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

Infliximab for the treatment of immune checkpoint inhibitor induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids (OW21)

February 2023

ONE WALES INTERIM DECISION

Infliximab for the treatment of immune checkpoint inhibitor induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids

The following One Wales Medicines Assessment Group (OWMAG) recommendation has been endorsed by health board Chief Executives.

Using the agreed starting and stopping criteria, infliximab can be made available within NHS Wales for the treatment of immune checkpoint inhibitor induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids.

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

The risks and benefits of the off-label use of infliximab for this indication should be clearly stated and discussed with the patient to allow informed consent. Providers should consult the relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

This advice will be reviewed after 12 months or earlier if new evidence becomes available.

Clinician responsibility
Clinicians will be obliged to collect and monitor patient outcomes. Evidence of clinical outcomes will be taken into consideration when reviewing the One Wales Medicines Assessment Group decision.

Health board responsibility
Health boards will take responsibility for implementing One Wales Medicines Assessment Group decisions and ensuring that a process is in place for monitoring clinical outcomes.

One Wales advice promotes consistency of access across NHS Wales.

Starting and stopping criteria for infliximab for the treatment of immune checkpoint inhibitor induced grade 3-4 enterocolitis after corticosteroids

Developed in collaboration with Velindre Cancer Centre.

Starting criteria:
Patients with severe or life threatening (grade 3/4) diarrhoea or colitis with **any** of the following symptoms/features present:

- 7 or more stools/day over baseline
- Severe abdominal pain
- Fever
- Dehydration
- Blood or mucus in stool
- Flexible sigmoidoscopy indicates presence of high-risk endoscopic features, mucosal ulceration or extensive colitis
- Colostomy patients

And symptoms are persisting for three or more days despite high dose methylprednisolone (1-2mg/kg/day)

Screening
Prior to commencing infliximab, pre-screening should be undertaken to exclude:

- Active or latent tuberculosis
- Hepatitis virus or HIV
- Current acute infections (viral, bacterial, fungal or parasitic)
- Moderate to severe heart failure (NYHA class III/IV)
- Gastrointestinal perforation

Patients with high tumour disease burden, those who are frail or elderly or where there is a contra-indication to the use of inflximab should be discussed with gastronterology and reviewed by Immunotherapy toxicity service and consideration given to using an alternative treatment option, which may include vedolizumab. This will be (see One Wales advice for vedolizumab).

Dose
The recommended treatment dose regimen for infliximab is 5 mg/kg by intravenous infusion on weeks zero, two and six. Not all cases will require three doses, treatment can be stopped before completing the course if there is sufficient response after the first or second dose however standard treatment is 3 doses.

Outcome data, including the number of doses used should be collected to inform future policy changes.

Only one course (three doses) may be issued in accordance with this advice. Requests for repeat courses or continuing treatment beyond three doses should be

explored through funding mechanisms such as the individual patient funding request process.

The infliximab product available at the lowest acquisition cost should be prescribed.

Once infliximab has been given switch to oral prednisolone and wean as per local steroid taper guidelines.

Monitoring

- Infusion-related reactions including anaphylactic shock
- Injection site for signs of phlebitis
- Daily stool chart
- Daily bloods e.g., FBC, U&E, LFTs, CRP
- Blood cultures if pyrexial
- National Early Warning Score (NEWS) assessment
- Fluid balance
- Faecal calprotectin

Prescribers should consult the relevant Summary of Product Characteristics (SmPC) for any additional monitoring requirements and potential adverse effects.

Stopping criteria:

- Treatment failure, progression of symptoms or minimal response
- Toxicity to treatment (that cannot or does not respond to temporary treatment interruption)
- Patient request

For patients who develop hepatotoxicity during treatment (alanine aminotransferase [ALT] increases or aspartate aminotransferase [AST] increases at or above 5 times the upper limit of normal), treatment should be discontinued.

Failure to respond to infliximab:
If there is no response or symptoms are deteriorating after one, two or three doses of infliximab then consider switching to vedolizumab with advice from Gastroenterology and/or consultant leads from Immunotherapy toxicity service.

