Cambridge University Hospitals NHS
NHS Foundation Trust

Cambridgeshire University Hospitals NHS Foundation Trust

New Medicine Report

SUMMARY

Name of Medicine (generic and brand)	Infliximab (currently biosimilar Inflectra®) is preferred product
Intended indication(s) for use	Rescue therapy in acute severe UC – intensified infliximab dosing [off-label]
Purpose of Document	To review information currently available on use of the drug, give guidance on potential use and assign a prescribing classification
Recommendation for Consideration	It is recommended to CUH JDTC and Cambridgeshire and Peterborough CCG JPG members, and through them to local NHS organisations, that the arrangements for use of infliximab are in line with restrictions agreed locally for drugs designated as [HOSPITAL ONLY; not to be prescribed in primary care] **Rationale for Recommendation** • Acute severe ulcerative colitis (ASUC) is a potentially life-threatening condition. The lifetime risk of a severe exacerbation requiring hospitalisation is between 15% and 25%. Severe flares of UC are associated with considerable morbidity and a mortality rate of approximately 1%. Following one or more episodes of severe flares, there is a 40% colectomy rate and one in five patients are predicted to undergo colectomy during their first hospital admission. • Patients with acute severe UC are known to develop lower serum infliximab levels than patients with moderately active disease- this is possibly due to a higher inflammatory burden and/or increased drug clearance/ leakage into the colonic lumen. However, it is also noted that drug trough levels are not always lower among total non-responders compared with responders • Although infliximab trough levels do not necessarily correlate to responders vs non –responders, infliximab-antibodies have proven to be higher and correlate with non-responders • Several cohort studies suggest that infliximab dose intensification is beneficial to at least 50% of acute severe UC patients and the results of case–controlled studies indicate that an intensified infliximab dosing regimen with 1–2 additional infusions in the first 3 weeks of treatment could reduce the early (3-month) colectomy rate by up to 80%. • The intention would be if, after initial improvement in symptoms or C-reactive protein (CRP), any rebound in inflammation during the induction period occurs this would trigger a repeat infusion (i.e., additional dose this was then followed by the standard 8-weekly maintenance regimen. • It is noted that this approach may only defer inevitable colectomy in some patients, however it would be prudent to consider using the intensified regime to avoid/delay colectomy Apart from this major surgery being more costly than the drug, the surgery is also likely to significantly affect psychological, emotional and physical well-being.
Status	Ratified by the CUH JDTC at the 23/4/19 meeting.

Prepared by	Hannah Weekes, Specialist Formulary Pharmacist
Date of last revision	15/3/19
Review Date	15/3/21

DETAILS OF MEDICINE	
Name of Drug (generic and brand)	Infliximab (currently biosimilar Inflectra®) is preferred product
BNF Drug Class	1.5.3> Cytokine inhibitors
Strength(s) and formulation(s)	Additional one-off dose 5-10mg/kg
Licensed indication(s)	Rheumatoid arthritis, adult Crohn's Disease, paediatric Crohn's Disease, Ulcerative Colitis, paediatric Ulcerative Colitis, Ankylosing spondylitis, Psoriatic arthritis, Psoriasis
Intended indication(s) for use (if different from above)	5 mg/kg given as an intravenous infusion followed by additional 5 mg/kg infusion doses at 2 and 6 weeks after the first infusion, then every 8 weeks thereafter. i.e., this intensified regimen is in addition to and therefore off-label
Place in therapy	Acute severe UC with suboptimal response to previous dose of infliximab (given as rescue therapy) which is also steroid-refractory
Monitoring requirements	Patients should be monitored for standard monoclonal antibody issues
Current treatment alternatives (where applicable)	None. This is additional to standard treatment
Future treatment alternatives	
Drug(s) that can be decommissioned (where applicable)	
EVIDENCE FOR USE & SAFETY	

Summary of evidence (Clinical Efficacy including any comparisons with existing treatments)	• Acute severe ulcerative colitis (ASUC) is a potentially life-threatening condition. The lifetime risk of a severe exacerbation requiring hospitalisation is between 15% and 25%. Severe flares of UC are associated with considerable morbidity and a mortality rate of approximately 1%. Following one or more episodes of severe flares, there is a 40% colectomy rate and one in five patients are predicted to undergo colectomy during their first hospital admission. Long-term colectomy rates remain high, despite salvage therapies, and are thought to range from 50% to 62% at 3 years. Intravenous steroids are first line for acute severe UC. If there is a poor response to these then rescue therapy is instigated (either cyclosporin or infliximab depending on the clinical situation). In this setting a proportion of patients will only experience a partial response to infliximab, which is thought to be due to the standard dosing being insufficient due to drug consumption and GI losses. In these patients there is evidence that an additional infliximab can induce full remission and avoid the need for a colectomy. The intention would be to use an additional 1 or 2 doses additional to the already agreed NICE TA. The availability of these extra doses may prevent surgery; colectomy .[1,2] • Infliximab, a cytokine inhibitor, is an established treatment for acute severe colitis, when there is no response (or inadequate response) to at least 3 days of intravenous steroids, and its use in this context is supported by national and international guidelines and NICE. Despite this, so-called “rescue” therapies, such as infliximab and ciclosporin, have a non-trivial failure rate up to ~40% in the short term (within 3 months), necessitating colectomy in approximately 45% of patients within 5 years. [3] Patients with acute severe UC are known to develop lower serum infliximab levels than patients with moderately active disease- this is possibly due to a higher inflammatory burden and/or increased drug clearance although it is also noted that drug trough levels are not always lower among total non-responders compared with responders.[1] • A study to compare infliximab trough and anti-infliximab antibody levels at a standard fixed time-point during induction between patients with acute severe and moderately severe UC was conducted. 16 patients with acute severe

