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 grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids and/or other immunosuppressant drugs like infliximab, or when infliximab is unsuitable **(OW22)**

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

Licence status
Vedolizumab (Entyvio®) is not licensed for treating immune checkpoint inhibitor (ICI) induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids and/or other immunosuppressant drugs like infliximab, or when infliximab is unsuitable; its use for this indication is off-label.

Clinical evidence
The clinical evidence for the use of vedolizumab in this setting comes from a systematic review with meta-analysis and four 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, one-hour monitoring post-infusion is sufficient for subsequent infusions).

Cost effectiveness
No relevant cost-effectiveness analyses were identified in the literature search.

Budget impact
Clinicians consulted by AWTTC estimate that ten people in Wales per year would be likely to be eligible to receive vedolizumab in this setting. It is assumed that people would have at least three vedolizumab doses, received within a single year. This is associated with an annual cost of [Commercial in confidence figure removed].

Impact on health and social care services
Patients with ICI induced enterocolitis in Wales are currently receiving vedolizumab 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.

Innovation and/or advantages
Vedolizumab may reduce the need for more invasive interventions for this cohort. Managing the toxicity of cancer treatments improves the chance for cancer to be cured for this cohort of patients.

Background

Clinicians in Wales consider there is an unmet need and have identified a cohort of patients who could benefit from this treatment. Vedolizumab was therefore considered suitable for assessment though the One Wales medicines process.

The All Wales Therapeutics and Toxicology Centre (AWTTC) sought opinions from clinical experts in Wales, who said the incidence of immune checkpoint inhibitor (ICI) 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 vedolizumab considered a treatment option for ICI induced enterocolitis refractory to infliximab or infliximab contraindicated ICI induced enterocolitis. Patients with ICI induced enterocolitis in Wales, for whom infliximab is unsuitable or refractory, 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 the treatment of ICI induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids and/or other immunosuppressant drugs like infliximab, or when infliximab is unsuitable.

Marketing authorisation date: Not applicable, off-label

Vedolizumab (Entyvio®) is not licensed for the treatment of ICI induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids and/or other immunosuppressant drugs like infliximab, or when infliximab is unsuitable.

The marketing authorisation holder of vedolizumab (Entyvio®) is not planning to apply for a licence to use vedolizumab for the indication under consideration.

Dosing information

The recommended dose is 300 mg intravenously on weeks zero, two and six[1].

Clinical background

Immune-related enterocolitis is one of the most common and severe immune-related adverse events (irAE) associated with ICI treatment[2,3]. 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[4].

Diarrhoea and colitis are considered separately within the National Cancer Institute's Common Terminology Criteria for Adverse Events (CTCAE) tool[2]:

- Grade 3-4 colitis presents with severe abdominal pain or peritoneal signs leading to life-threatening consequences or urgent intervention indicated.
- Grade 3-4 diarrhoea presents with 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) recommend that the CTCAE tool not 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[2].

Incidence/prevalence

Incidence of ICI induced enterocolitis will vary greatly depending on the ICI treatment and dosage used[5]. 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 while 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%)[2]. Incidence of all grade colitis is estimated to be 2% and 7% respectively. Incidence of severe (grade 3-4) colitis is estimated to be 0.2% with anti-PD-1 treatment, 0.04% with anti-PD-L1 treatment 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 one- and two-thirds of those receiving anti-CTLA-treatment and approximately 12.5% of those receiving anti-PD-1 treatments[6]. There are no definitive estimates for the number of patients who fail on infliximab treatment and would go on to receive vedolizumab, but this is likely to be in the region of 20% based on data from retrospective studies[7,8].

Clinicians consulted by AWTTC estimated that ten people in Wales per year would be likely to be eligible to have vedolizumab for ICI induced grade 3-4 enterocolitis that has not responded to corticosteroids or infliximab or where infliximab is unsuitable.

Current treatment options and relevant guidance

Treatment of ICI induced grade 3-4 enterocolitis that has not responded to corticosteroids or infliximab is currently treated off licence in Wales with vedolizumab through local agreements.

A number of national and international guidelines have been on published on this topic with some variations in their recommendations[2,3,9-11]. Generally, for patients with grade 3-4 enterocolitis, early introduction of infliximab or vedolizumab should be considered in addition to steroids in patients with high-risk features on initial endoscopy examination or severe ulcerative presentation on colonoscopy. They may

also be started where there is no response to high dose steroids usually within two to three days[2,3,9,11] 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 on a case by case basis[11]. Pre-existing IBD not is 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[2]. 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[2].

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).

Summary of evidence on clinical effectiveness

AWTTC conducted a literature search and identified a systematic review with meta-analysis and four retrospective studies.

Efficacy

Burdett et al. (2020) retrospectively examined cancer-specific outcomes of patients (n = 19) who received immunosuppressive medicine in addition to corticosteroids for irAE management after ICI therapy[12]. All 14 patients who had irAE colitis received infliximab. Three patients had infliximab refractory colitis and received vedolizumab, a fourth patient received ciclosporin. Doses were not specified in the report. The cancer outcomes (radiological response) of the three patients who received vedolizumab after infliximab therapy were partial response for one and two had progressive disease[12].

Abu-Sbeih et al. (2018) examined clinical outcomes of vedolizumab as an alternative treatment for ICI induced enterocolitis in a retrospective study (n = 28)[13]. Less than half of the patients had grade 3-4 enterocolitis (n = 13). 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 dose was two (Interquartile range [IQR] 1 to 3). Patients received vedolizumab (300 mg each infusion) at a median 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% (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 clinically failed, three vedolizumab infusions (median) were needed to achieve a satisfactory result compared with instances when infliximab had not been used (two infusions required). CR was reached by 67% of patients for whom infliximab did not work and by 95% of patients who did not receive infliximab[13].

