The East of England
Priorities Advisory Committee
Hosted by PrescQIPP

GUIDANCE STATEMENT

Infliximab for the management of diarrhoea or colitis associated with Immune Checkpoint Inhibitor (ICPI) therapy

PAC recommendations

East of England Priorities Advisory Committee recommendations

- Infliximab is recommended for the treatment of severe Immune Checkpoint Inhibitor (ICPI) related diarrhoea or colitis grade 3 or 4, in line with the treatment pathway outlined in appendix 1.
- Treatment must be initiated and monitored under the guidance of a gastroenterologist and oncologist.
- Ipilimumab monotherapy and in combination with nivolumab must be permanently discontinued in patients with grade 3 or 4 diarrhoea or colitis. Other Immune Checkpoint Inhibitors (nivolumab monotherapy, pembrolizumab, atezolizumab) must be permanently discontinued in patients with grade four diarrhoea or colitis.
- All other causes, including cytomegalovirus (CMV) infection/reactivation and other viral, bacterial and parasitic aetiology, must be excluded along with any other clinical contraindications (e.g. gastrointestinal perforation or sepsis) before starting infliximab.
- A single dose of biosimilar infliximab 5mg/kg should be considered as a second line option for corticosteroid-refractory grade 3 or 4 diarrhoea or colitis related to the ICPI therapy, following treatment with systemic high-dose intravenous corticosteroids for three to five days.
- A second dose of infliximab at two weeks may be necessary for some patients. Very rarely a third dose may be required.
- Outcome data must be provided to the Clinical Commissioning Group (CCG) to inform future policy.
- These recommendations will be reviewed on publication of guidelines from the British Society of Gastroenterology or other national guidelines.

Key points

- Ipilimumab, an Immune Checkpoint Inhibitor monoclonal antibody, is recommended by NICE as a treatment option for patients with advanced (unresectable or metastatic) melanoma, and in combination with nivolumab for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma
- Ipilimumab is associated with Immune-related Adverse Events (IrAEs), which can be severe or life-threatening. The most common immune-related adverse reactions are gastrointestinal symptoms, mainly diarrhoea and colitis

- Other ICPIs currently used in the UK include nivolumab, pembrolizumab and atezolizumab. IrAEs, including colitis, have also been observed during treatment with these agents, with colitis occurring less frequently than with ipilimumab.
- Data from a phase 3 trial (MDX010-20) and several supportive phase 1 and 2 trials was used to gain marketing authorisation for ipilimumab from the European Medicines Agency for the treatment of advanced melanoma.
- The MDX010-20 trial protocol suggested the use of oral or intravenous corticosteroids for the management of colitis. The use of infliximab or any other Tumour Necrosis Factor (TNF) alfa inhibitor was not mentioned in the trial protocol.
- At the end of the MDX010-20 trial, four patients received infliximab for diarrhoea of grade 3 or higher or colitis.
- The manufacturer of ipilimumab was unable to provide the rationale for the use of infliximab. However, it has been suggested that the use of a TNF alfa inhibitor such as infliximab in patients who failed to response to steroids is based on its use for Crohn's disease and ulcerative colitis.
- After MDX010-20, infliximab 5mg/kg was included in other trial protocols involving ipilimumab for the management of grade 3 or 4 diarrhoea.
- The SPC for ipilimumab states that addition of an alternative immunosuppressive agent to the corticosteroid regimen should be considered in corticosteroid-refractory immune-related colitis if other causes are excluded. In clinical trials, a single dose of infliximab 5mg/kg was added unless contraindicated.
- The West Midlands Cancer Alliance and Thames Valley Strategic Clinical Network have issued guidelines for managing immune-oncology related immune related adverse events. A stat dose of biosimilar infliximab 5mg/kg, followed by an additional dose at two weeks is recommended for the management of grade 3 or 4 diarrhoea or colitis if the symptoms fail to resolve after three to five days of high dose intravenous corticosteroids.
- No other TNF alfa inhibitors have been used for the management of severe ICPI induced diarrhoea or colitis
- There is no data available on safety, adverse effect profile or efficacy of infliximab in patients treated with ICPIs. As both classes of drugs can be immunosuppressive, their effects might be additive and increase the incidence of neutropenia and severe infections.
- According to the recent MHRA warning, in patients with immune-related colitis who are refractory to corticosteroids, the addition of an immunosuppressive agent (such as infliximab) should only be considered if the other causes have been excluded, including cytomegalovirus infection or reactivation.
- Guidelines on the management of ICPI induced colitis from the British Society of Gastroenterology are currently in development. These recommendations will be reviewed in the light of new evidence and publication of national guidelines.