Reference:
Merck Sharp Dohme. Infliximab (Remicade) 100 mg powder for concentrate for solution for infusion. Available at: https://www.medicines.org.uk/emc/product/3831/smpc. Accessed 14 December 2022

One Wales Medicines Assessment Group summary of decision rationale

Medicine: **infliximab**
Indication: **for the treatment of immune checkpoint inhibitor induced grade 3 4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids**
Meeting date: **28th November 2022**

Criteria	OWMAG opinion
Clinical effectiveness	OWMAG note that although diarrhoea and colitis are considered separately within the National Cancer Institute's Common Terminology Criteria for Adverse Events tool, for the purposes of this assessment the British Socity of Gastroenterology definition of ICI induced enterocolitis should be used. OWMAG note that the main clinical effectiveness evidence is from a number of retrospective studies and two network meta-analyses (NMAs). When reported, the group note that infliximab dosage used was consistent with that recommended in national and international guidelines while dosing schedule frequency varied with generally no more than three doses received. The majority of studies demonstrated clinical benefit in terms of enterocolitis symptom improvement. Both NMAs found infliximab to be relatively effective in terms of disease response, taking significant study heterogeneity into consideration. OWMAG note the anecdotal evidence provided by clinical experts reporting positive clinical outcomes for patients they had treated with infliximab. OWMAG considers that the evidence provided demonstrated clinical effectiveness.
Cost-effectiveness	No cost-effectiveness evidence was presented. However, OWMAG acknowledged that that their may be additional cost savings for infliximab in terms of the potential for earlier discharge from hospital and a reduction in the number of future hospitilisations as well as less need for more costly interventions such as surgery. There were potential health related benefits for patients in terms of reducing the amount and length of steroid courses (and the side effects associated with steroid use), reducing the need for invasive surgery and improving symptom control, thereby improving quality of life.
Budget impact	OWMAG considers the clinical estimate of patient numbers reported to be subject to uncertainty and may be a conservative estimate.

	The group note that mortality rates and additional screening and monitoring for bacterial, viral and fungal infections and adverse event costs have not been included in the budget impact. OWMAG consider that the budget impact of infliximab may be lower due to costs saved with a reduction in length and number of hospital stays. OWMAG acknowledge that a proportion of patients with ICI induced enterocolitis in Wales are, already receiving infliximab through local agreement routes. Also, as ICI usage grows, it is acknowledged that patient numbers are anticipated to double over the coming years, resulting in additional budgetary impact in Wales. OWMAG consider that the base case provided in the report is a reasonable estimate of the associated cost to NHS Wales.
Other factors	As usage of ICIs increases, incidence of immune-related adverse events such as enterocolitis will also increase. OWMAG considers that ICI treatment for malignancies will not be a viable option if clinicians are unable to treat this associated toxicity. OWMAG consider the effect of infliximab on the quality of life of the patients to be positive, in particular with respect to the reduction in hospital stays and improvement or resolution of debilitating symptoms. OWMAG noted the concerns of patients in terms of being able to go out due to worries over access to toilets and risk of incontinence. Patients may feel unable to go out and this can be isolating. OWMAG acknowledge the need for enterocolitis to be treated promptly, currently patients are often transferred to gastroenterology services before receiving treatment with the potential for delay in treatment. There are no licensed alternative treatment options routinely available. Infliximab may reduce the need for more invasive surgical interventions for this condition.
Final recommendation	OWMAG recommends the use of infliximab for the treatment of immune checkpoint inhibitor induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids. This recommendation is subject to the development of appropriate start/stop criteria.

Summary of rationale	There is some evidence to support infliximab as an effective treatment option for ICI induced enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids. There are no licensed alternative treatment options and without access to infliximab for this indication ICI treatment for malignancies will not be a viable option. A proportion of the patient population in Wales are already receiving this treatment via local agreement routes, supporting the use on an All Wales basis would ensure equity of access. The review after 12 months will provide more clarity around patient numbers and the number of doses of infliximab administered.