treatment. The clinical expert explained that she had only used rituximab as fourth line treatment for myasthenia gravis (MG) as per current One Wales advice. She explained that these patients would have been diagnosed with MG for at least

four years to have cycled through current lines of treatment. For example, azathioprine can take up to 18 months to have a positive effect on MG. She also described the typical course of the disease to be 'front heavy' with the first year being particularly 'bumpy', often requiring repeated hospital admissions. The opinion of neurologists treating MG is that the earlier the treatment with rituximab, the sooner patients were more likely to benefit. She also highlighted the hidden costs of adverse effects associated with long term, high-dose steroids including increased risk of fractures, cataracts and diabetes.

To date the clinical expert and her colleagues have not had opportunity to prescribe rituximab as a first line treatment. Additional resources are associated with the administration of rituximab including chair time and a nurse to carry out the infusion.

The Chair asked about use of a new medicine, efgartigimod that is now being appraised by NICE, and what impact will this have on the potential patient pathway for these patients? The clinical expert explained that it is unclear at the moment but is likely to be a significantly more costly treatment than rituximab and is administered as four infusions over the course of eight weeks. When compared with rituximab, which is administered once every six to twelve months, rituximab may be more attractive to patients. Although the first dose of efgartigimod would be administered in hospital, subsequent doses can be administered at home by nurses funded by the marketing authorisation holder. The other medicine in the pipeline, ravulizumab, is also likely to be more costly and the clinical expert expects the treatment criteria for both medicines are likely to be more restrictive.

The Chair opened discussion on clinical effectiveness to the group. The group asked for clarity about the place in therapy of efgartigimod. Dr Hill agreed that it would be reserved for refractory disease rather than first line. The group asked if the use of rituximab first line would lower the number of potential patients who would go on to require treatment with efgartigimod. The clinical expert was unable to provide a view on this as there is not enough experience yet of first line rituximab treatment. However, she would like to think that use of rituximab first line would help prevent disease becoming established.

The group then asked how potential candidates for first line treatment with rituximab would be identified. Dr Hill explained that younger patients (under 45 years) would be offered thymectomy and therefore would expect to be excluded. There is no definitive way of identifying patients who have particularly troublesome disease as there is poor correlation between disease manifestation and antibody titre levels.

The group asked the assessment lead about the validity of secondary endpoints in the Rinomax study, particularly with respect to the dropout rate in the placebo arm and Quality of Life (QoL) over such a short follow up time period. Clare Elliott agreed that the secondary endpoints had not been met and the QoL results suggested an improvement in the rituximab group although the change was not significant. She informed the group that she had been in contact with the author of the Rinomax study however no further follow up data are available

at present. A registry is used in Sweden (where the Rinomax study took place) for MG patients and they are looking at opportunities to publish these data which would include the Rinomax group. Dr Hill postulated that the high dropout rate in the placebo group receiving steroids alone would make it difficult to assess a difference between the two treatment arms. Although she did agree that some patients do respond well to steroid treatment and no treatment escalation is required.

The Chair asked the clinical expert about the dosing regimen and numbers of patients who would be expected to require repeated doses of rituximab. Are the estimates provided in the evidence status report (ESR) with all patients receiving a second dose reasonable? Dr Hill suggested that in some observational studies patients, on average, required 1.2 low dose infusions per year. The Chair asked about long-term outcomes. The clinical expert has no long-term data (published or anecdotal) but anticipates data will become available in newer papers. Clare Elliott and Gail Woodland explained that the author of the Rinomax paper will be using data from their patient registry to report on long term outcomes. The scenarios provided in the ESR give an estimated range of possible patient numbers. Patients may go on to receive thymectomy after which they would not receive further doses of rituximab or patients may respond and relapse six to twelve months after the first dose and go on to receive additional doses. Both models expect that patients who receive four doses of rituximab will continue to receive doses every 6 months. Dr Hill mentioned the origin of the lower, 500 mg, dose regimen. The Rinomax study was conducted in Sweden where they have experience of using the lower dose for multiple sclerosis and there are good observational data to support the lower dose. She suggested that the lower dose may be associated with a lower risk of adverse events but there are no data as yet to support this.

