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

Evidence Status Report: infliximab for the treatment of immune checkpoint inhibitor induced enterocolitis **(OW21)**
Reassessment to include:
grade 2 enterocolitis, when symptoms have not responded to first-line immunosuppression with corticosteroids, as an alternative option to vedolizumab;
grades 2–4 enterocolitis requiring multiple challenge with corticosteroids;
dose escalation of infliximab when there is an inadequate response to the standard dose.

Report prepared by the All Wales Therapeutics and Toxicology Centre
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Key findings

Licence status

Infliximab is not licensed for treating immune checkpoint inhibitor (ICI)-induced grade 2–4 enterocolitis, when symptoms have not responded to first-line immunosuppression with corticosteroids or require multiple challenge with corticosteroids and dose escalation following inadequate response to standard dose. The use of infliximab for this indication is off-label.

Clinical evidence

The clinical evidence for the use of infliximab in this setting comes from interim results from an ongoing clinical trial, a systematic review with meta-analysis, and retrospective studies. Despite limitations of retrospective study design, in most studies, infliximab showed clinical benefit in terms of symptom improvement or symptom response to infliximab (complete or partial). Patient deaths were typically from other causes (infection or cancer progression).

Safety

No new safety signals have been observed for infliximab in this indication.

Patient factors

Infliximab is administered by intravenous infusion over a two-hour period. Due to risk of acute infusion-related reactions, patients should be monitored during and for at least one to two hours post-infusion.

Cost effectiveness

There are no published studies on the cost-effectiveness of infliximab in combination with oral corticosteroids for treating immune checkpoint inhibitor (ICI) induced grade 2 enterocolitis, when symptoms have not responded to first-line immunosuppression with corticosteroids or require multiple challenges with corticosteroids. AWTTC cost analyses identified that this intervention is associated with an incremental cost of [commercial in confidence figure removed].

AWTTC threshold analysis, with a limited cost perspective, identified that treatment

with infliximab in combination with corticosteroids would require an improvement of [commercial in confidence figure removed] QALYs to be considered cost-effective. There is insufficient evidence to inform a decision on cost-effectiveness.

Budget impact
Clinicians consulted by AWTTC estimate that 12 people in Wales per year would be likely to be eligible to receive infliximab in this setting. It is assumed that people would have one to three 5 mg/kg infliximab doses although one patient is predicted to require dose escalation to 10 mg/kg due to lack of response. All doses are assumed to be received within a single year. This is associated with an annual cost of between [commercial in confidence figures removed], depending on which infliximab product is used. The number of eligible patients is likely to increase over time as more people receive ICIs. The budget impact is subject to uncertainty.

Impact on health and social care services
Patients with ICI-induced grade 3–4 enterocolitis (not responding to corticosteroids) in Wales are currently receiving infliximab through a One Wales recommendation (OW21) issued in February 2023. Patients with grade 2 colitis may receive infliximab through local agreements.

Innovation and/or advantages
Infliximab may reduce the need for more invasive interventions for this condition, and may improve patients' quality of life and allow them to be discharged earlier. Infliximab treatment may help patients to receive subsequent cancer treatments, titrate steroids down, and carry on with their lives at home. Managing the toxicity of cancer treatments improves the chance for cancer to be cured for this cohort of patients.

Background

In 2023 AWTTC reviewed the One Wales recommendation to use infliximab to treat ICI-induced enterocolitis grade 3–4 that had not responded to corticosteroids. The review identified a change to the European Society for Medical Oncology (ESMO) guidelines for treating ICI colitis. The One Wales Medicines Assessment Group (OWMAG) proposed that, in accordance with the new treatment guidelines, infliximab should be reassessed for the broader indication of treating ICI-induced grade 2–4 enterocolitis that had not responded to corticosteroid treatment or to multiple challenges with corticosteroids, and to consider the use of a higher (10 mg/kg) dose of infliximab.

The All Wales Therapeutics and Toxicology Centre (AWTTC) sought opinions from clinical experts in Wales, who said the incidence of immune checkpoint inhibitor (ICI) induced enterocolitis will increase over the next few years as the use of cancer immunotherapies increases. Clinical experts expressed a need for effective ICI toxicity management, with infliximab considered standard of care for severe or steroid-refractory ICI-induced enterocolitis, and supported the reassessment of infliximab for the proposed broader indication.

Patients with ICI-induced grade 2 enterocolitis in Wales currently receive infliximab through local agreements. In the absence of other licensed treatments, a One Wales decision would ensure equity of access to this treatment across the country.

Target group

The indication under consideration is an extension to the current One Wales recommendation to include:

- patients with ICI-induced grade 2 enterocolitis when symptoms have not responded to first-line immunosuppression with corticosteroids, as an alternative to vedolizumab
- patients with grade 2–4 enterocolitis who are corticosteroid-dependent requiring multiple challenges with corticosteroids
- dose escalation to 10 mg/kg when there has been an inadequate response to standard 5 mg/kg dosing.

Marketing authorisation date: Not applicable, off-label

Infliximab is not licensed for the treatment of ICI-induced grade 2–4 enterocolitis, when symptoms have not responded to first-line immunosuppression with corticosteroids, or to multiple challenges with corticosteroids or dose escalation following inadequate response for this indication.

There are no plans to license infliximab for the indication under consideration.

Dosing information

The recommended dose is 5 mg/kg given as an intravenous infusion[1]. A second dose may be repeated 14 days later, with a maximum of three infusions to be given (weeks 0, 2 and 6). The ESMO guidelines recommend considering a higher dose of 10 mg/kg to treat refractory colitis[2].

Clinical background

Immune-related enterocolitis is one of the most common and severe immune-related adverse events (irAE) associated with ICI treatment[3,4]. ICIs are a recent advancement in cancer immunotherapy. They negatively target regulators of the immune response which results in immune system activation and anti-tumour immunity. This specific immune system activation can potentially affect any organ system at the same time, most commonly the skin, gut, liver and endocrine system.

Symptoms of gastrointestinal irAE include nausea, vomiting, diarrhoea, abdominal pain, and blood and mucous in the stool. Gastrointestinal irAE symptoms typically begin four to seven weeks after starting ICI treatment but can occur, or recur, up to 12 months or more after stopping treatment. Gastrointestinal irAE are the most common cause of ICI treatment interruption, permanent discontinuation and treatment related death[5].

