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

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

Report prepared by the All Wales Therapeutics and Toxicology Centre
November 2022

Key findings

Licence status
Infliximab 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; its use for this indication is off-label.

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

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

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

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

Budget impact
Clinicians consulted by AWTTC estimate that twenty people in Wales per year would be likely to be eligible to receive infliximab in this setting. It is assumed that people would have one to three infliximab doses, received within a single year. This is associated with an annual cost of between [Commercial in confidence text removed], depending on which infliximab product is used. The incidence 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 enterocolitis in Wales are currently receiving infliximab through local agreements. In the absence of other licensed treatments, a One Wales decision would ensure equity of access to this treatment across the country.

Innovation and/or advantages
Infliximab may reduce the need for more invasive interventions for this condition. 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. Infliximab 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) induced enterocolitis will increase over the next few years as the use of cancer immunotherapies increases. Clinical experts expressed a need for effective ICI toxicity management, with infliximab considered standard of care for severe or steroid-refractory ICI induced enterocolitis. Patients with ICI induced enterocolitis in Wales are currently receiving infliximab through local agreements. In the absence of other licensed treatments, a One Wales decision would ensure equity of access to this treatment across the country.

Target group

The indication under consideration is the treatment of ICI induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids (intravenous methylprednisolone, 1-2 mg/kg) after three to five days. Treatment is preferably within two weeks of onset, especially for patients with high-risk endoscopic features.

Marketing authorisation date: Not applicable, off-label

Infliximab is not licensed for the treatment of ICI induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids.

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

Dosing information

The recommended dose is 5 mg/kg[1]. A second dose may be repeated 14 days later, with a maximum of three infusions to be given (weeks 0, 2 and 6).

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 colitis is estimated to be 2% and 7% respectively. Incidence of severe (grades 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[5]. 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 treatment[6].

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

Current treatment options and relevant guidance

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

A number of national and international guidelines have been published on this topic with some variation in their recommendations[2,3,7-12]. 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[2,3,8-12], but up to five days[7]. 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[8]. Although pre-existing IBD is not a contraindication to receiving ICIs according to the BSG, they do advise prompt assessment of disease activity before starting an ICI, regular monitoring during treatment and rapid treatment escalation in the event of relapse. 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].

In case of no response to infliximab (up to three doses), subsequent treatment options include off-label vedolizumab, calcineurin inhibitors, mycophenolate mofetil (MMF) and faecal microbiota transplant[2,11]. In acute severe enterocolitis, there are safety concerns about sequential use of powerful immunosuppressive agents immediately after infliximab failure[2]. For severe enterocolitis that is refractory to treatment, or following intestinal perforation, surgical management might be required[2].

A single dose of infliximab 5 mg/kg is effective in at least 65% of cases but a second dose may be required due to symptomatic relapse or incomplete response[2]. The BSG advise completing the standard induction regimen of 5 mg/kg at weeks zero, two and six to maximise the opportunity for complete mucosal healing. The value of additional doses of infliximab following the standard three infusions has not been established[2].

The West Midlands, East of England, Gloucestershire and Oxford areas of England all have developed guidelines for patients with severe (grades 3-4) enterocolitis[6,13-15]. These are all broadly in line with the recommendations included above.

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

Summary of evidence on clinical effectiveness

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

Efficacy

Araujo et al. (2021) examined efficacy and hepatotoxicity of infliximab treatment for steroid refractory irAEs due to ICIs in cancer patients (n = 56) in a retrospective study[16]. Colitis was the most frequent irAE (n = 37), followed by pneumonitis (n = 6), myocarditis (n = 2) and hepatitis (n = 1) and various others (n = 10). Infliximab dosage used was not reported, although the median number of treatments was one (range 1 to 3). Fourteen patients (25%) required more than one dose which was separated by a median of 40.5 days (range 12 to 867). Colitis resolved in 32 of the 37 patients and was the most likely to respond to infliximab treatment compared with the other irAEs combined (odds ratio [OR] 6.73; 95% confidence interval [CI]: 1.56 to 29.04; p = 0.011). There were no cases of infliximab-induced hepatotoxicity[16].