Background

Ipilimumab, an Immune Checkpoint Inhibitor monoclonal antibody, is recommended as a treatment option for patients with previously treated advanced (unresectable or metastatic) melanoma.[1] Ipilimumab is also recommended as a treatment option for adults with previously untreated advanced (unresectable or metastatic) melanoma.[2] It is also indicated in combination with nivolumab for the first-line treatment of adult patients with intermediate/poor-risk advanced renal cell carcinoma.[3]

Ipilimumab is associated with IrAEs resulting from increased or excessive immune activity (immune-related adverse reactions), likely to be related to its mechanism of action. Immune-related adverse reactions, which can be severe or life-threatening, may involve the gastrointestinal, liver, skin, nervous, endocrine, or other organ systems. The most common gastrointestinal symptom is diarrhoea, which can be a sign of colitis or bowel perforation.[3]

Other ICPI, currently used in the UK, include nivolumab, pembrolizumab and atezolizumab (via Cancer Drug Fund). IrAEs can also be observed during treatment with these agents.[4-6] Ipilimumab can be used in combination with nivolumab for the treatment of advanced (unresectable or metastatic) melanoma.[7] Immune-related adverse reactions have occurred at higher frequencies in combination therapy compared with nivolumab monotherapy.[3,4]

The two main forms of inflammatory bowel diseases are Crohn's disease and ulcerative colitis. Both conditions are associated with the presence of diarrhoea.[8,9] Choice of drug treatment may include aminosalicylates, corticosteroids and biological drugs for ulcerative colitis, and glucocorticosteroids, aminosalicylates, antibiotics, immunosuppressives and tumour necrosis factor (TNF) alfa inhibitors for Crohn's disease.[10,11] A TNF alfa inhibitor, such as infliximab, is recommended as a treatment option in adults, whose disease has not responded or responded inadequately to conventional therapy.[12,13]

The SPC for ipilimumab states that addition of an alternative immunosuppressive agent to the corticosteroid regimen should be considered in corticosteroid-refractory immune-related colitis if other causes are excluded. In clinical trials, a single dose of infliximab 5mg/kg was added unless contraindicated.[3]

The aim of this document is to review the recommended management options for diarrhoea and/or colitis related to ICPI therapy and summarise the evidence for using infliximab for this indication.

Clinical evidence

In May 2011, ipilimumab (YERVOY®) was approved by the European Medicines Agency (EMA) for the treatment of advanced melanoma in adults who have received prior therapy. The Marketing Authorisation was granted based on the evidence from one phase 3 trial (MDX010-20) and seven supportive phase 1 and 2 trials.[14]

In MDX010-20, a randomised double-blind trial, a total of 676 patients with unresectable stage III or IV melanoma, whose disease had progressed while they were receiving therapy for metastatic disease, were randomly assigned, in a 3:1:1 ratio, to receive ipilimumab plus a glycoprotein 100 (gp100) peptide vaccine (403 patients), ipilimumab alone (137), or gp100 alone (136). Ipilimumab, at a dose of 3mg/kg of body weight, was administered with or without gp100 every three weeks for up to four treatments (induction). Eligible patients could receive reinduction therapy. The primary endpoint was overall survival.[15]

The most common adverse events were IrAE, which most often affected the skin and gastrointestinal tract. The most common gastrointestinal IrAE were diarrhoea and colitis.