Diarrhoea and colitis are considered separately within the US National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) tool[3]

- Grade 2 colitis (moderate severity) presents as abdominal pain and mucous or blood in the stool
- Grade 3–4 colitis (severe to life-threatening severity) presents with severe abdominal pain or peritoneal signs leading to life-threatening consequences or urgent intervention indicated
- Grade 2 diarrhoea presents as an increase of 4 to 6 stools a day over baseline
- Grade 3–4 diarrhoea presents as an increase to at least seven stools a day over baseline, hospitalisation indicated, severe increase in ostomy output

compared to baseline or limiting self-care activities of daily living. This leads to life-threatening consequences or urgent intervention indicated.

The British Society of Gastroenterology (BSG) recommends that the CTCAE tool is not to be used exclusively for treatment decisions. The BSG defines ICI-induced enterocolitis as inflammation of the gastrointestinal tract, that is typically associated with gastrointestinal symptoms, most notably diarrhoea[3].

Incidence

Incidence of ICI-induced enterocolitis will vary greatly depending on the ICI treatment and dosage used[6]. Incidence of all grade diarrhoea is estimated to be 10% and 33% with anti-programmed cell death protein (PD)-1 and anti-cytotoxic T-lymphocyte-associated protein (CTLA)-4 treatment, respectively. Incidence of all grade colitis is estimated to be 2% and 7%, respectively. Incidence of grade 1–4 and severe (grades 3–4) colitis is estimated to be 1.2% and 0.2%, respectively, with anti-PD-1 treatment, 0.3% and 0.04% with anti-PD-L1 treatment, and 11.2% and 4.9% with anti-CTLA-4 treatment[6]. The proportion of people who develop steroid-refractory colitis is not known but has been estimated to be between 33.3% and 66.6% of those receiving anti-CTLA-treatment and approximately 12.5% of those receiving anti-PD-1 treatment[7].

Clinicians consulted by AWTTC estimated that twelve people in Wales per year would be likely to be eligible to have infliximab for ICI-induced grade 2–4 enterocolitis that has not responded to corticosteroids.

Current treatment options and relevant guidance

Treatment of ICI-induced grade 2 enterocolitis that has not responded to corticosteroids is currently treated off-licence in Wales with infliximab through local agreements. Treatment of ICI-induced grade 3–4 enterocolitis unresponsive to corticosteroids is treated in Wales by infliximab or vedolizumab under the One Wales recommendations OW21 and OW22[8,9].

The Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up were updated in 2022[2]. For patients presenting with grade 2 symptoms, ICI therapy should be withheld and symptomatic management with oral corticosteroids at 40–60 mg/day should be initiated, tapered over 4–8 weeks. Upon remission, ICI may be considered taking into account the risk of enterocolitis recurrence and the oncological benefit of restarting the ICI. In the case of relapse or where the patient is found to be refractory to corticosteroids, ESMO recommends infliximab or vedolizumab treatment and rapid corticosteroid tapering. Vedolizumab is recommended for more moderate disease (grade 2) and infliximab for more severe disease (grade 3–4). This seems to be due to vedolizumab taking longer to elicit a response and therefore being less suitable when time to treatment success is critical. The updated ESMO guidelines also include the option of switching between biologics, or considering a higher dose of infliximab (10 mg/kg) for refractory colitis[2].

The current One Wales recommendation states that infliximab at a dose of 5 mg/kg for up to three doses may be used if a patient's condition is not responsive to corticosteroids for grade 3–4 enterocolitis. Vedolizumab may be used for patients whose condition is unresponsive to infliximab or for whom infliximab is not appropriate.

Clinicians in Wales said that they would welcome the opportunity to extend the group of patients receiving infliximab to include patients with grade 2 disease. Dose escalation to 10 mg/kg may be considered when there is no response to the 5 mg/kg dose, and this would be discussed with gastroenterology colleagues.

A number of national and international guidelines have been published on this topic with some variation in their recommendations[3,4,10-15].

The UK Oncology Nursing Society's Acute Oncology Initial Management Guidelines (version 4.0) include Guideline 21: immune-related adverse event: diarrhoea and colitis. The guideline recommends screening on Day 1 for suitability for infliximab administration in cases of severe or life-threatening colitis (grades 3 and 4) and also for moderate colitis (grade 2)[12].

For milder forms of disease, the British Society of Gastroenterology (BSG) recommend initiating treatment with oral corticosteroids[2]. Should there be no response within 3–5 days, BSG advise switching to intravenous methylprednisolone. If there is still no response within three days, they then recommend to escalate to infliximab at 5 mg/kg for a maximum of three infusions. For patients with high-risk endoscopic features there may be a lower threshold for early escalation to infliximab. In acute severe enterocolitis, there are safety concerns about sequential use of powerful immunosuppressive agents immediately after infliximab failure[3]. For severe enterocolitis that is refractory to treatment, or following intestinal perforation, surgical management might be required[3].

A single dose of infliximab 5 mg/kg is effective in at least 65% of cases but a second dose may be required due to symptomatic relapse or incomplete response[3]. The BSG advise completing the standard induction regimen of 5 mg/kg at weeks zero, two and six to maximise the opportunity for complete mucosal healing. The value of additional doses of infliximab following the standard three infusions has not been established[3].

Clinical experts advise that patients would initially have clinical review and investigations including routine blood tests, stool cultures and faecal calprotectin. They would then undergo radiology assessment and start primary immunosuppression with intravenous methylprednisolone followed by endoscopy. If the enterocolitis does not respond to primary treatment then infliximab would be considered after three to five days.

For patients receiving intravenous corticosteroids, or for patients with high-risk endoscopic features, screening for tuberculosis, varicella zoster virus, HIV and hepatitis B and C should take place in anticipation of treatment escalation; however, this should not delay treatment initiation[3].

Summary of evidence on clinical effectiveness

For the review of the OW21 recommendation and for reassessment of the broader use of infliximab to include grade 2 enterocolitis and dose escalation with infliximab, AWTTC conducted a literature search for additional evidence, and excluded studies that had very small numbers of patients, or in which the grade of colitis was not specified by treatment. Evidence identified included a case series investigating the use of 10 mg/kg infliximab for refractory enterocolitis, three retrospective studies, and interim results from an ongoing clinical trial were identified. All are discussed below. In addition, the Canadian Agency for Drugs and Technologies in Health (CADTH)

recently published a rapid review summarising the evidence available for the use of infliximab as treatment for ICI therapy-related toxicities. However, this did not include any new evidence for ICI-induced enterocolitis to that already identified by AWTTC[16].