Bergqvist et al. (2017) examined the use of vedolizumab for corticosteroid dependent and/or partially refractory ICI induced enterocolitis in a retrospective study (n = 7)[14]. 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. The patient with grade 3 diarrhoea had previously failed on infliximab therapy. All six patients were able to have their prednisolone dose successfully tapered. The remaining patient was given vedolizumab prior to 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)[14].

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[7]. 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) 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. Overall survival (OS) was more favourable for patients receiving vedolizumab (n = 62) compared with infliximab (n = 94; p = 0.027)[7].

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[5]. 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[5].

Ibraheim et al. (2020) conducted a NMA to investigate the effectiveness of anti-inflammatory therapy (corticosteroids, infliximab or vedolizumab) in ICI induced enterocolitis[8]. The pooled response to vedolizumab based on three studies (n = 50) was 85% (95% CI: 60 to 96),heterogeneity across the three studies was not found to be significant (I^2 = 52%, p = 0.12)[8].

Studies in progress

Treatment of Immune Checkpoint Inhibitor-Related Colitis with Infliximab or Vedolizumab: A Randomized Trial (NCT04407247). Estimated study completion date, December 2022[15].

Open Label Randomized Controlled Clinical Trial of Vedolizumab Versus Conventional Treatment for Checkpoint Inhibitor Induced Colitis (NCT04797325). Estimated study completion date, April 2025[16].

Safety

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[7].

The BSG reports a tendency for higher corticosteroid dosing in ICI induced enterocolitis, compared with ulcerative colitis, often in combination with infliximab[2]. This may result in a greater risk of *Pneumocystis jirovecii* infection for those patients receiving ICIs and the authors suggest *Pneumocystis jirovecii* infection prophylaxis should be considered only when combinations of high dose corticosteroids and infliximab (or other immunosuppressive medicines such as vedolizumab) are unavoidable[2].

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)[1].

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[1].

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

Discussion

Evidence for the off-label use of vedolizumab to treat ICI induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids and/or other immunosuppressant drugs like infliximab, or when infliximab is unsuitable, comes from four retrospective studies and two NMAs. Overall the data are limited, with some data suggesting treatment efficacy after infliximab failure. When compared to infliximab, vedolizumab may be associated with lower hospitalisation and recurrent infection rates. 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).

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, and that vedolizumab would be used for infliximab refractory disease or for those patients where use of infliximab is contraindicated. 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 shows 49% of patients are still alive with more than 75% treatment free[17]. 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.

The clinicians go on to state that vedolizumab rather than infliximab is preferable when patients have significant disease burden and limited systemic options other than immunotherapy. Infliximab blocks TNF alpha, reducing inflammatory response throughout the body and this reduces the efficacy of the immunotherapy cancer treatment. Vedolizumab however 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[2].There may therefore be a role for vedolizumab for patients deemed to be unsuitable for infliximab.

Clinicians suggest further additional benefits of vedolizumab. 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[1]. 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[18]. Prescribers should be aware however of the potential increased risk of opportunistic infections or infections for which the gut is a defensive barrier[1]. 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[1].

The National Institute for Health and Care Excellence (NICE) recommends vedolizumab for the treatment of moderately to severely active ulcerative colitis in adults (TA342)[19]. 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)[20]. 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.

Patients with ICI induced enterocolitis in Wales are currently receiving vedolizumab 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.

Cost-effectiveness evidence

No studies on the cost-effectiveness of vedolizumab for this indication were identified. Cost effectiveness evidence for the use of vedolizumab to treat ulcerative colitis and Crohn's disease was not considered to be a suitable proxy for this intervention given that patient characteristics, treatment and clinical course would not be the same for this patient cohort. Associated costs and benefits therefore would be quite different leading to significant uncertainty with any comparisons.

Budget impact

Across published guidance and literature, the vedolizumab (Entyvio®) treatment regimen was typically 300 mg on weeks zero, two and six. Medicine and administration costs for this regimen are shown in Table 1. Clinicians estimate that 200 patients in Wales are investigated for ICI induced diarrhoea each year. Of this group they estimate that around ten people in Wales per year would have stage 3-4 enterocolitis that either does not respond to infliximab treatment or for whom infliximab treatment is unsuitable and would be eligible for treatment with vedolizumab. It is assumed that people would have three vedolizumab doses, received within a single year. The acquisition cost for ten patients is shown in Table 2.

Table 1. Estimated annual costs for vedolizumab (Entyvio®) per patient in Wales

	Treatment cost	Administration cost†	Total annual cost per patient
Vedolizumab (Entyvio®) 300 mg*	¶¶	£1,469	¶¶
NA: not applicable *Three doses, confidential NHS Wales contract price plus VAT ¶¶ commercial in confidence figure removed † 2020-2021 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)[21]			

Table 2. Estimated annual acquisition costs for vedolizumab for ten patients in Wales

	Year 1
Number of patients	10
Total annual costs for three vedolizumab (Entyvio®) doses	¶¶
¶¶ commercial in confidence figure removed	

Budget impact issues

Vedolizumab (Entyvio®) simple PAS cost 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.

Clinicians consider vedolizumab to be a third line of treatment for ICI induced enterocolitis after infliximab. For patients who do not respond to vedolizumab, treatment options include surgical intervention (colectomy). Other treatment options that have been suggested in guidelines include mycophenolate mofetil, tacrolimus and ciclosporin.

As patients with ICI induced enterocolitis in Wales are generally receiving vedolizumab through local agreements, current treatment costs are already being absorbed to some extent by health boards. However, the usage of ICIs is growing and incidence will increase over time, it is anticipated that patient numbers will double 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.

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