Table 1: Immune-related adverse events affecting gastrointestinal tract by number of patients (percent) in the safety population[15]

	Ipilimumab plus gp100(N=380)			Ipilimumab alone (N=131)			gp100 alone (M=132)		
	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4	Total	Grade 3	Grade 4
Any IrAE	221 (58.2)	37 (9.7)	2 (0.5)	80 (61.1)	16 (12.2)	3 (2.3)	42 (31.8)	4 (3.0)	0
GastrointestinalIrAE	122 (32.1)	20 (5.3)	2 (0.5)	38 (29.0)	10 (7.6)	0	19 (14.4)	1 (0.8)	0
diarrhoea	115 (30.3)	14(3.7)	0	36 (27.5)	6 (4.6)	0	18 (3.6)	1 (0.8)	0
colitis	20 (5.3)	11 (2.9)	1 (0.3)	10 (7.6)	7 (5.3)	0	1 (0.8)	0	0

Protocol guidelines for the management of IrAE included the administration of corticosteroids (orally or intravenously), a delay in a scheduled dose, or discontinuation of therapy. For severe symptoms (colitis manifested as grade 3 or 4 diarrhoea), prednisolone 60mg or equivalent was suggested to control initial symptoms. The dose was supposed to be gradually tapered over at least one month. Lower doses of prednisolone were considered for less severe cases of colitis. The use of infliximab or any other TNF alfa inhibitor was not mentioned in the trial protocol.[16]

After administration of corticosteroids, the median time to the resolution of diarrhoea of grade 2 or higher was 2.0 weeks for 40 of 44 patients in the ipilimumab-plus-gp100 group and 2.3 weeks for 14 of 15 patients in the ipilimumab alone group. In addition to corticosteroids, four patients received infliximab for diarrhoea of grade 3 or higher or colitis.[15]

Bristol-Myers Squibb, the manufacturer of ipilimumab (YERVOY®), was unable to provide the rationale for the use of infliximab in the MDX010-20 trial.[17] It has been suggested that the use of a TNF alfa inhibitor, such as infliximab, in patients who failed to response to steroids is based on its use for Crohn's disease and ulcerative colitis.[18]

After MDX010-20, several other clinical trials with ipilimumab and/or nivolumab have been conducted for the treatment of metastatic melanoma.[19-21] Infliximab 5mg/kg was included in trial protocols for the management of grade 3 or 4 diarrhoea where there was no improvement or worsening of symptoms after 3-5 days of high-dose corticosteroids.[22-24]

The use of infliximab for adverse effect management has varied between 0.6% to 13% in the clinical trials.[15,21] The use of infliximab was not mentioned in nivolumab vs. dacarbazine trial paper.[19]

The West Midlands Cancer Alliance and Thames Valley Strategic Clinical Network have issued guidelines for managing immune-oncology related IrAEs.[25,26] Grade 1 cases should be managed symptomatically with loperamide, oral hydration and electrolyte replacement. Grade 2 diarrhoea should be managed with low dose oral corticosteroids in addition to symptomatic treatment. Grade 3 or 4 events should be treated with high dose intravenous corticosteroids in addition to symptomatic treatment.

A stat dose of biosimilar infliximab 5mg/kg is recommended if the gastrointestinal symptoms fail to resolve after three to five days of intravenous corticosteroids. Expert opinion and pooled clinical data suggest that an additional dose of biosimilar infliximab 5mg/kg at two weeks would be required.[27,28] If symptoms persist for more than three to five days or worsen after infliximab, colectomy should be considered.[26]

Some authors have hypothesized that prophylactic oral budesonide, a locally acting corticosteroid with low systemic bioavailability, could ameliorate the gastrointestinal side effects of ipilimumab. A randomised, double-blind, placebo controlled phase 2 trial was conducted to determine whether prophylactic budesonide could reduce the rate of grade 2 and higher diarrhoea in ipilimumab-treated patients with advanced melanoma. Budesonide did not affect the rate of grade 2 and higher diarrhoea and therefore should not be used prophylactically with ipilimumab therapy.[29]

Evidence: strengths and weaknesses

- There are no specific recommendations regarding treatment of drug-induced colitis.
- The use of infliximab for the management of diarrhoea and/or colitis related to ICPIs therapy is based on its efficacy in Crohn's disease and ulcerative colitis.
- No other TNF alfa inhibitors have been used in clinical trials with ICPIs.
- There is no data available on safety, adverse effect profile or efficacy of infliximab in patients treated with ICPIs.
- Infliximab use varies considerably between ipilimumab and/or nivolumab trials, ranging from 0.6% in nivolumab group (nivolumab plus ipilimumab vs monotherapy trial) to 13% in nivolumab plus ipilimumab group (nivolumab plus ipilimumab vs ipilimumab trial).