Efficacy

Nguyen at al. (2024) conducted a retrospective, observational study of 44 patients in a UK hospital, who developed colitis during treatment with ICI medicines for melanoma[17]. The study compared two different grading systems (CTCAE grading and an overall grading that included additional symptoms) to evaluate the severity of ICI-induced colitis. Treatment and outcome were evaluated to compare the impact of the two categories; the study concluded that including additional symptoms in severity grading is meaningful and related to outcome of colitis. Using CTCAE, 17 patients had grade 2 colitis and 9 had grade 3; by overall grading 7 patients had mild colitis, 19 had moderate colitis and 18 had severe colitis. A total of 29 patients were treated with steroids; 17 of them needed infliximab added: 12 with an overall grading of severe colitis (six with CTCAE grade 3, five grade 2 and one grade 1) and 5 with an overall grading of moderate colitis (three with grade 2 and two with grade 1). Seven patients (15.9%) needed a second dose of infliximab. Of refractory cases, two were indicated for vedolizumab treatment and a third dose of infliximab was ordered for two cases as well. The median time to resolution of colitis for the whole group was 28 days (range 0–282 days). Treatment modality and time to resolution were associated with severity of colitis assessed by complete overall grade ($P < 0.0001$) rather than CTCAE grading ($P > 0.05$)[17].

Dahl et al. (2022) conducted a retrospective study, in which140 patients with grade 1–4 enterocolitis (86% were CTCAE grade 1–2 for colitis and 42% were CTCAE grade 1–2 for diarrhoea) were treated with an average of two infusions (range 1–9)[18.] The first dose used was 5 mg/kg intravenous infliximab in 76% of patients (n = 106) and 23% (n = 32) were treated with high-dose 10 mg/kg infliximab (due to high dose being the treatment standard at one of three treatment centres, rather than as an escalation option). The higher dose was not associated with a faster time to normal stool pattern. Treatment success rate was 73% after two or more doses of infliximab and in responsive patients, mean time to initial response was three days with complete remission after 31 days. A total of 38 patients achieved sustained corticosteroid-free clinical remission (no need for treatment) at Week 10 and another 38 had clinical remission at Week 30. The median survival time for infliximab-treated patients was longer compared to a control group who were receiving an ICI but did not require infliximab treatment (836 days [95% confidence interval [CI], 620 to 1,232] versus 390 days [95% CI, 341 to 462], $p<0.001$)[18].

Machado et al. (2023) conducted a retrospective study of 81 patients with ICI-induced enterocolitis treated with intravenous infliximab (most with 5 mg/kg)[19]. The median number of infliximab doses was one (interquartile range 1–2). Treatment success rate was 73.7% (115 of 156) in the full population of medically treated patients who received infliximab, vedolizumab or combined treatment. Six patients (7.2%) received 10 mg/kg infliximab, either as a starting dose or as part of dose-escalation. New immune-related adverse events (irAEs) occurring in a median time frame of six to seven months after infliximab treatment were observed for 17 of 81 patients (21%), with some patients having more than one irAE. These involved the skin in nine patients, endocrine system in nine patients, and liver in six patients. The study concluded that infliximab has high efficacy for treatment of moderate-to-severe ICI colitis and may delay the recurrence of new irAEs beyond six months after treatment completion[19].

High dose infliximab
In a case series by **Harris et al. (2022)** of 10 patients treated at the Memorial Sloan Kettering Centre (USA) for immune-related severe colitis, high-dose infliximab (10 mg/kg) was started after non-response (n = 2) or incomplete response (n = 8) to a median of 2 doses of infliximab 5 mg/kg[20]. Five (50%) patients had a clinical response to an initial high dose of infliximab (10 mg/kg) after a median of four days (interquartile range 3–6 days). Five patients (50%) were refractory to one or more high doses of infliximab and were treated with vedolizumab. Symptoms in three of these five patients responded to vedolizumab; two patients who had persistent symptoms subsequently underwent faecal microbiota transplantation, with good response[20].

Study in progress: Wang et al. (2023) reported interim results from a study comparing infliximab with vedolizumab to treat grade 2 or higher ICI-related colitis (NCT04407247)[21]. A total of 15 patients had been enrolled; two patients had been lost to follow-up and one had withdrawn consent. Of the 13 patients reported on, seven received 5 mg/kg infliximab and six received 300 mg vedolizumab at Weeks 0, 2 and 6. Two-week remission rates were 100% and 83.3% in the infliximab arm and the vedolizumab arm, respectively. Five patients (71.4%) treated with infliximab and three patients (50%) treated with vedolizumab achieved steroid-free remission by one month. Two patients from each arm were able to resume ICI therapy. The study is expected to complete at the end of December 2024, with a target recruitment of 100 participants[21].

For the original OW21 assessment, AWTTC's literature search identified a systematic review with meta-analysis, and a number of retrospective studies; the most relevant are discussed below.

Araujo et al. (2021) examined efficacy and hepatotoxicity of infliximab treatment for steroid refractory irAEs due to ICIs in cancer patients (n = 56) in a retrospective study[22]. Colitis was the most frequent irAE (n = 37), followed by pneumonitis (n = 6), myocarditis (n = 2) and hepatitis (n = 1) and various others (n = 10). Infliximab dosage used was not reported, although the median number of treatments was one (range 1 to 3). Fourteen patients (25%) required more than one dose which was separated by a median of 40.5 days (range 12 to 867). Colitis resolved in 32 of the 37 patients and was the irAE most likely to respond to infliximab treatment compared with the other irAEs combined (odds ratio [OR] 6.73; 95% confidence interval [CI]: 1.56 to 29.04; p = 0.011). There were no cases of infliximab-induced hepatotoxicity[22].