Berni Sewell presented an overview of the cost effectiveness evidence.

Berni Sewell reported that no cost effectiveness models were available. A cost consequence analysis, based on the Rinomax trial and the observational study, had been provided in the ESR. Using data provided in the clinical trial and observational study the health economist suggested that use of first line rituximab would be likely to fall in the more effective and less costly quadrant of the cost-effectiveness plane. However, this was subject to significant uncertainty with a lack of robust clinical trial data.

The Chair opened discussion on cost effectiveness. Dr Hill highlighted that participants in the Rinomax trial were allowed to receive rescue treatment during the first eight weeks of the trial. She was keen to stress that when someone is first diagnosed it is often in an emergency situation and may require admission to intensive care or receive plasma exchange. Rituximab would be used to prevent the recurrent relapses, particularly in the first year after diagnosis. The Chair highlighted that the main cost saving is driven by the cost of intravenous immunoglobulin (IVIG), is this realistic? Dr Hill agreed that it was their first treatment strategy and costs are very high. She also mentioned that in Swansea Bay University Health Board they have facilities to administer peripheral plasma exchange, which is less costly than central administration but

this is the only health board in Wales with this capacity. Berni Sewell asked about the patient numbers included in appendix one which were based on the trial data. No patients in the rituximab group received IVIG whilst 14 of the control group did. Dr Hill agreed that there is considerable uncertainty around these numbers.

The group asked about the number of patients currently requiring repeated admission to hospital and the estimate of 50 eligible patients in Wales. Dr Hill estimated that in Swansea Bay there were approximately three to four patients with repeated attendance. The estimate for Wales derived from discussions with colleagues and is likely to be between 40 to 50 patients.

The Chair asked the health economist for an estimate of the cost effectiveness beyond one year. Berni Sewell stated that it is very difficult to estimate as the number of patients requiring different number of repeat doses is unknown. Dr Hill reiterated the potential long-term costs associated with steroid use which had not been factored into the budget impact.

The Chair opened discussion on the budget impact and invited Gail Woodland to comment. She pointed out that NHS reference costs and NHS Wales contract pricing for medicines had been used to provide the most realistic estimate of budget impact. The upper estimate of patient numbers had been used to avoid underestimating potential costs for the treatment. It was confirmed that there is no registry for MG patients in Wales to record data and provide a better idea as to the frequency and number of rituximab infusions required by patients. Gail Woodland agreed that it would be useful to have this data for the One Wales review to feedback to OWMAG. Collection of outcome data will be discussed outside of the meeting.

The Chair opened discussion on the patient and public perspective. The lay representative, Malcolm Latham, suggested that the potential for rituximab to relieve symptoms and require fewer interventions and hospitalisations would be welcomed by patients. He highlighted that patients are concerned about taking steroids for the long term and the associated side effects, so reduction or discontinuation of steroid use would be welcomed. A reduction in hospital attendances is another important factor for patients and their families who may worry about the associated costs in both time and money. Patient with this condition may still be in employment, an effective treatment with fewer relapses and hospital attendances would benefit their working life.

The clinical expert was thanked and left the meeting. The Chair summarised the mornings' discussions and asked the group if there were any other points to raise. The ABPI representative wanted to clarify what would happen to advice if one of the newly licensed medicines for MG became available through Health Technology Appraisal. Gail Woodland informed the group that it is not yet currently known where the new medicines will sit in the treatment pathway. If one of the medicines did get recommended for first line use then this would be used in preference to rituximab as a suitable licensed alternative. She also reminded the group that there was still the One Wales advice for the use of rituximab as fourth line and above at the higher dose which is an option for

refractory patients. It may be that this option is reserved for patients who do not respond to the new medicines or those patients who are already receiving alternative treatments for MG.

The Chair closed discussion and invited members to vote:

Date of advice: Monday 20 March 2023

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

- as a first-line add-on treatment for generalised myasthenia gravis in adults;
- as a fourth-line or later treatment option for refractory generalised myasthenia gravis in adults.

6. AOB

Gail Woodland informed members that there will not be an OWMAG meeting in April.