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

Evidence Status Report: vedolizumab (Entyvio®) for the treatment of immune checkpoint inhibitor-induced enterocolitis. Reassessment to include grade 2 enterocolitis when symptoms have not responded to first-line immunosuppression with corticosteroids, or require multiple challenge with corticosteroids **(OW22)**

Report prepared by the All Wales Therapeutics and Toxicology Centre
July 2024

Key findings

Licence status
Vedolizumab (Entyvio®) 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. The use of vedolizumab for this indication is off-label.

Clinical evidence
The clinical evidence for the use of vedolizumab in this setting comes from an ongoing clinical trial, a systematic review with meta-analysis, and retrospective studies (one of which had been included in the systematic review). The level of evidence available was limited but showed a clinical benefit in terms of overall survival and sustained clinical remission compared with infliximab.

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

Patient factors
Vedolizumab is administered by intravenous infusion over 30 minutes. Patients should be monitored during and for two hours post-infusion for the first two infusions. For subsequent infusions, one-hour monitoring post-infusion is sufficient.

Cost effectiveness
There are no published studies on the cost-effectiveness of vedolizumab in combination with oral corticosteroids for treating 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 vedolizumab in combination with corticosteroids would require an improvement of [commercial in confidence figure removed] quality-adjusted life years (QALYs) over a lifetime horizon 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 vedolizumab in this setting. It is assumed that people would have three vedolizumab doses, within a single year. This is associated with an annual cost of [commercial in confidence figure removed]. 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 in Wales are currently receiving vedolizumab through a One Wales recommendation (OW22) issued in February 2023. Patients with grade 2 colitis may receive vedolizumab through local agreements.

Innovation and/or advantages
Vedolizumab 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. Vedolizumab 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 vedolizumab to treat ICI-induced enterocolitis grade 3–4 that has not responded to first-line immunosuppression with corticosteroids and infliximab, or when infliximab is unsuitable. The review identified a change to the European Society for Medical Oncology (ESMO) guidelines for treating ICI-induced colitis, to include vedolizumab as an option to treat moderate (grade 2) ICI-induced enterocolitis. Clinical experts expressed an interest in revising the One Wales advice to broaden the patient group to include grade 2 disease, and to include patients with grade 2–4 disease whose condition is settling and re-flaring and requires multiple steroid escalations.

The One Wales Medicines Assessment Group (OWMAG) proposed that, in accordance with the new treatment guidelines, vedolizumab should be reassessed for the broader indication of treating ICI-induced grade 2 enterocolitis that had not responded to corticosteroid treatment, and grades 2–4 enterocolitis that require multiple challenges with corticosteroids.

The All Wales Therapeutics and Toxicology Centre (AWTTC) sought opinions from clinical experts in Wales, who said the incidence of 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 and supported the reassessment of vedolizumab for the proposed broader indication.

Patients with ICI-induced grade 2 enterocolitis in Wales are currently receiving vedolizumab through local agreement routes. 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 recommendation to include the treatment of ICI-induced grade 2 enterocolitis, when symptoms have not responded to first-line immunosuppression with corticosteroids, or in patients with grades 2–4 enterocolitis who are corticosteroid-dependent requiring multiple challenges with corticosteroids.

The current One Wales advice (OW22) recommends vedolizumab for the treatment of immune checkpoint inhibitor induced grade 3–4 enterocolitis, where symptoms have not responded to first-line immunosuppression with corticosteroids and infliximab, or when infliximab is unsuitable[1].

Marketing authorisation date: Not applicable, off-label

Vedolizumab (Entyvio®) is not licensed for the treatment of ICI-induced grade 2 enterocolitis, when symptoms have not responded to first-line immunosuppression with corticosteroids or to multiple challenges with corticosteroids, or for ICI-induced grade 3–4 enterocolitis when infliximab is ineffective or unsuitable.

The marketing authorisation holder of vedolizumab (Entyvio®) [commercial in confidence information removed].

Dosing information

The recommended dose is 300 mg administered intravenously on weeks 0, 2 and 6[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 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 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 diarrhoea for combination treatment (anti-CTLA-4 and anti-PD-1) is higher, and can be nearly half of those receiving combination treatment (47%)[3]. 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. 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 vedolizumab for ICI-induced grade 2–4 enterocolitis that has not responded to corticosteroids or when infliximab is unsuitable.

Current treatment options and relevant guidance

Treatment of ICI-induced grade 2 enterocolitis that has not responded to corticosteroids or infliximab is currently treated off-licence in Wales with vedolizumab through local agreements. Treatment of ICI-induced grade 3–4 enterocolitis unresponsive to corticosteroids or infliximab is treated in Wales by vedolizumab under the One Wales recommendation OW22[1].

The Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up were updated in 2022[8]. Vedolizumab and infliximab are recommended for grade 2–4 enterocolitis refractory to corticosteroids, with infliximab recommended for more severe forms of disease and vedolizumab for moderate disease. 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[8]. The current One Wales recommendation states that vedolizumab 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.

Several national and international guidelines have been on published on this topic with some variations in their recommendations[3,4,9-11]. Generally, for patients with grade 3–4 enterocolitis, early introduction of vedolizumab or infliximab should be considered in addition to steroids in patients with high-risk features on initial

endoscopy examination or severe ulcerative presentation on colonoscopy. Treatment may also be started where there is no response to high-dose steroids usually within two to three days[3,4,9,11] but up to five days[10]. This includes patients with pre-existing inflammatory bowel disease (IBD) and, for this patient group, the need for ongoing maintenance infusions of infliximab or vedolizumab should be discussed case by case[11]. Pre-existing IBD is not a contraindication to receiving ICIs according to the BSG, who advise prompt assessment of disease activity before starting an ICI, regular monitoring during treatment and rapid treatment escalation in the event of relapse[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 had not resolved and either infliximab was contraindicated or the enterocolitis had not responded to infliximab (up to three doses) then vedolizumab would be considered (up to three doses).

Clinicians in Wales say that there may be a role for the use of vedolizumab to treat refractory grade 2 colitis. In addition, clinicians have identified a group of patients whose condition is settling and re-flaring and requires multiple steroid escalations; these patients might benefit from earlier treatment with vedolizumab. Clinicians would therefore welcome the option to use vedolizumab for patients with grade 2 refractory ICI-induced enterocolitis, and for patients whose condition requires multiple steroid challenges and who may benefit from earlier treatment with vedolizumab.

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 OW22 recommendation and for reassessment of the broader use of vedolizumab to include grade 2 enterocolitis, AWTTC conducted a literature search for additional evidence. AWTTC excluded studies that had very small numbers of patients, or in which the grade of enterocolitis was not specified by treatment. Evidence identified included three retrospective studies and interim results from an ongoing clinical trial. All are discussed below.

Efficacy

Real world data

[confidential data removed]

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[12]. The CTCAE grade and overall grade (mild, moderate, severe) were used to assess the severity of colitis; and treatment and outcome were evaluated to compare the impact of the two categories. 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 28 patients were treated with steroids; 17 of them needed infliximab added and two patients were indicated for vedolizumab treatment. 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 ($P > 0.05$)[12].

Dahl et al. (2022) analysed the safety and efficacy of infliximab in ICI-induced enterocolitis; vedolizumab was required as a rescue treatment in 13 infliximab-refractory patients with ICI enterocolitis[13]. A complete or partial response was achieved in 77% of these 13 patients. On average the initial time to response was six days (interquartile range 5 to 12 days)[13].

In the **Machado et al.** study (n = 59) the median duration of corticosteroid treatment was 35 days when using vedolizumab, compared to 52 days for infliximab[14]. Treatment success rate was 73.7% (115 of 156) in the full population of patients who received infliximab, vedolizumab or combined treatment. New immune-related adverse events (irAEs) occurring in a median time frame of six to seven months after vedolizumab treatment were observed for seven patients, with some patients having more than one irAE. The most common new irAE was myositis or arthritis (4 patients), followed by elevated transaminases (3) and pneumonitis (2). The study concluded that vedolizumab 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[14].

Studies in progress

Wang et al. (2023) reported interim results from a randomised controlled trial (RCT) comparing infliximab with vedolizumab to treat grade 2 or higher ICI-related colitis (NCT04407247)[15]. A total of 15 patients had been enrolled so far, 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 intravenously and six received 300 mg vedolizumab intravenously 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%) given infliximab and three patients (50%) given 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[15].

For the original OW22 assessment, AWTTC's literature search identified a systematic review with meta-analysis and several retrospective studies; the most relevant are discussed below.