Alexander et al. (2021) examined outcomes of infliximab treatment for corticosteroid refractory ICI-induced enterocolitis in a retrospective study based in the UK (n = 127)[5]. Infliximab dosage used was not reported. The primary outcome for colitis was corticosteroid-free clinical remission (CFCR). CFCR was defined as CTCAE grade 0 for diarrhoea at 12 weeks after starting infliximab, in the absence of corticosteroid therapy greater than a daily dose of oral prednisolone 5 mg (or equivalent corticosteroid), and without the need for other rescue therapy such as vedolizumab or colectomy. Infliximab dosing frequency ranged from one (n = 62), two (n = 32), three (n = 28), four (n = 4) to five or more doses (n = 1). Before starting infliximab, all patients reported diarrhoea symptoms, with 96 reporting diarrhoea of grade 3 or 4 and 30 of grade 2. At 12 weeks, eight patients had died (none from colitis). Of the remaining patients (n = 119), 62.2% were in clinical remission (CR [n = 74]) and 41.2% were in CFCR (n = 49). Of the CFCR group, 83.7% had CR

within seven days of starting infliximab (n = 41) of which 65.3% responded within 48 hours (n = 32). At 26 weeks, nine more patients had died, while five had inadequate follow-up. Of the remaining patients (n = 105), 71.4% were in CR (n = 75) and 50.9% were in CFCR (n = 54); 32 of these patients had been CFCR at 12 weeks. During the six months following the start of infliximab treatment, 37% needed rescue therapy (n = 47), such as mycophenolate mofetil (n = 23) and vedolizumab (n = 11), and there were four colectomies (3.1%). None of the outcome measures were reported by initial CTCAE grade[5].

Wang et al. (2018) examined corticosteroid and infliximab treatment on ICI-induced enterocolitis and OS in a retrospective study (n = 327)[23]. Infliximab dosage used was not reported. Diarrhoea was observed in 36% (n = 117), 12% (n = 38) had diarrhoea but did not receive steroids or infliximab while 24% (n = 79) had diarrhoea and received either corticosteroids alone (n = 44) or with infliximab (n = 35). A greater proportion of grade 2 and higher diarrhoea required infliximab as well as corticosteroid treatment (97%), rather than corticosteroid treatment alone (73%; p = 0.005). Immunosuppressive treatment was not different according to grade of colitis. OS did not differ between patients who received corticosteroids alone or those who received corticosteroids plus infliximab (for steroid-refractory enterocolitis), this effect persisted for patients with stage IV cancer[23].

Comparative effectiveness

Zou et al. (2021) compared the clinical efficacy and safety of infliximab and vedolizumab in patients (n = 184) with ICI-induced enterocolitis in a retrospective study[24]. Dosage concentration was not specified for either medicine. Median follow-up was 14 months (interquartile range [IQR] 8 to 27). A total of 153 patients had confirmed histological inflammation by endoscopy. Patients received either infliximab (n = 94), vedolizumab (n = 62) or a combination of both biologics sequentially (n = 28). 53 patients had grade 1–2 diarrhoea (33 treated with infliximab); 103 had grade 3–4 diarrhoea (61 treated with infliximab). 87 patients had grade 1–2 colitis (57 treated with infliximab) and 69 had grade 3–4 colitis (37 treated with infliximab). Median duration from first dose to either symptom remission or improvement to grade 1 was 13 days (IQR 8 to 29) for infliximab and 18 days (IQR 10 to 40) for vedolizumab (n = 138; p = 0.012). Median duration of hospitalisation was 14 days (IQR 8 to 19.8) for infliximab and 10 days (IQR 5 to 15) for vedolizumab (n = 107; p = 0.043). There were significantly more instances of individuals requiring multiple hospitalisations (p = 0.005) for infliximab (n = 26) compared with vedolizumab (n = 10). There were significantly more instances of recurrent ICI-induced enterocolitis (p = 0.007) for infliximab (n = 27) compared with vedolizumab (n = 8). There was no significant difference in the overall number of hospitalisations (p = 0.367), the level of clinical remission (p = 0.785) or immunosuppressant associated infection (p = 0.184) between groups. OS was more favourable for patients receiving vedolizumab (n = 62) compared with infliximab (n = 94; p = 0.027)[24].

Network meta-analyses

Nielsen et al. (2022) conducted a network meta-analysis (NMA) to assess the incidence and management of ICI-induced enterocolitis[6]. To assess the efficacy of biologics in the management of ICI-induced enterocolitis, 25 publications were identified (n = 613) focussing on infliximab (20), vedolizumab (3) or both (2). The authors considered the included studies to be of good quality. Infliximab (5 mg/kg) resulted in CR for 87% (95% CI: 79% to 94%; n = 502) and vedolizumab (300 mg) resulted in 88% CR (95% CI: 62% to 100%; n = 111). Both treatments were

considered to be equally effective. Inclusion criteria and disease grading differed across the included studies[6].

Ibraheim et al. (2020) conducted an NMA to investigate the effectiveness of anti-inflammatory therapy (corticosteroids, infliximab or vedolizumab) in ICI-induced enterocolitis[25]. The pooled response to infliximab was 81% (95% CI: 73 to 87) with significant heterogeneity between 17 studies (I^2 = 49%, p = 0.01). The authors considered the significant heterogeneity observed due to inclusion criteria differences and a lack of standardisation in how treatment response was recorded across the studies, amongst other reasons[25].

Safety

Safety data provided by clinicians in Wales for seven patients treated with infliximab for stage 3 or 4 ICI-induced enterocolitis reported that [confidential data removed].

For those studies which reported on infliximab safety, treatment complications or adverse events mostly involved infections[24], and in one study affected a fifth of the patients treated with infliximab[5]. Alexander et al. (2021) reported that in 127 patients treated with infliximab, 26 (20.5%) developed infections requiring antibiotic treatment. Eight patients required intravenous antibiotics and/or hospitalisation for infection and four deaths were attributable to infection (hospital-acquired pneumonia [n = 2], sepsis [n = 1], peritonitis [n = 1])[5]. Other reported adverse events following infliximab treatment included anaphylaxis (n = 1), bradycardia requiring atropine and critical care (n = 1), grade 3 maculopapular rash (n = 1) and squamous cell carcinoma of the skin (n = 1)[5]. Infection rates were also reported to be higher for those who received infliximab and for those on more or prolonged steroid treatment courses[23,24]. Lesage et al. (2019) reported no adverse events following infliximab treatment in 27 patients and no colitis-related deaths[26].

Dahl et al (2022) analysed safety, and reported that infliximab and vedolizumab in combination with high doses of corticosteroids are associated with high rates of infections and thromboembolic events[18]. Infection risk is a known adverse event for infliximab, vedolizumab and corticosteroids. The author noted that thromboembolic events could have been attributed to a number of factors, including: severe colitis, dehydration, malignancy, inflammation, hospitalisation and corticosteroid use. To account for some of these risks the authors included only thromboembolic events within 90 days after the first infliximab treatment. There were almost no events after this timeframe. It is recommended that all patients being treated for severe ICI-induced colitis should be assessed for thromboembolic risk[18].