Alexander et al. (2021) examined outcomes of infliximab treatment for corticosteroid refractory ICI induced enterocolitis in a retrospective study based in the UK (n = 127)[4]. Infliximab dosage used was not reported. The primary outcome for colitis was corticosteroid free clinical remission (CFCR). CFCR was defined as CTCAE grade 0 for diarrhoea at 12 weeks after starting infliximab, in the absence of corticosteroid therapy greater than a daily dose of prednisolone 5 mg (or equivalent

corticosteroid), and without the need for other rescue therapy such as vedolizumab or colectomy. Infliximab dosing frequency ranged from one (n = 62), two (n = 32), three (n = 28), four (n = 4) to five or more doses (n = 1). Before starting infliximab, all patients reported diarrhoea symptoms, with 96 reporting diarrhoea of grade 3 or 4. At 12 weeks, eight patients had died (none from colitis). Of the remaining patients (n = 119), 62.2% were in clinical remission (CR [n = 74]) and 41.2% were in CFCR (n = 49). Of the CFCR group, 83.7% had CR within seven days of starting infliximab (n = 41) of which 65.3% responded within 48 hours (n = 32). At 26 weeks, nine more patients had died, while five had inadequate follow-up. Of the remaining patients (n = 105), 71.4% were in CR (n = 75) and 50.9% were in CFCR (n = 54); 32 of these patients had been CFCR at 12 weeks. During the six months following the start of infliximab treatment, 37% needed rescue therapy (n = 47), such as MMF (n = 23) and vedolizumab (n = 11), and there were four colectomies (3.1%)[4].

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[17]. 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. Four patients had grade 4 colitis and two required colectomies for refractory disease. One patient death followed refractory colitis causing necrotic bowel (but declined colectomy); a second had hematochezia and high-stoma output in the context of colitis which was refractory to infliximab and bowel resection. The cancer outcomes (radiological response) of the patients who received just infliximab (n = 12) included complete response (n = 2), partial response (n = 1), stable disease (n = 1), progressive disease (n = 7) and one without available information. In this retrospective analysis, the administration of immunosuppressive agents did not appear to alter responses to immune checkpoint inhibitor therapy[17].

Lesage et al. (2019) examined real-life incidence of severe ICI induced colitis treated with infliximab in a retrospective study (n = 27)[18]. Infliximab dosage used was 5 mg/kg. Colitis/diarrhoea was graded as per CTCAE criteria. Severe colitis was defined as occurrence of grade 3-4 enterocolitis resistant to high-dosage systemic steroids. Complete response to infliximab was defined as a return to baseline number of stools per day and partial response as a return to grade 1 diarrhoea. All patients had received and were refractory to high dose intravenous systemic steroids. Twenty-six patients received infliximab as second-line therapy and one patient as third-line therapy after adalimumab failure. Partial response was recorded for 22% (n = 6) and CR was recorded for 74% (n = 20); 80% (n = 16) of whom had CR after one dose. One patient failed to respond and was later diagnosed with colonic perforation. Median overall survival (OS) and progression free survival (PFS) was 12 months and 3 months respectively (median follow-up 10 months)[18].

Wang et al. (2018) examined corticosteroid and infliximab treatment on ICI induced enterocolitis and OS in a retrospective study (n = 327)[19]. Infliximab dosage used was not reported. Diarrhoea was observed in 36% (n = 117), 12% (n = 38) had diarrhoea but did not receive steroids or infliximab while 24% (n = 79) had diarrhoea and received either corticosteroids alone (n = 44) or with infliximab (n = 35). A greater proportion of grade 2 and higher diarrhoea required infliximab as well as corticosteroid treatment (97%), rather than corticosteroid treatment alone (73%; p = 0.005). Immunosuppressive treatment was not different according to grade of colitis. OS did not differ between patients who received corticosteroids alone or those

who received corticosteroids plus infliximab (for steroid refractory enterocolitis), this effect persisted for patients with stage IV cancer[19].

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[20]. Dosage concentration was not specified for either medicine. Median follow-up was 14 months (Interquartile range [IQR] 8 to 27). A total of 153 patients had confirmed histological inflammation by endoscopy. Patients received either infliximab (n = 94), vedolizumab (n = 62) or a combination of both biologics sequentially (n = 28). Median duration from first dose to either symptom remission or improvement to grade 1 was 13 days (IQR 8 to 29) for infliximab and 18 days (IQR 10 to 40) for vedolizumab (n = 138; p = 0.012). Median duration of hospitalisation was 14 days (IQR 8 to 19.8) for infliximab and 10 days (IQR 5 to 15) for vedolizumab (n = 107; p = 0.043). There were significantly more instances of individuals requiring multiple hospitalisations (p = 0.005) for infliximab (n = 26) compared with vedolizumab (n = 10). There were significantly more instances of recurrent ICI induced enterocolitis (p = 0.007) for infliximab (n = 27) compared with vedolizumab (n = 8). There was no significant difference in the overall number of hospitalisations (p = 0.367), the level of clinical remission (p = 0.785) or immunosuppressant associated infection (p = 0.184) between groups. OS was more favourable for patients receiving vedolizumab (n = 62) compared with infliximab (n = 94; p = 0.027)[20].

Network meta-analyses

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

Ibraheim et al. (2020) conducted a NMA to investigate the effectiveness of anti-inflammatory therapy (corticosteroids, infliximab or vedolizumab) in ICI induced enterocolitis[21]. The pooled response to infliximab was 81% (95% CI: 73 to 87) with significant heterogeneity between 17 studies (I^2 = 49%, p = 0.01). The authors considered the significant heterogeneity observed due to inclusion criteria differences and a lack of standardisation in how treatment response was recorded across the studies, amongst other reasons[21].