Abu-Sbeih et al. (2018) examined clinical outcomes of vedolizumab as an alternative treatment for ICI-induced enterocolitis (n = 28) in a retrospective study[16]. Fifteen patients (54%) had grade 2 enterocolitis. All patients had steroid-refractory gastrointestinal irAE. Nine patients received infliximab in addition to corticosteroids, symptoms were persistent or recurrent after one month of infliximab. Five of these patients had already received mesalamine. Median infliximab doses administered was two (interquartile range [IQR] 1 to 3). Patients had vedolizumab (300 mg each infusion) administered at a median of three doses (IQR 1 to 4). Mean follow-up was 15 months. Median duration from start of vedolizumab to symptom improvement was five days (IQR 1 to 30). Sustained clinical remission of enterocolitis was reached by 84% of patients (n = 24). Vedolizumab clinically failed in four patients. Patients with clinical remission (CR) of enterocolitis had shorter mean overall disease course (five months) compared with those who did not reach CR (eight months). Where infliximab failed clinically, three vedolizumab doses (median) were needed to achieve a

satisfactory result compared with instances when infliximab had not been used (two doses required). CR was reached by 67% of patients for whom infliximab did not work and by 95% of patients who did not receive infliximab[16].

Bergqvist et al. (2017) examined the use of vedolizumab for corticosteroid dependent (n = 4) and/or partially refractory ICI-induced enterocolitis (n = 3) in a retrospective study (n = 7)[17]. Patients received vedolizumab (300 mg each infusion) at time points zero, two and six weeks or until regression was observed. The median number of vedolizumab infusions given was two (range two to four). When starting vedolizumab treatment, five patients had grade 1 diarrhoea and one patient had grade 3 diarrhoea. All six patients had their prednisolone dose successfully tapered. The remaining patient was given vedolizumab before ICI treatment to prevent aggravation of underlying colitis; however, this was unsuccessful. Median time from vedolizumab treatment start to steroid-free remission from enterocolitis was 56 days (range 52 to 92 days)[17].

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[18]. Dosage concentration was not specified for either medicine. Median follow-up was 14 months (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). Median duration from first dose to either symptom remission or improvement to grade 1 was 13 days (IQR 8 to 29 days) for infliximab and 18 days (IQR 10 to 40 days) for vedolizumab (n = 138; p = 0.012) with a median steroid exposure of 51 days (IQR 41 to 68 days) for infliximab and 35 days (IQR 27 to 43 days) for vedolizumab (p = <0.001).

Median duration of hospitalisation was 14 days (IQR 8 to 19.8 days) for infliximab and 10 days (IQR 5 to 15 days) for vedolizumab (n = 107; p = 0.043). There were significantly more instances of individuals requiring multiple hospitalisations (p = 0.005) for infliximab (28%, n = 26) compared with vedolizumab (16%, 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 percentage of patients requiring hospitalisation (p = 0.367), the level of clinical remission (p = 0.785) or immunosuppressant associated infection (p = 0.184) between groups. Overall survival (OS) was more favourable for patients receiving vedolizumab (n = 62) compared with infliximab (n = 94; p = 0.027)[18].

Network meta-analyses

Nielsen et al. (2022) conducted a network meta-analysis (NMA) to assess the incidence of ICI-induced enterocolitis with monotherapy, combination therapy and management of both[6]. To assess the efficacy of biologics in the management of ICI-induced enterocolitis, 25 publications were identified (n = 613) reporting 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[19]. The pooled response to vedolizumab based on three studies (n = 50) was 85% (95% CI: 60 to 96). Infliximab was effective in 81% (95% CI: 73 to 87) of patients. Heterogeneity across the three studies was not found to be significant (I^2 = 52%, p = 0.12)[19].

Studies in progress

Treatment of Immune Checkpoint Inhibitor-Related Colitis with Infliximab or Vedolizumab: A Randomised Trial (NCT04407247)[20]. Interim data have been reported[15]. The estimated study completion date is end of December 2024[20].

Open-label Randomised Controlled Clinical Trial of Vedolizumab Versus Conventional Treatment for Checkpoint Inhibitor Induced Colitis (NCT04797325). Estimated study completion date is April 2025[21].

Safety

Clinicians in Wales reported outcome data. Of 5 patients with enterocolitis treated with vedolizumab, [confidential data removed].

Zou et al. (2021) reported infections affecting a fifth of the population receiving steroids and selective immunosuppressants (such as vedolizumab). Otherwise, safety was not reported within the remaining studies[18].

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[13]. Infection risk is a known adverse event for infliximab, vedolizumab and corticosteroids. 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[13].

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 such as vedolizumab) are unavoidable[3].

The Summary of Product Characteristics (SmPC) for vedolizumab (Entyvio®) lists contraindications; these include: active severe infections such as tuberculosis, sepsis, cytomegalovirus, listeriosis and opportunistic infections such as progressive multifocal leukoencephalopathy (PML)[2].