The BSG reports a tendency for higher corticosteroid dosing in ICI-induced enterocolitis, compared with ulcerative colitis, often in combination with infliximab[3]. This may result in a greater risk of *Pneumocystis jirovecii* infection for those patients receiving ICIs and the authors suggest *P. jirovecii* infection prophylaxis should be considered only when combinations of high-dose corticosteroids and infliximab (or other immunosuppressive medicines) are unavoidable[3].

The Summary of Product Characteristics (SmPC) for infliximab (Remicade®) lists contraindications; these include tuberculosis, sepsis, abscesses, other severe opportunistic infections, patients with moderate or severe heart failure (NYHA class III/IV)[1]. Infliximab should be used with caution in patients with mild heart failure (NYHA class I/II) and patients closely monitored; infliximab treatment must be discontinued if any new or worsening symptoms of heart failure develop[1].

The SmPC special warnings include details about infliximab's association with acute infusion-related reaction including anaphylactic shock and delayed hypersensitivity reactions[1]. Infliximab (or any anti-TNF alpha medicines) increases patient susceptibility to serious infections. Tuberculosis, bacterial infections (such as sepsis and pneumonia), invasive fungal, viral and other infections have been observed in patients treated with infliximab. Patients receiving infliximab must be monitored closely for infections before, during and after treatment, with monitoring continuing up to six months after infliximab was last given. Infliximab treatment must be stopped if a patient develops a serious infection or sepsis and caution exercised when considering infliximab for patients with chronic or recurrent infections, including concomitant immunosuppressive therapy. Particular attention regarding infection risk should be paid when treating elderly populations[1].

The SmPC lists very common (occurring in ≥ 1 in 10 people) adverse reactions as: viral infection (e.g. influenza, herpes virus infection), headache, upper respiratory tract infection, sinusitis, abdominal pain, nausea, infusion-related reaction and pain[1].

Patient factors

Clinicians in Wales reported patient outcome data in 2023 for seven patients with grade 3 ICI-induced colitis who were treated with infliximab. The data show clinical remission after infliximab treatment in all of the patients treated.

During the assessment of infliximab for ICI-induced grade 3–4 colitis, the One Wales Medicines Assessment Group (OWMAG) considered comments from clinical experts in Wales who shared their experience using infliximab in patients with ICI-induced colitis. The experts reported that patients had significant improvements in quality of life: the reduction in bowel movements allowed patients to sleep at night, and patients could be discharged earlier. One hospital in Wales administers infliximab as a day case to further reduce hospital stays. Infliximab treatment had helped patients to receive subsequent cancer treatments, titrate steroids down, and carry on with their lives at home.

The OWMAG also considered comments from the patient organisation 'Melanoma Focus'. The organisation highlighted that as a result of the availability of infliximab for this indication, patients could return home from hospital sooner; and re-admission could be prevented because infliximab treatment for symptom flares can be given as a day case. Melanoma Focus supported the co-creation of guidelines for grade 1–4 colitis between gastroenterology and oncology teams, and supported the use of infliximab (or vedolizumab) if grade 3–4 symptoms worsen on steroid treatment.

Melanoma Focus also updated their original submission to include patients with grade 2 disease who are unresponsive to steroid treatment. They state that despite grade 2 colitis being milder than grade 3, it can still significantly impact patients' quality of life. Socialising and working can be impacted as there is often little warning of when a toilet is needed. Diarrhoea even a small number of times a day can cause anal inflammation leading to pain and haemorrhoids. The organisation also highlight that it is always desirable to have people on steroids for as little time as possible due to side effects.

Discussion

Most of the evidence for the off-label use of infliximab to treat ICI-induced grade 2–4 enterocolitis, where symptoms have not responded to first-line immunosuppression

with corticosteroids comes from retrospective studies. When reported, the infliximab dosage used was consistent with that recommended in national and international guidelines (5 mg/kg). The dosing schedule frequency varied between studies although generally no more than three doses were administered. Patient selection and grading, as well as outcome measurements are inconsistently reported across the studies (due to the nature of their design and limitations in the most widely used grading tool CTCAE). Interim data have also been reported from 15 patients in a clinical study comparing infliximab with vedolizumab to treat grade 2 or higher ICI-related colitis.

The evidence for dose escalation to 10 mg/kg is limited. Three studies included a dose of 10 mg/kg but only one reports specifically on its use where standard dose has failed. In this group success rate was 50% with the remainder going on to receive either vedolizumab or faecal microbiota transplantation with good response.

The National Institute for Health and Care Excellence (NICE) recommends infliximab (or adalimumab) for adults with severe active Crohn's disease whose disease has not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy (TA187)[27]. NICE recommends infliximab for the treatment of acute exacerbations of severely active ulcerative colitis only in patients in whom ciclosporin is contraindicated or clinically inappropriate, based on a careful assessment of the risks and benefits of treatment in the individual patient (TA163)[28]. It is acknowledged that the acute treatment strategy for ICI-induced enterocolitis may follow a similar pathway to the treatment for Crohn's and ulcerative colitis. However, there are differences in terms of patient and disease characteristics, the length of treatment, morbidity and mortality rates. Therefore, comparing the use of infliximab for these indications and trying to predict clinical and cost effectiveness for ICI induced enterocolitis from the data used for Crohn's and ulcerative colitis is subject to significant uncertainty.

It is reported that the early use of immunotherapies such as vedolizumab and infliximab to treat ICI-induced enterocolitis may ensure a more favourable overall patient outcome when compared to steroids alone as immunotherapy use is associated with a shortened course of steroid treatment[18]. A retrospective review by Wang et al. (2018) assessing the impact of ICI-induced diarrhoea and colitis and their immunosuppressive treatment on patient outcomes found that patients who received long duration of steroid treatment (> 30 days) had a numerically higher infection rate than those who received steroid for shorter duration (40.4 vs. 25.8%, $p = 0.160$). Likewise, long duration of steroid without infliximab was associated with increased risk of infection compared to short duration of steroid with infliximab (42.9% vs. 14.3%, $p = 0.089$)[18].

Clinicians have stated that there are some patients who require multiple treatment courses with steroids for relapses and note concerns regarding the increased risk of steroid-related adverse events due to repeated exposure[29-35]. They would welcome the option to use infliximab in this patient group to with the aim to prevent future relapses.