Safety

Evidence for an interaction between monoclonal antibodies and TNF inhibitors is very limited. As both groups of drugs can be immunosuppressive, their effects might be additive and increase the incidence of neutropenia and severe infections.[30]

At the time of writing this document, Medicines and Healthcare Regulatory Agency (MHRA) has issued a warning regarding ipilimumab and reports of cytomegalovirus (CMV) gastrointestinal infection or reactivation. Patients on ipilimumab who present with diarrhoea or other symptoms of colitis, and those who do not respond to steroid treatment for immune-related colitis, should be investigated to exclude other causes, including infections such as CMV. In those patients, the addition of an immunosuppressive agent should only be considered if other causes have been excluded, including CMV infection or reactivation.[31]

Place in therapy

Based on experience from clinical trials, the manufacturer of YERVOY® has developed recommendations for the management of diarrhoea or colitis. Treatment depends on the severity of symptoms, which is graded according to the National Cancer Institute's Common Terminology Criteria for Adverse Events, version 5.0.[3,32]

Grade 1 (mild) or 2 (moderate)

Patients with mild to moderate diarrhoea (an increase of up to six stools per day) or suspected mild to moderate colitis (e.g. abdominal pain or blood in stools) may remain on ipilimumab. Symptomatic treatment (e.g. loperamide, fluid replacement) and close monitoring are advised. If symptoms recur or persist for five to seven days, ipilimumab should be withheld and corticosteroid therapy (e.g. prednisolone 1mg/kg orally once daily or equivalent) should be initiated. If resolution to Grades 0-1 or return to baseline occurs, ipilimumab may be resumed.[3]

Grade 3 (severe) or 4 (life-threatening)

Ipilimumab must be permanently discontinued in patients with severe diarrhoea or colitis, and systemic high-dose intravenous corticosteroid therapy (e.g. methylprednisolone 2mg/kg/day) should be initiated immediately. Once diarrhoea and other symptoms are controlled, the corticosteroid should be tapered over the period of at least one month to avoid recurrence.[3]

In the case of corticosteroid-refractory diarrhoea or colitis, addition of an alternative immunosuppressive agent to the corticosteroid regimen may be considered if other causes are excluded (including CMV infection/reactivation and other viral, bacterial and parasitic etiology). A single dose of infliximab 5mg/kg has been suggested, except where gastrointestinal perforation or sepsis is suspected.[3]

For nivolumab, pembrolizumab and atezolizumab, administration of other systemic immunosuppressants may be considered in patients whose immune-related adverse reactions cannot be controlled with corticosteroid use.[4-6]

Appendix 1 outlines the patient pathway for managing ICPI induced diarrhoea or colitis, adapted from The West Midlands Cancer Alliance and Thames Valley Strategic Clinical Network.[25,26]

Cost impact and cost effectiveness

ICPIs are funded and commissioned by NHS England.[33] Management of chemotherapy-associated adverse effects however, such as diarrhoea or colitis, is funded and commissioned by the CCGs. Infliximab is not currently routinely commissioned for the management of ipilimumab-induced diarrhoea or colitis. Most healthcare providers would need to submit an exceptional funding request to get the additional payment.