The SmPC special warnings include details about vedolizumab's association with acute hypersensitivity reactions including anaphylaxis, recommending administration occur in a healthcare setting equipped to manage such reactions. Vedolizumab selectively targets the gut and treatment should not be started in patients with active, severe infections until they are controlled; treatment should be stopped if a severe infection develops. Patients should be monitored for infections before, during and

after treatment. Some integrin antagonists (including vedolizumab) have been associated with PML and patients should be monitored for any new onset or worsening of neurological signs and symptoms, and consider neurological referral if they occur. The patient is to be given a Patient Alert Card. If PML suspected, vedolizumab treatment must be stopped and permanently discontinued if confirmed[2].

The SmPC lists very common (occurring in ≥ 1 in 10 people) adverse reactions as: nasopharyngitis, headache and arthralgia[2].

Patient factors

[Confidential data removed].

During the assessment of vedolizumab 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 vedolizumab in patients with ICI-induced colitis.

The experts reported that, similar to infliximab, vedolizumab helps a rapid wean from steroids, which reduces the risks associated with long-term steroid exposure. It also reduces the risk of more surgical intervention. They added that vedolizumab's gut specificity is particularly beneficial for this toxicity. Decisions on switching treatment from infliximab to vedolizumab are made case-by-case after consideration of clinical symptom progression plus faecal calprotectin and blood results.

The OWMAG also considered comments from the patient organisation 'Melanoma Focus'. The organisation highlighted that as a result of the availability of vedolizumab for this indication, patients could return home from hospital sooner. Melanoma Focus supported the co-creation of guidelines for grade 1–4 colitis between gastroenterology and oncology teams, and supported the use of vedolizumab if grade 3–4 symptoms worsen on steroid treatment. They stated the critical importance of being able to treat immunotherapy toxicity quickly. In the instance that the toxicity is refractory to steroids, the quicker that a second-line treatment can be given, the more efficacious it can be.

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 and earlier intervention with vedolizumab offers benefit to patients. 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 vedolizumab to treat ICI-induced grade 2–4 enterocolitis, where symptoms have not responded to first-line immunosuppression with corticosteroids, comes from retrospective studies and two NMAs. When compared to infliximab, vedolizumab may be associated with lower rates of multiple hospitalisations and recurrent infection. When reported, vedolizumab dosage used was consistent with that recommended in national and international guidelines (300 mg; three infusions). 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. It is therefore difficult to assess efficacy by symptom grade.

Clinical experts state that vedolizumab, for this indication, is given to patients who are usually mid-treatment or post-treatment for cancer (specifically those cancers that are indicated for ICI treatment such as melanoma or lung cancers). The indication is rare, given that immunotherapy is a relatively new treatment option for a growing number of cancer indications. The incidence is expected to rise as the use of immunotherapy does. 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 show that 49% of patients are still alive with more than 75% treatment-free[22]. 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 vedolizumab.

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[23]. 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)[23].

Clinicians have stated that there are some patients who require multiple treatment courses with steroids for relapses and note concerns regarding the increase risk of steroid-related adverse events due to repeated exposure[24-30]. They would welcome the option to use vedolizumab in this patient group to with the aim to prevent future relapses. One retrospective study specifically reported use in patients who were corticosteroid dependent and/or had partially refractory ICI-induced enterocolitis. The majority of patients had grade 1 diarrhoea (n = 5) and all were able to taper their steroid dose down, median time to steroid-free remission being 56 days[17].

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[1,31]. 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[27]. In addition, cumulative doses of corticosteroids are associated with an increased risk of fractures, high blood sugar, cataracts, weight gain, skin and sleep problems[32]. Short-term oral corticosteroid use has cumulatively been associated with osteoporosis, hyperglycaemia and muscle weakness, even when given for <7 days[29]. Allowing use of vedolizumab 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.

Infliximab blocks TNF-alpha, reducing inflammatory response throughout the body and this reduces the efficacy of the immunotherapy cancer treatment. However, vedolizumab works only in the bowel and thus has the advantage of not affecting the efficacy of the cancer treatment. The BSG state that the gut-selective mechanism of action of vedolizumab, which would not be anticipated to interfere with the efficacy of ICI therapy, might be an especially attractive option for ICI-induced enterocolitis[3].