disease and 16 patients with moderately severe disease refractory to steroids were compared. Mean infliximab trough levels at day 14 were significantly lower in patients with acute severe UC compared to moderately severe UC (7.15 ± 5.3 vs. 14.4 ± 11.2 µg/mL, P = 0.007). Seven patients (three acute, severe and four moderately active UC) were primary non-responders to infliximab induction therapy. Infliximab level at day 14 did not differ between responders and non-responders (9.8 ± 9 vs. 12.1 ± 10.6 µg/mL, respectively, P = N.S.). However, week 2 median antibody-to-infliximab levels were numerically higher among primary non-responders (3.4 ± 5.7 vs. 1.2 ±4 µg/mL. The study concluded controlled trials are warranted to examine whether a prior-intensified infliximab induction protocol would lead to an improved outcome in acute severe UC.[1]

- A meta-analysis concluded, 31–35% cases of acute severe ulcerative colitis (ASUC) are steroid-refractory. Infliximab and ciclosporin salvage therapies have improved patient outcomes in randomised controlled trials. Short-term response rates (within 3 months) have ranged from 40% – 54% for ciclosporin and 46–83% for infliximab. Long-term clinical response rates (≥1 year) have ranged from 42%–50% for ciclosporin and 50–65% for infliximab. Short-term and long-term colectomy rates have been respectively:

  26–47% and 36–58% for ciclosporin, and 0–50% and 35–50% for infliximab. Mortality rates for ciclosporin and infliximab-treated patients have been: 0–5% and 0–2%, respectively. On the basis of the evidence, the group who performed this analysis, proposed a treatment strategy for steroid-resistant ASUC which suggests after 5 days of inadequate clinical response, a medical salvage agent should be decided upon considering any contra-indications to agents, and previous exposure to a thiopurine; one of which, treatment options includes administering IV infliximab (IFX) 3x infusions (5mg/kg) – An accelerated (3 infusion in 4 weeks) or intensified induction regimen (10 mg/kg) can also be considered.[2]

- Another meta-analysis considering dose optimisation of infliximab identified 400 citations and 76 eligible studies and concluded that increased infliximab clearance occurs in patients with acute severe UC and is driven by the total inflammatory burden and leakage of drug into the colonic lumen. Several cohort studies suggest that infliximab dose intensification is beneficial to at least 50% of acute severe UC patients and the results of case–controlled studies indicate that an intensified infliximab dosing regimen with 1–2 additional infusions in the first 3 weeks of treatment could reduce the early (3month) colectomy rate by up to 80%, although these data require prospective validation. Although there are many factors involved, in one published retrospective study, infliximab and anti-drug antibody concentrations of hospitalised patients with acute severe UC were compared with those of patients with moderate-to-severe active UC 2 weeks after the first, or scheduled infusion (5 mg/kg). Patients with acute severe UC had significantly lower week 2 infliximab concentrations than those with less severe disease.[3]
- Uptodate.com recommends studies are needed to identify the optimal dosing regimen for anti-tumour necrosis factor therapy in severe ulcerative colitis. A retrospective study of 50 hospitalized patients with steroid-refractory acute, severe, ulcerative colitis compared colectomy rates in patients who received standard infliximab dosing with an accelerated dosing regimen consisting of three induction doses of infliximab within a median period of 24 days. NB. standard induction regime is 5mg/kg at 0, 2 and 6 weeks followed by maintenance every 8 weeks, whereas intensified regimen patients receive their 3 induction doses (5 mg/kg), with the timing of each infusion guided by clinical need (worsening symptoms or inflammatory markers), permitting induction dosing during a much shorter period. After initial improvement in symptoms or C-reactive protein (CRP), any rebound in inflammation during the induction period triggered a repeat infusion (i.e., additional dose, this was then followed

	by the standard 8-weekly maintenance regimen. Although colectomy rates during induction therapy were significantly