Comparative costs of biosimilar infliximab 350mg dose (5mg/kg) for a 70kg patient are shown in table 2. Infliximab is excluded from the NHS PbR tariff.[34]

Table 2: Comparative drug costs of infliximab 100mg powder for concentrate for solution for infusion vials

Brand	Cost per vial List price (a)	Cost per vial NHS contract price EoE (b)	Cost per single 400mg dose (c)	Cost per 2 x 400mg doses (d)
Flixabi®	£377.00	£80.00	£320.00	£640.00
Inflectra®	£377.66	£100.00	£400.00	£800.00
Remsima®	£377.66	£100.00	£400.00	£800.00
Remicade®	£419.62	£176.24	£704.96	£1,409.92

[a] Drug Tariff prices (March 2019)[35]

[b] NHS East of England contract prices (March 2019)[36]

[c] Rounded up to 400mg dose, NHS East of England contract price

[d] Rounded up to 2 x 400mg doses, NHS East of England contract price

The first dose of infliximab would be administered as inpatient. Subsequent doses could then be administered as a day case if the patient is fit for discharge.[28] The reduction in length of inpatient stay would offset the cost of infliximab treatment.

Day case activity costs for IV infliximab administration is between £241 (HRG code FD02H) and £269 (HRG code FD02G) per session, not including Market Forces Factor (MFF).[37]

Table 3: Indicative costs per dose administered as a day case

Brand	Cost for 400mg dose	Day case activity costs	Total cost
Flixabi®	£320.00	£241 - £269	£561 - £589
Inflectra®	£400.00	£241 - £269	£641 - £669
Remsima®	£400.00	£241 - £269	£641 - £669
Remicade®	£704.96	£241 - £269	£946 - £974

The alternative option to infliximab treatment is to use a prolonged course of intravenous corticosteroids. Patients would remain an inpatient for the entire duration of treatment, and risk complications of steroid toxicity. In severe inadequately treated cases, patients may require a colectomy.[28] There is currently no published data on the average length of stay for patients with grade ≥3 diarrhoea or the percentage of patients requiring colectomy.

The cost of colectomy varies according to the severity of the patient's condition and the complexity of the procedure. This is usually between £6,248 and £18,172 per procedure, there would also be ongoing stoma care costs including clinic appointments and consumables. NB. These costs do not include MFF.[37]

Estimated patient numbers

Evidence from the pooled clinical experience shows that grade 3/4 diarrhoea is seen in up to 10% of patients on ipilimumab therapy and 1-2% of cases treated with nivolumab, pembrolizumab or atezolizumab.[27] According to current recommendations, presence of diarrhoea of grade ≥3 requires permanent discontinuation of ipilimumab therapy. Total annual cost of infliximab therapy would vary depending on the number of patients being treated with ipilimumab, and the incidence of steroid-refractory grade ≥3 diarrhoea.

The number of patients who develop grade 3/4 diarrhoea who are refractory to treatment with steroids is not known. It is estimated that one third to two thirds of patients treated with ipilimimab with acute colitis either do not respond to high-dose intravenous steroids, or have a relapse requiring an increase in the corticosteroid dosage during the course of steroid tapering.[38] For patients treated with nivolumab or pembrolizumab, up to 12.5% did not respond to corticosteroid treatment.[39] No information was available for patients treated with atezolizumab at the time of writing.

Estimated cost impact for the East of England (EoE) (drug costs only)

Drug	Estimated no. patients receiving drug per year EoE*	No. patients who develop grade 3/4 diarrhoea**	Estimated no. patients requiring infliximab assuming 33% are refractory to steroids	Estimated no. patients requiring infliximab assuming 66% are refractory to steroids
Ipilimumab	119	12	4	8
Atezolizumab	108	2	1	1
Nivolimumab	285	6	2	4
Pembrolizumab	583	12	4	8
Total number of patients per year	1095	32	11	21
EoE cost per year for 1 dose infliximab***			£7,359	£14,049
EoE Cost per year for 2 doses infliximab***			£14,718	£28,098

*Number of patients receiving each drug in the EoE over a one year period from February 2018 to January 2019. Information provided by NHS England Specialised Commissioning and Cambridge University Hospital. Individual patients may have received more than one agent, so these numbers overestimate overall exposure to ICPIs.

**Assumes 10% of patients on ipilimumab and 2% of patients on pembrolizumab, nivolumab or atezolizumab develop grade 3/4 diarrhoea.

*** Based on average dose of biosimilar infliximab at £400 per dose, including activity costs based on HRG code FD02G (not including MFF).