Clinicians suggest vedolizumab has further additional benefits. Infliximab induces widespread immunosuppression thus increasing the risk of latent and serious infections, whereas vedolizumab targets the gut and has no identified systemic immunosuppressive activity[2]. Therefore, vedolizumab is likely to present fewer risks of complications from treating ICI-induced enterocolitis. Clinicians state that there is increasing evidence to support the use of vedolizumab in older patients who are particularly at risk from opportunistic infections secondary to immunosuppression with infliximab. Much of the supporting data has been extrapolated from IBD evidence[33]. However, prescribers should be aware of the potential increased risk of opportunistic infections or infections for which the gut is a defensive barrier[2]. The SmPC states that vedolizumab should not to be initiated in patients with active, severe infections until the infections are controlled. Caution should be exercised when considering the use of vedolizumab in patients with a controlled chronic severe infection or a history of recurring severe infections. Patients should be monitored closely for infections before, during and after treatment[2].

The National Institute for Health and Care Excellence (NICE) recommends vedolizumab for the treatment of moderately to severely active ulcerative colitis in adults (TA342)[34]. NICE recommends vedolizumab for treating moderately to severely active Crohn's disease only if a TNF-alpha inhibitor has failed or a TNF-alpha inhibitor cannot be tolerated or is contraindicated (TA352)[35]. 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 vedolizumab 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.

Cost-effectiveness evidence

An AWTTC literature review did not identify any cost-effectiveness studies of vedolizumab for treating ICI-induced grade 2 enterocolitis, when symptoms have not responded to first-line immunosuppression with corticosteroids or require multiple challenge with corticosteroids.

Cost-consequence analysis

An AWTTC cost-consequence analysis compares the cost of intravenous vedolizumab in combination with oral corticosteroids in the treatment of ICI-induced grade 2 enterocolitis with standard of care. 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 vedolizumab procurement and administration. The analysis adopts a life-time 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 vedolizumab is 300 mg given intravenously on Weeks 0, 2 and 6; this is in addition to corticosteroids.

Cost of intervention and comparator

The confidential NHS Wales contract price for vedolizumab 300 mg is [commercial in confidence figure removed] (excluding VAT). The administration cost for the delivery of vedolizumab 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. Subsequent delivery is costed at £326.46[36]. The delivery of three doses of vedolizumab with administration costs equals [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 vedolizumab for grade 2 enterocolitis are broad and evidence is heterogenous. Three studies across the severity grade (grades 1–4) found that vedolizumab 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 vedolizumab in combination with corticosteroids to be 88% (95% CI: 62% to 100%)[19]. 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 vedolizumab 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[37]. This cost was calculated by applying the oral corticosteroid relative risk of seven adverse events to the prevailing incidence rate and then multiplying by associated costs[32]. Fractures were the main cost driver across the seven discrete adverse events. The seven adverse events 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[23].

Adverse events associated with vedolizumab 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 nasopharyngitis, headache and arthralgia[2].

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[38]. Welsh clinical experts suggest that intervention at grade 2 with vedolizumab 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 vedolizumab 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 vedolizumab. 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. Vedolizumab cost-consequence analysis

Vedolizumab plus standard of care: 300 mg vedolizumab given intravenously on Weeks 0, 2 and 6 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 88% (95% CI 62% to 100%)[19]. • Reduction in continued oral steroid use and steroid burden (adverse events and healthcare costs) • Lower infection rates (14.3%)† [23] • Vedolizumab 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**: • Unknown curative rate, patients have not responded to first-line immunosuppression with corticosteroids • Continued oral steroid use and steroid burden (adverse events and healthcare costs) • Higher infection rates (42.9%)† [23] **Clinical opinion** • Higher hospitalisation rate compared to vedolizumab 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 vedolizumab, AWTTC conducted a threshold analysis to estimate the minimum required quality-adjusted life year (QALY) gain required for vedolizumab 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 QALY gain of [commercial in confidence figure removed].

A disease burden QALY is calculated to contextualise the threshold; this consists of estimates of the disease duration and health-related quality of life (HRQoL) decrement.

An AWTTC literature review identified a recent study that reports the median time to resolution with grade 2 colitis of 52 days[12]. No direct evidence of the 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[39]. Therefore, a subsequent targeted literature review was 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 QoL decrement of 0.20[40]. 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[34] which reported estimates of 0.88 for ulcerative colitis remission and 0.42 for active disease. 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[41]. 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 that 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 scenario analyses to assess the influence of key variables and assumptions. The comparator in the base case is the continuation of oral corticosteroids, a plausible comparator is infliximab. The recommended dose of

infliximab is 5 mg/kg[42]. 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[8].