Patients with grade 2 enterocolitis who are unresponsive to corticosteroids are likely to progress to stage 3 disease. At this point they will become eligible for treatment with either infliximab or vedolizumab under the One Wales recommendations OW21 and OW22[8,9]. Higher doses of corticosteroids are associated with a greater risk of

fractures, developing diabetes/hyperglycaemia, cataracts, glaucoma, cardiovascular and cerebrovascular events. Psychiatric disturbances are also more common with higher dose corticosteroid use[32]. In addition, cumulative doses of corticosteroids are associated with an increased risk of fractures, high blood sugar, cataracts, weight gain, skin and sleep problems[36]. Short-term oral corticosteroid use has cumulatively been associated with osteoporosis, hyperglycaemia and muscle weakness, even when given for <7 days[34]. Allowing use of infliximab earlier in the pathway may prevent the worsening of symptoms requiring hospitalisation, lessen steroid burden and maintain or improve the quality of life for these patients.

Clinical experts state that, as immunotherapy has an increasing number of treatment indications for cancer, the incidence of ICI-induced enterocolitis is predicted to increase. This will lead to more hospital stays and, as such, it is imperative that NHS Wales is able to offer ICI immunotherapy safely. Clinicians state that ICIs offer the possibility of cure for patients with stage IV metastatic disease which is a paradigm shift for cancer care. In melanoma, where ICI has been used for the longest duration, 6.5-year data shows 49% of patients are still alive with more than 75% treatment free[37]. To be able to offer patients the possibility of durable outcomes, clinicians feel it is imperative they can manage toxicity effectively with treatments such as infliximab.

Clinical experts state that, as infliximab blocks TNF alpha and reduces systemic inflammatory responses, it can reduce the efficacy of immunotherapy cancer treatment. For this reason, infliximab poses a risk to cancer treatment success when patients have significant disease burden and limited treatment options (other than immunotherapy).

Cost-effectiveness evidence

Infliximab for treating ICI-induced grade 2 enterocolitis, when symptoms have not responded to first-line immunosuppression with corticosteroids or require multiple challenges with corticosteroids.

Cost-consequence analysis

An AWTTC cost-consequence analysis compares the cost and clinical outcomes of intravenous infliximab in combination with the current standard of care in the treatment of ICI-induced grade 2 enterocolitis with current standard of care alone. Standard of care in this setting consists of symptomatic management with oral corticosteroids at 40–60 mg/day.

The cost-consequence analysis includes the costs of infliximab procurement and administration. The analysis adopts a lifetime horizon and an NHS Wales/Personal and Social Services perspective. The analysis accounts for the costs and outcomes associated with the acute disease in addition to considering longer term clinical and cost impacts. The recommended dose of infliximab is 5 mg/kg[1]. A second dose may be repeated 14 days later, with a maximum of three infusions to be given (weeks 0, 2 and 6). The ESMO guidelines recommend considering a higher dose of 10 mg/kg to treat refractory colitis[14].

Cost of intervention and comparator

Infliximab procurement costs are informed by a confidential NHS Wales contract price with a unit cost of a 100 mg vial ranging between [commercial in confidence figures removed]. NHS Wales prescribing figures from 2023 for infliximab 100 mg are used to calculate a weighted average procurement cost; details are offered in

Appendix 1. The weighted average cost per 100 mg vial is [commercial in confidence figure removed] excluding VAT.

The average patient weight is calculated using population averages with an equal percentage of males and females. The recommended dose of 5 mg/kg for an average patient weight of 77.25 kg results in 4 vials per administration[38,39]. There is an assumption of no vial sharing; wastage is applied. The total infliximab procurement cost for a single administration is [commercial in confidence figure removed] excluding VAT.

The administration cost for the delivery of infliximab is sourced from the NHS reference costs 2021/22 with cost code SB12Z used for the first administration and SB15Z for additional delivery. The first administration cost is £207.59. Delivery of subsequent dose is costed at £326.46[40]. The total cost for an initial dose of 5 mg/kg of infliximab is [commercial in confidence figure removed] excluding VAT. Whilst not included in the base case, treatment with 10 mg/kg is recommended to treat refractory colitis by the ESMO guidelines; this dose would cost [commercial in confidence figure removed] excluding VAT per subsequent delivery (maximum 2)[2].

The base case distribution of patients across the differing delivery modalities has been informed by clinical experts. It is assumed patients receive three doses of infliximab at 5 mg/kg. The cost for the delivery of infliximab is [commercial in confidence figure removed] excluding VAT. The delivery costs of corticosteroids are assumed equal in the intervention and comparator arm the net intervention cost is therefore [commercial in confidence figure removed] excluding VAT.

Comparative clinical effectiveness

The summary of evidence on clinical effectiveness section outlines the clinical literature searches from which the effectiveness outcomes included in the cost-consequence analysis, are taken. Clinical outcomes associated with infliximab for grade 2 enterocolitis are broad and evidence is heterogenous. Seventeen studies across the severity grade (grades 1–4) found that infliximab showed a clinical benefit in terms of symptom improvement or symptom response (complete or partial). Evidence from a network meta-analysis calculates the pooled response rate of infliximab in combination with corticosteroids to be 81% (95% CI: 73% to 87%)[25]. There is a lack of evidence as to the clinical efficacy for patients in the comparator arm who continue treatment with corticosteroids and who are corticosteroid dependent.

The curative potential of infliximab may allow for a reduction in continued oral corticosteroid use, either in reduction of dose for those achieving partial response or in treatment discontinuation for those with complete response. The Summary of evidence on clinical effectiveness section outlines the wide range of adverse events associated with continued oral corticosteroids. Steroid burden is associated with an increase in continued care costs estimated to be £165 in 2007 per patient per year, the cost inflated using the PSSRU inflation indexes to 2022/23 prices is £252[41]. This cost was calculated by applying the oral corticosteroid relative risk of seven adverse events (AEs) to the prevailing incidence rate and then multiplying by associated costs[36]. Fractures were the main cost driver across the seven discrete AEs. The seven AEs are chosen due to the availability of relative risk estimates as opposed to severity ranking or incidence rates.

In addition to the seven relative risks included in the steroid burden economic study there is an increased infection risk associated with prolonged steroid use. A retrospective study pooling colitis grade 2 and 3 identified a relationship between longevity of steroid treatment and infection rates. The study findings suggest that early intervention with infliximab in combination with corticosteroids offers favourable outcomes compared to a longer duration of steroid without infliximab with infection rates of 14.3% and 42.9%, respectively; this finding was not statistically significant (P = 0.089)[23].

Adverse events associated with infliximab which were very common (observed in greater than 1 in 10 patients), have been listed in the safety section of the clinical review; they are viral infection (e.g. influenza, herpes virus infection), headache, upper respiratory tract infection, sinusitis, abdominal pain, nausea, infusion-related reaction and pain.