It is anticipated that drug costs would be offset by a reduction in length on in patient stay.

Options considered by PAC

- Recommended
- Not recommended

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Document history

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Appendix 1: Patient pathway for managing ICPI induced diarrhoea or colitis, adapted from The West Midlands Cancer Alliance and Thames Valley Strategic Clinical Network[25, 26]

Grade	Investigations	Management	Follow up
Mild (grade 1) Diarrhoea: <4 stools/day over baseline	Baseline bloods:FBC, U&E, LFTs, TFTs, CRP Stool microscopy and culture Clostridium difficile toxin Faecal calprotectin	Oral fluids Loperamide Avoid high fibre and lactose	Regular contact with patient to assess symptoms Continue ICPI therapy If symptoms persist (≥5 days) or worsen: • Treat as grade 2 or 3/4
Moderate (grade 2) Diarrhoea: 4-6 stools/day over baseline Colitis: abdominal pain, mucus or blood in stool	Baseline bloods: FBC, U&E, LFTs, TFTs, CRP Stool microscopy and culture Clostridium difficile toxin Faecal calprotectin Abdominal x-ray	PO prednisolone 0.5-1mg/kg/day + PPI cover Stop loperamide Oral fluids	Withhold ICPI therapy If symptoms resolve or improve to mild within 72 hours: • Taper steroids over at least 1 month • Resume ICPI therapy • If symptoms persist or worsen: treat as grade 3/4 • Permanently discontinue ICPI therapy Gastroenterology advice/review
Severe or Life-Threatening (grade 3 + 4) Diarrhoea: ≥7 stools/day over baseline Colitis: severe abdominal pain, peritoneal signs	**Urgent referral to gastroenterologist** Baseline bloods: FBC, U&E, LFTs, TFTs, CRP Stool microscopy and culture Clostridium difficile toxin Faecal calprotectin CT abdomen/pelvis Flexible sigmoidoscopy with biopsies Screen for infliximab administration suitability (CMV, TB, Hepatitis B and C, HIV, NYHA class III/IV) Dietician review	IV methylprednisolone 0.5-1mg/kg/day IV hydration and fluid balance Stop loperamide	Permanently discontinue ICPI therapy If symptoms resolving: • Continue IV methylprednisolone for at least 3-5 days then • Switch to PO prednisolone 1mg/kg/day and taper over at least 1 month • If symptoms persist or worsen within 72 hours: • Add infliximab 5mg/kg (if no contraindications) after gastroenterology review • Dose may be repeated after 2 weeks if necessary

Infliximab should not be given to patients with:

- Bowel perforation
- Tuberculosis or other active/severe infections
- Moderate or severe heart failure (NYHA class III/IV)

Appendix 2: Assessment against Ethical and Commissioning Principles

1. **Treatment assessed**

   Infliximab for the management of diarrhoea or colitis associated with Immune Checkpoint Inhibitor (ICPI) therapy.

2. **East of England Priorities Advisory Committee Recommendation**

   Infliximab is recommended for the treatment of severe Immune Checkpoint Inhibitor (ICPI) related colitis grade 3 or 4, in line with the treatment pathway outlined in Appendix 1.

3. **Clinical Effectiveness**

   There is limited data on the clinical effectiveness of infliximab for the management of diarrhoea and/or colitis related to ICPIs. Its use is based on its efficacy in Crohn's disease and ulcerative colitis.

4. **Cost Effectiveness**

   There is no cost effectiveness data on the use of infliximab for the management of diarrhoea and/or colitis related to ICPIs therapy, however costs of treatment may be offset by areduction in length of in patient stay, reduction in steroid related toxicity and avoidance of progression to colectomy.

5. **Equity**

   No issues identified.

6. **Need for healthcare (incorporates patient choice and exceptional need)**

   A small group of patients who do not respond to first and second line therapies would benefit from this treatment.

7. **Needs of the community**

   No issues identified.

8. **Policy driver**

   None.

9. **Disinvestment**

   There is a lack of data on cost-effectiveness, however the cost of the treatment is likely to be offset by a reduction in the patient's length of stay, and therefore should not result in the need for disinvestment in other areas.