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). Administration of infliximab incurs the same cost as vedolizumab. The average patient weight is included according to an equal gender distribution at 77.25 kg[43,44]. The scenario assumes three cycles of infliximab 5 mg/kg with no vial sharing which cost a total of [commercial in confidence figure removed]. The intervention cost of vedolizumab is [commercial in confidence figure removed]resulting in a net intervention cost of [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[19]. Including other disease grades may be misleading if there is a significant interaction between severity and curative rates. There is evidence suggesting that lower less severe grades respond more quickly to therapeutic intervention[12].
- 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, 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 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.

Budget impact

Clinicians in Wales estimate that 2 extra patients with grade 2 enterocolitis would be eligible for treatment with vedolizumab per year in addition to the 10 patients with grade 3–4 enterocolitis estimated in the original assessment, thereby giving 12 patients in total.

The vedolizumab treatment regimen is typically 300 mg given intravenously on weeks 0, 2 and 6. It is assumed that people would have three vedolizumab doses, received within a single year. Medicine and administration costs for this regimen are shown in Table 2.

Table 2. Estimated annual costs for vedolizumab (Entyvio®) per patient in Wales

	Treatment cost	Administration cost†	Total annual cost per patient
Vedolizumab (Entyvio®) 300 mg*	¶¶	£861	¶¶
*Three doses, confidential NHS Wales contract price plus VAT † 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 five doses (HRG code SB15Z)[36] ¶¶ commercial in confidence figure removed			

The total annual costs for 12 patients are given in Table 3.

Table 3. Estimated annual costs for vedolizumab for 12 patients in Wales

	Year 1
Number of patients	12
Total annual costs for three vedolizumab (Entyvio®) doses	¶¶
¶¶ commercial in confidence figure removed	

Budget impact issues

The confidential NHS Wales contract price for vedolizumab (Entyvio®) has been used in the calculations.

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. Additional screening and monitoring and adverse event costs are also excluded from the budget impact.

The majority of eligible patients in Wales with grade 3–4 ICI-induced enterocolitis that hasn't responded to infliximab or for whom infliximab is unsuitable, can already receive vedolizumab under the existing OW22 recommendation[1]. Expanding the population to include patients with steroid-refractory grade 2 enterocolitis or requiring multiple re-challenge with corticosteroids is estimated to result in 2 additional patients per year. The recalculated yearly budget impact is [commercial in confidence figure removed] compared to a budget impact of [commercial in confidence figure removed] for the original assessment.

However, 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

Vedolizumab (Entyvio®) 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.

References

1. All Wales Therapeutics and Toxicology Centre. Vedolizumab (Entyvio®) powder for solution for infusion. Reference number: OW22. Assessment information. Feb 2023. Available at: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/one-wales-vedolizumab-entyvio-for-ici-induced-enterocolitis-ow22/. Accessed Jun 2024.
2. Takeda UK Ltd. Entyvio®. Summary of Product Characteristics. May 2024. Available at: https://www.medicines.org.uk/emc/product/5442/smpc. Accessed May 2024.
3. Powell N, Ibraheim H, Raine T et al. British Society of Gastroenterology endorsed guidance for the management of immune checkpoint inhibitor-induced enterocolitis. *The Lancet Gastroenterology and Hepatology.* 2020;5:679-697.
4. Schneider BJ, Naidoo J, Santomasso BD et al. Management of Immune-Related Adverse Events in Patients Treated With Immune Checkpoint Inhibitor Therapy: ASCO Guideline Update. *Journal of Clinical Oncology.* 2021;39(36):4073-4126.
5. Alexander JL, Ibraheim H, Sheth B et al. Clinical outcomes of patients with corticosteroid refractory immune checkpoint inhibitor-induced enterocolitis treated with infliximab. *Journal for ImmunoTherapy of Cancer.* 2021;9.
6. Nielsen DL, Juhl CB, Chen IM et al. Immune checkpoint Inhibitor–Induced diarrhea and Colitis: Incidence and Management. A systematic review and Meta-analysis . *Cancer Treatment Reviews.* 2022;109.
7. East of England Priorities Advisory Committee. Infliximab for the management of diarrhoea or colitis associated with Immune Checkpoint Inhibitor (ICPI) therapy. 2019. Available at: https://medicines.bedfordshirelutonandmiltonkeynes.icb.nhs.uk/wp-content/uploads/2020/10/Infliximab-for-colitis-assoc-with-immune-checkpoint-therapyss-1.pdf. Accessed May 2024.
8. Haanen J, Obeid M, Spain L et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guideline for diagnosis, treatment and follow-up. *Annals of Oncology.* 2022;33(12):1217-1238.
9. Thompson JA, Schneider BJ, Brahmer J et al. Management of Immunotherapy-Related Toxicities, Version 1.2020. *Journal of the National Comprehensive Cancer Network.* 2020;18(3):230-241.
10. Brahmer J, Abu-Sbeih H, Ascierto PA et al. Society for Immunotherapy of Cancer (SITC) clinical practice guideline on immune checkpoint inhibitor-related adverse events. *Journal for ImmunoTherapy of Cancer.* 2021;9(6).
11. Amiot A, Laharie D, Malamut G et al. Management of immune checkpoint inhibitor in patients with cancer and pre-existing inflammatory bowel disease: recommendations from the GETAID. *Digestive and Liver Disease.* 2022;54(9):1162-1167.
12. Nguyen TL, Tew A, Kirton L et al. Evaluation of colitis induced by immune checkpoint inhibitors therapy in melanoma patients by an overall grading scale. *Journal of Oncology Pharmacy Practice.* 2024;0(0):doi:10.1177/10781552241248057.
13. Dahl EK, Abed OK, Kjeldsen J et al. Safety and efficacy of infliximab and corticosteroid therapy in checkpoint inhibitor-induced colitis. *Alimentary Pharmacology & Therapeutics.* 2022;56(9):1370-1382.
14. Machado AP, Shatila M, Glitza Oliva IC et al. Impact of selective immunosuppressive therapy on subsequent immune-related adverse events