Study in progress

Treatment of Immune Checkpoint Inhibitor-Related Colitis with Infliximab or Vedolizumab: A Randomized Trial (NCT04407247). Estimated study completion date, December 2022[22].

Safety

For those studies which reported on infliximab safety, treatment complications or adverse events mostly involved infections[20], and in one study affected a fifth of the patients treated with infliximab[4]. Alexander et al. (2021) reported that eight patients

required intravenous antibiotics and/or hospitalisation for infection and four deaths that were attributable to infection (hospital-acquired pneumonia [n = 2], sepsis [n = 1], peritonitis [n = 1])[4]. Other reported adverse events following infliximab treatment included anaphylaxis (n = 1), bradycardia requiring atropine and critical care (n = 1), grade 3 maculopapular rash (n = 1) and squamous cell carcinoma of the skin (n = 1)[4]. Infections rates were also reported to be higher for those who received infliximab and for those on more or prolonged steroid treatment courses[19,20]. Lesage et al. (2019) had no adverse events following infliximab treatment reported (and no colitis related deaths)[18].

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) are unavoidable[2].

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

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

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

Discussion

Evidence for the off-label use of infliximab to treat ICI induced grade 3-4 enterocolitis, where symptoms have not responded to first line immunosuppression with corticosteroids comes from retrospective studies. When reported, infliximab dosage used was consistent with that recommended in national and international guidelines (5 mg/kg). The dosing schedule frequency varied between studies although generally no more than three were received. 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).

The National Institute for Health and Care Excellence (NICE) recommends infliximab (or adalimumab) for adults with severe active Crohn's disease whose disease has

not responded to conventional therapy (including immunosuppressive and/or corticosteroid treatments), or who are intolerant of or have contraindications to conventional therapy (TA187)[23]. NICE recommends infliximab for the treatment of acute exacerbations of severely active ulcerative colitis only in patients in whom ciclosporin is contraindicated or clinically inappropriate, based on a careful assessment of the risks and benefits of treatment in the individual patient (TA163)[24]. It is acknowledged that the acute treatment strategy for ICI induced enterocolitis may follow a similar pathway to the treatment for Crohn's and ulcerative colitis. However, there are differences in terms of patient and disease characteristics, the length of treatment, morbidity and mortality rates. Therefore, comparing the use of infliximab for these indications and trying to predict clinical and cost effectiveness for ICI induced enterocolitis from the data used for Crohn's and ulcerative colitis is subject to significant uncertainty.

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

Clinical experts state that, as immunotherapy has an increasing number of treatment indications for cancer, the incidence of ICI induced enterocolitis is predicted to increase. This will lead to more hospital stays and, as such, it is imperative that NHS Wales is able to offer ICI immunotherapy safely. Clinicians state that ICIs offer the possibility of cure for patients with stage IV metastatic disease which is a paradigm shift for cancer care. In melanoma, where ICI has been used for the longest duration, 6.5-year data shows 49% of patients are still alive with more than 75% treatment free[25]. To be able to offer patients the possibility of durable outcomes, clinicians feel it is imperative they can manage toxicity effectively with treatments such as infliximab.

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

Cost-effectiveness evidence

No studies on the cost-effectiveness of infliximab for this indication were identified. Cost effectiveness evidence for the use of infliximab 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 infliximab treatment regimen was typically 5 mg/kg with a maximum of three doses given. 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 twenty people in Wales per year would have stage 3-4 enterocolitis that is steroid refractory and would be eligible for treatment with infliximab. It is assumed that people would have one to three infliximab doses,

received within a single year. The acquisition cost for twenty patients is shown in table 2.

Table 1. Estimated annual costs for infliximab per patient in Wales

	Treatment cost	Administration cost†	Total annual cost per patient
Infliximab (5 mg/kg; one dose)*	¶¶	£527	¶¶
Infliximab (5 mg/kg; two doses)*	¶¶	£998	¶¶
Infliximab (5 mg/kg; three doses)*	¶¶	£1469	¶¶

NA: not applicable
*Confidential NHS Wales contract price plus VAT, using lowest and mid-range price and the average weight for a British adult (77.25 kg)[26,27]. Assumes vial wastage.
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† 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 two doses (HRG code SB15Z)[28]

Table 2. Estimated annual acquisition costs for infliximab for twenty patients in Wales

	Year 1
Number of patients	20
Total annual costs for single infliximab dose	¶¶
Total annual costs for two infliximab doses	¶¶
Total annual costs for three infliximab doses	¶¶

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Budget impact issues

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

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

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

As patients with ICI induced enterocolitis in Wales are generally receiving infliximab through local agreement routes, 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

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

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