Clinical experts highlighted benefits in terms of a reduction in symptoms and an overall increase to patient health-related quality of life (HRQoL). This HRQoL impact is described in the patient organisation submission in terms of a disruption to usual activities and pain or discomfort. In addition to the curative impact on enterocolitis, a reduction in continued oral steroid use may also have an overall net HRQoL impact.

ESMO guidance and clinical experts have highlighted the need for hospital monitoring for grade 3–4 enterocolitis[2]. Welsh clinical experts suggest that intervention at grade 2 with infliximab in combination with corticosteroids may reduce progression to grade 3–4 and therefore result in a lower overall hospitalisation rate. The prudent healthcare element to the use of infliximab for the treatment of grade 2 ICI enterocolitis is centred upon the timely treatment which avoids progression to more severe grades of enterocolitis. Clinical experts have informed that patients with grade 2 who are unresponsive to steroids may progress to grade 3–4 at which point they can routinely access infliximab. The proportion of patients who would progress from grade 2 to grade 3–4 is unknown. Offering treatments with a high partial/full curative rate may avoid subsequent progression or exacerbation.

The cost consequence analysis is summarised in Table 1.

Table 1. Infliximab cost-consequence analysis

Infliximab plus standard of care: Three doses of infliximab at 5 mg/kg and oral corticosteroids at 40–60 mg/day	**Standard of care:** Oral corticosteroids at 40–60 mg/day
Additional cost to deliver: ¶¶* **Clinical considerations**: • High rate for symptom improvement or symptom response 81% (95% CI: 73% to 87%)[25]. • Short duration of steroid with infliximab associated with lower infection rates during the treatment duration, however, this difference was not statistically significant (14.3%)† [23] • Infliximab related AEs **Clinical opinion** • Lower hospitalisation rate due to reduction of progression to grade 3–4. • Improved QoL due to reduction in symptoms relative to standard of care.	**Clinical considerations**: • No evidence on the curative rate, patients have not responded to first-line immunosuppression with corticosteroids • Continued oral steroid use and steroid burden (adverse events and healthcare costs) • Long duration of steroid without infliximab associated with higher infection rates during the treatment duration, however, this was not statistically significant (42.9%)† [23] **Clinical opinion** • Higher hospitalisation rate compared to infliximab with standard of care due to relative response rate. • Reduced QoL due to continued symptoms compared to infliximab with standard of care.
* Costs are limited to procurement and administration costs. † insignificant difference (P=0.089) AE: adverse event; CI: confidence interval; QoL: quality of life ¶¶ commercial in confidence figure removed	

Threshold analysis

Using this net cost of infliximab, AWTTC conducted a threshold analysis to estimate the minimum required quality-adjusted life year (QALY) gain for infliximab to be deemed cost-effective. Applying a cost-effectiveness threshold of £20,000 per quality-adjusted life year to the net intervention cost of [commercial in confidence figure removed] requires a minimum QALY gain of [commercial in confidence figure removed]. A disease burden QALY is calculated to contextualise the threshold; this consists of disease duration and health-related quality of life (HRQoL) decrement.

An AWTTC literature review identified a recent study that reports a median time to resolution with grade 2 colitis of 52 days[17]; however, no direct evidence of impact on HRQoL for this indication was identified.

An alternative method to inform the scale of disease burden is to utilise literature from comparable conditions. An AWTTC literature search identified one relevant publication reporting no significant difference between ICI colitis and two conventional inflammatory bowel diseases (ulcerative colitis and Crohn's disease) for a range of quality of life measures[42]. A subsequent targeted literature review was

therefore undertaken to search for evidence on the HRQoL burden of ulcerative colitis and Crohn's disease. Two publications were identified, offering relevant data.

The HRQoL decrement associated with ICI enterocolitis is the difference between the immunotherapy patient cohort HRQoL and those experiencing ICI colitis. Mapping EQ-5D figures from an assessment of ulcerative colitis patients in remission compared to moderate or severe disease status suggests a HRQoL decrement of 0.20[43]. Applying the median grade 2 colitis duration of 52 days offers a QALY decrement of 0.028.

Alternative HRQoL figures are offered by NICE TA342 which reported estimates of 0.88 for ulcerative colitis remission and 0.42 for active disease[44]. Applying the median duration of 52 days to the utility decrement of 0.46 results in a disease burden estimate of 0.065.

An alternative approach to estimating the HRQoL decrement associated with ICI colitis was undertaken to assess the robustness of the previous HRQoL decrement estimation approach. A targeted literature search aimed to identify publications on the EQ-5D burden of adverse events in patients undergoing immunotherapy, one paper was identified which reports the disutility associated with treatment-related adverse events of any grade as −0.005[45]. This generic adverse event disutility can be multiplied by the median duration of 52 days to offer a QALY reduction of 0.001.

The disease burden estimates of 0.028 and 0.065 incorporate evidence which is specific to ulcerative colitis as opposed to the more general approach of adverse events; the disease specific estimates are considered more plausible.

Scenario analyses

AWTTC undertook a range of scenario analyses to assess the influence of key variables and assumptions. The main cost driver is the acquisition cost of infliximab. Currently the price of 100 mg vial of infliximab ranges between [commercial in confidence figures removed]. The lowest cost delivery of 3 cycles of 5 mg/kg with administration is [commercial in confidence figure removed]; the highest cost is [commercial in confidence figure removed]. Guidance for clinicians is to prescribe the lowest cost option. Prescribing data from Wales suggests that the lowest cost option is the most frequently delivered.

The base-case analysis assumes 3 cycles of infliximab at 5 mg/kg, to assess the robustness of the cost estimates to the delivery modality the minimum delivery dosing and maximum doses are calculated. The minimum dose is 1 cycle of infliximab at 5 mg/kg, with administration cost equalling [commercial in confidence figure removed]; the maximum dose is 5 mg/kg followed by 2 cycles of 10 mg/kg, with administration cost equalling [commercial in confidence figure removed].

The QALY burden in the main analysis uses a HRQoL decrement of 0.20 with a duration of 52 days to offer a QALY reduction of 0.028. Varying the duration by ±20% results in a QALY burden of 0.034 when increased by 20% and by 0.024 when decreased by 20%. There is a high level of uncertainty in the assumptions and figures used to calculate the QALY burden approach. Caution should be applied when incorporating this metric into decision making.