after immune checkpoint inhibitor-induced colitis treatment. *American Journal of Clinical Oncology.* 2023;46(8):350-365.
15. Wang YH, Varatharajalu K, Shatila M et al. Randomized clinical trial of infliximab versus vedolizumab for immune checkpoint inhibitor related colitis. Presented at Digestive Disease Week. 6-9 May 2023. *Gastroenterology*. 164 (6 Suppl). DOI: 10.1016/S0016-5085%2823%2903549-7. Accessed May 2024.
16. Abu-Sbeih H, Ali FS, Alsaadi D et al. Outcomes of vedolizumab therapy in patients with immune checkpoint inhibitor–induced colitis: a multi-center study. *Journal for ImmunoTherapy of Cancer.* 2018;6(142).
17. Bergqvist V, Hertervig E, Gedeon P et al. Vedolizumab treatment for immune checkpoint inhibitor-induced enterocolitis. *Cancer Immunology, Immunotherapy.* 2017;66:581-592.
18. Zou F, Faleck D, Thomas A et al. Efficacy and safety of vedolizumab and infliximab treatment for immune-mediated diarrhea and colitis in patients with cancer: a two-center observational study. *Journal for ImmunoTherapy of Cancer.* 2021;9.
19. Ibraheim H, Baillie S, Samaan MA et al. Systematic review with meta-analysis: effectiveness of anti-inflammatory therapy in immune checkpoint inhibitor-induced enterocolitis. *Alimentary Pharmacology & Therapeutics.* 2020;52:1432-1452.
20. M.D. Anderson Cancer Center. NCT04407247: Treatment of Immune Checkpoint Inhibitor-Related Colitis With Infliximab or Vedolizumab: A Randomized Trial. May 2024. Available at: https://clinicaltrials.gov/ct2/show/NCT04407247. Accessed May 2024.
21. University of Copenhagen. NCT04797325: Open Label Randomized Controlled Clinical Trial of Vedolizumab Versus Conventional Treatment for Checkpoint Inhibitor Induced Colitis. Aug 2022. Available at: https://clinicaltrials.gov/ct2/show/NCT04797325. Accessed May 2024.
22. Wolchok JD, Chiarion-Sileni V, Gonzalez R et al. CheckMate 067: 6.5-year outcomes in patients (pts) with advanced melanoma. *Journal of Clinical Oncology.* 2021;39(15_suppl):9506-9506. Available at: https://ascopubs.org/doi/abs/10.1200/JCO.2021.39.15_suppl.9506.
23. Wang YH, Abu-Sbeih H, Mao E et al. Immune-checkpoint inhibitor-induced diarrhea and colitis in patients with advanced malignancies: retrospective review at MD Anderson. *Journal for ImmunoTherapy of Cancer.* 2018;6(37):1-13.
24. Waljee AK, Rogers MAM, Lin P et al. Short term use of oral corticosteroids and related harms among adults in the United States: population based cohort study. *BMJ.* 2017;357:j1415.
25. Min KH, Rhee CK, Jung JY et al. Characteristics of adverse effects when using high dose short term steroid regimen. *Korean Journal of Audiology.* 2012;16:65-70.
26. Yasir M, Goyal A, and Sonthalia S. Corticosteroid adverse effects. In StatPearls [Internet}. Treasure Island (FL): StatPearls Publishing; 2024 Jan-. Jul 2023. Available at: https://www.ncbi.nlm.nih.gov/books/NBK430685/. Accessed Jul 2024.
27. Warrington TP, and Bostwick JM. Psychiatric adverse effects of corticosteroids. *Mayo Clinic Proceedings.* 2006;81(10):1361-1367.
28. Joseph RM, Hunter AL, Ray DW et al. Systemic glucocorticoid therapy and adrenal insufficiency in adults: a systematic review. *Seminars in Arthritis and Rheumatism.* 2016;46:133-141.