	lower with the accelerated regimen as compared with the standard regimen (7 versus 40 percent), there were no significant differences between the two groups in the two-year follow-up period. The use of infliximab blood levels may be helpful in determining the reasons for lack or loss of efficacy. Infliximab has been identified in the stool of patients with severe colitis, suggesting possible dumping of the protein-based therapy into the gastrointestinal lumen, as has been seen with other albumin and other proteins and low body weight. Uptodate suggests intensified infliximab dosing strategy in response to clinical or laboratory signs of breakthrough inflammation merits consideration in prospective studies • It would seem prudent to consider the use of intensified infliximab dosing in severe acute colitis, where only a partial response is seen, to avoid colectomy at least in the short term. Apart from this major surgery being more expensive it also is likely to affect psychological, emotional and physical well-being. In 2 out of 3 patients who have received this therapy in house- this has been successful in inducing remission and avoiding colectomy (at least in the short term),
Numbers Needed to Treat (NNT)	N/A
Safety profile	There is little evidence to indicate that patients treated with higher doses of infliximab or those with greater drug exposure (higher serum concentrations) are at an increased risk of side-effects such as serious infection. This observation, which is consistent with those observed with other monoclonal antibodies in IBD and other immune diseases, is likely a result of the high target specificity of these agents, such that increased exposure does not result in engagement of "off target" mechanisms. The TREAT registry observed patients with CD at 5 years in who had received dose escalation from 5 mg/kg to 10 mg/kg. In addition, no association was found between infliximab serum trough concentrations and serious infection in the ACT trials. However, it should be noted that in some other indications, and with combination therapy with other immunosuppressant agents, there were observed increased infection risk and mortality risk rates when lower or higher doses were used (i.e., generally repeated exposure to higher doses. Therefore, this still warrants caution and increased vigilance when prescribing infliximab dose intensification in acute severe UC patients who already carry a high overall burden of complications and are usually receiving concomitant corticosteroids and immunosuppressives.
Numbers Need to Harm (NNH)	N/A

FINANCIAL IMPLICATIONS	
Impact for NHS Cambridgeshire and Peterborough CCG	10 patients per annum are expected to need this additional dosing **Costs removed for confidentiality purposes.**
Costs (prices from *Reference*)	
Comparative cost (prices from *Reference*)	

DECISION FROM OTHER LOCAL/NATIONAL ORGANISATIONS		
	Cambridge University Hospitals NHS Foundation Trust	

Is the drug on local provider formularies?	Cambridgeshire and Peterborough NHS Foundation Trust	N/A
	North West Anglia NHS Foundation Trust	N/A
	Papworth Hospital NHS Foundation Trust	N/A
	The Queen Elizabeth Hospital Kings Lynn	Unknown
Was this drug approved by other local area prescribing committees?	Bedfordshire & Luton JPC	Unknown
	Hertfordshire MMC	Unknown
	Lincolnshire Prescribing and Clinical Effectiveness Forum	Unknown
	Norfolk & Waveney TAG	Unknown
	Northamptonshire Prescribing Advisory Group	Unknown
	Suffolk D&T	Unknown
	Mid Essex Area Prescribing Committee	Unknown
	North East Essex Medicines Management Committee	Unknown
Has the drug been considered by other bodies and what were their recommendations?	A NICE TA exists to support standard regimen treatment	

SCRIPTSWITCH MESSAGE	
Suggested wording for ScriptSwitch message	

Requesting Clinician details	
Full Name	Dr James Lee
Job role	Consultant gastroenterologist
Date of request	Feb 2019
Declaration of Interests	
Where a clinician has not submitted a request, comments obtained from appropriate local clinicians/specialists are included	

References

1.) Ungar, B., Mazor, Y., Weisshof, R., et al. (2016) Induction infliximab levels among patients with acute severe ulcerative colitis compared with patients with moderately severe ulcerative colitis. *Alimentary Pharmacology & Therapeutics.* Jun;43(12):1293-9. Accessed via pdf
2.) Seah, D. and De Cruz, P. (2016). Review article: the practical management of acute severe ulcerative colitis. *Alimentary Pharmacology & Therapeutics,* 43: 482–513. Accessed via pdf
3.) Hindryckx, P., Novak, G., Vande Casteele, N., Laukens, D., Parker, C., Shackelton, L., Narula, N., Khanna, R., Dulai, P., Levesque, B., Sandborn, W., D'Haens, G., Feagan, B. and Jairath, V. (2017). Review article: dose

optimisation of infliximab for acute severe ulcerative colitis. *Alimentary Pharmacology & Therapeutics*, 45(5), pp.617-630. Accessed via pdf

4.)

5.) Cohen, RD., Stein, AC., Approach to adults with steroid-refractory and steroid-dependent ulcerative colitis. Last updated Jan 2019. *Uptodate.com.* Accessed via pdf

Written by and comments to	Hannah Weekes, Specialist Formulary Pharmacist