Cost-effectiveness evidence limitations

- There are no published cost-effectiveness studies for this intervention.
- The clinical effectiveness estimate is reported without the context of a comparator curative rate; this is due to the uncertainty as to the curative rate for patients who have previously not responded to corticosteroids. There may be patients achieving partial/total symptom reduction with oral steroids who continue treatment with corticosteroids and who are corticosteroid dependent.
- The cost consequence analysis is limited to intervention and administration costs. The cost impact of adverse events and ongoing healthcare resource use are not included as there is insufficient supporting evidence. Total costs are therefore underestimated for the intervention and the comparator.
- The meta-analysis informing the clinical evidence pools studies from across the disease grade, including grade 1–4[25]. Including other disease grades may be misleading if there is a significant interaction between severity and curative rates. There is evidence suggesting that less severe grades respond more quickly to therapeutic intervention[17].
- The time horizons in the included clinical studies are insufficient to capture any potential intermediate or longer-term clinical effects; this prohibits drawing any robust conclusions as to the lifetime cost-effectiveness.
- The HRQoL estimates are sourced from ulcerative colitis, whilst the equality of impact is supported by the published evidence; direct immune checkpoint inhibitor-induced enterocolitis data would be preferred, and therefore the estimates should be treated with caution. A further limitation is equality of impact evidence, in that the data was collected during the SARS-CoV-2 pandemic where impacts to daily routines may have masked the influence of the study health conditions.
- The burden of disease data is highly uncertain; the three estimates of the impact of enterocolitis in this patient group are inconsistent. This uncertainty and heterogeneity mean it is not possible to draw robust conclusions.
- The time to symptom resolution for grade 2 ICI-induced enterocolitis figure of 52 days includes the broader population and not those who have not responded to first-line immunosuppression. The time horizon may be longer in those who are less likely to respond to steroid treatment.
- Outcomes include evidence from clinical opinion in the absence of published literature. Whilst clinical expert opinion is an important component in the evidence hierarchy it is more susceptible to bias and uncertainty than well conducted randomised control trials.
- Net costs are highly sensitive to the delivery modality, particularly the amount of cycles administered. Variation in delivery modality may result in significant changes to the net intervention cost.

Budget impact

Welsh clinicians estimate that around 12 people in Wales per year would receive treatment with infliximab. This includes patients with grade 3–4 enterocolitis who are eligible under the existing One Wales recommendation (OW21) plus those eligible under the extensions for use considered in this reassessment. This is a reduction from the 20 patients per year estimated for the original assessment.

The infliximab treatment regimen is typically 5 mg/kg given as an intravenous infusion up to a maximum of three doses. Clinicians estimate that 1 of the 12 patients

would require dose escalation to 10 mg/kg due to lack of response to the first 5 mg/kg dose. It is assumed that all eligible patients would receive between one and three doses of infliximab within a single year. Medicine and administration costs per patient are shown in Table 2. The total annual costs for 12 patients are given in Table 3.

Table 2. Estimated annual costs for infliximab per patient in Wales

	Treatment cost range*	Administration cost†	Total annual cost range per patient
Infliximab (1 dose of 5 mg/kg)	¶¶	£208	¶¶
Infliximab (2 doses of 5 mg/kg)	¶¶	£534	¶¶
Infliximab (3 doses of 5 mg/kg)	¶¶	£861	¶¶
Infliximab (1 dose of 5 mg/kg and 1 dose of 10 mg/kg)	¶¶	£534	¶¶
Infliximab (1 dose of 5 mg/kg and 2 doses of 10 mg/kg)	¶¶	£861	¶¶

*Confidential NHS Wales contract price plus VAT, using lowest and mid-range price and the average weight for a British adult (77.25 kg) [27,28]. Assumes vial wastage[38,39].

† 2021–2022 National Schedule of Reference Costs: assumes 'Deliver Simple Parenteral Chemotherapy at first attendance' (HRG code SB12Z) for the first dose, followed by 'Deliver Subsequent Elements of a Chemotherapy Cycle' for the other two doses (HRG code SB15Z)[40]

¶¶ commercial in confidence figure removed

Table 3. Range of total annual costs for infliximab for 12 patients in Wales

	Year 1
Number of patients	12
Total annual costs for single infliximab dose at 5 mg/kg	¶¶
Total annual costs for 11 patients receiving two doses of 5 mg/kg and 1 patient receiving one dose of 5 mg/kg and one dose of 10 mg/kg	¶¶
Total annual costs for 11 patients receiving three doses of 5 mg/kg and 1 patient receiving one dose of 5 mg/kg and two doses of 10 mg/kg	¶¶
¶¶ commercial in confidence figure removed	

Budget impact issues

Infliximab biosimilar NHS Wales contract costs have been used in the calculations; costs may be higher for other products.

The budget impact has not considered mortality rates. Due to the nature of the indication, it is assumed that this patient group would be more likely to receive treatment for a short interval of time. Costs of additional screening and monitoring for bacterial, viral and fungal infections and adverse event costs are also excluded from the budget impact.

Clinicians consider infliximab to be a second-line treatment for grade 2–4 ICI-induced enterocolitis after corticosteroids, although vedolizumab would be the preferred option for patients with grade 2 (see separate evidence review). For patients who do not respond to infliximab, treatment options include vedolizumab and surgical intervention (colectomy). Other treatment options that have been suggested in guidelines include mycophenolate mofetil, tacrolimus and ciclosporin.

The majority of eligible patients with ICI-induced enterocolitis in Wales can already receive infliximab through the existing OW21 recommendation for grade 3–4 colitis. The first review of this recommendation after 12 months of implementation indicated that the actual number of patients being treated is lower than originally predicted. Therefore, the estimated eligible population considered for this reassessment has been revised down even after accounting for the additional patients covered by the expanded indication; the recalculated yearly budget impact range of between [commercial in confidence figures removed] is lower than the range calculated for the original assessment of between [commercial in confidence figures removed].

Outcome data for seven patients provided by Welsh clinicians report that five patients received three 5 mg/kg doses of infliximab, [confidential data removed]. Based on this, it is likely that the majority of patients will receive three doses and so the yearly budget impact is likely to be at the higher end of the estimate. The use of ICIs is continually growing and it is anticipated that patient numbers will increase over the next few years, which will have an additional budgetary impact in Wales.

Additional factors

Prescribing unlicensed medicines

Infliximab is not licensed to treat this indication and is therefore prescribed ‘off label’. Prescribers should consult their relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

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Appendix 1: Weighted cost of infliximab

[commercial in confidence data removed]