29. Heaney LG, Schleich F, Korn S et al. Recognising the long-term burden of short course oral corticosteroids. Presented at 2021 ERS International Congress. 5-8 September 2021. European Respiratory Journal 2021; 58: Suppl. 65, PA3548.
30. National Institute for Health and Care Excellence. Clinical Knowledge Summary: Corticosteroids - oral. . Jan 2024. Available at: https://cks.nice.org.uk/topics/corticosteroids-oral/management/corticosteroids/. Accessed Jul 2024.
31. All Wales Therapeutics and Toxicology Centre. Infliximab powder for solution for infusion. Reference number: OW21. Assessment information. Feb 2023. Available at: https://awttc.nhs.wales/accessing-medicines/medicine-recommendations/one-wales-infliximab-for-ici-induced-enterocolitis-ow21/. Accessed Jun 2024.
32. Manson SC, Brown RE, Cerulli A et al. The cumulative burden of oral corticosteroid side effects and the economic implications of steroid use. *Respiratory Medicine.* 2009;103:975-994.
33. Attauabi M, Hoglünd C, Fassov J et al. Vedolizumab as first-line biological therapy in elderly patients and those with contraindications for anti-TNF therapy: a real-world, nationwide cohort of patients with inflammatory bowel diseases. *Scandinavian Journal of Gastroenterology* 2021;56(9).
34. National Institute for Health and Care Excellence. Technology Appraisal 342. Vedolizumab for treating moderately to severely active ulcerative colitis. Jun 2015. Available at: https://www.nice.org.uk/guidance/ta342. Accessed May 2024.
35. National Institute for Health and Care Excellence. Technology Appraisal 352 Vedolizumab for treating moderately to severely active Crohn's disease after prior therapy. Aug 2015. Available at: https://www.nice.org.uk/guidance/ta352. Accessed May 2024.
36. NHS England. 2021/22 National Cost Collection Data Publication. 2023. Available at: https://www.england.nhs.uk/publication/2021-22-national-cost-collection-data-publication/. Accessed Jun 2024.
37. Personal Social Services Research Unit. Unit costs of health and social care, 2022. 2022. Available at: https://www.pssru.ac.uk/unitcostsreport/. Accessed Jul 2024.
38. Haanen JBAG, Carbonnel F, Robert C et al. Management of toxicities from immunotherapy: ESMO Clinical Practice Guidelines for diagnosis,treatment and follow-up. *Annals of Oncology.* 2017;28(4):119-142.
39. Torkizadeh M, Ibraheim H, Radhakrishnan S et al. Health-related quality of life in patients with checkpoint inhibitor enterocolitis. Presented at BSG Annual Meeting. 8-12 November 2021. *Gut*. 70 (4 Suppl). PMO-46.
40. Vaizey CJ, Gibson PR, Black CM et al. Disease status, patient quality of life and healthcare resource use for ulcerative colitis in the UK: an observational study. *Frontline Gastroenterology.* 2014;5(3):183-189.
41. Kaufman HL, Hunger M, Hennessey M et al. Nonprogression with avelumab treatment associated with gains in quality of life in metastatic Merkel cell carcinoma. *Future Oncology.* 2018;14(3):255-266.
42. Merck Sharp & Dohme (UK) Limited. REMICADE®. Summary of Product Characteristics. Jul 2022. Available at: https://www.medicines.org.uk/emc/product/3831/smpc. Accessed Oct 2022.
43. Onaverage. Average Weight of a Man. Available at: https://www.onaverage.co.uk/body-averages/average-weight-of-a-man. Accessed Jun 2024.

44. Onaverage. Average Weight of a Female. Available at: https://www.onaverage.co.uk/body-averages/average-female-weight. Accessed Oct 2024.

Appendix 1: Weighted cost of infliximab

[commercial in confidence figures removed]