Surrey Heartlands Integrated Care System Area Prescribing Committee (APC)

Integrated Care Partnerships (ICPs) (Surrey Downs, Guildford & Waverley, North West Surrey, East Surrey (as part of the CRESH system) & associated partner organisations.

Evidence review for Area Prescribing Committee (APC)

Medicine details	
Name, brand name	Infliximab (Inflectra or other biosimilar)
Manufacturer	Inflectra/ biosimilar
Proposed indication	Licensed indications include: - treatment of moderately to severely active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with a corticosteroid and/or an immunosuppressant; or who are intolerant to or have medical contraindications for such therapies. - treatment of fistulising, active Crohn's disease, in adult patients who have not responded despite a full and adequate course of therapy with conventional treatment (including antibiotics, drainage and immunosuppressive therapy). - treatment of moderately to severely active ulcerative colitis in adult patients who have had an inadequate response to conventional therapy including corticosteroids and 6-mercaptopurine (6-MP) or azathioprine (AZA), or who are intolerant to or have medical contraindications for such therapies. **Proposed indication <u>(unlicensed):</u>** - **Treatment of chronic refractory pouchitis which has not responded to antibiotics and/or steroids.**
Requested by	Dr Kalliopi Alexandropoulou, Consultant gastroenterologist.

SUMMARY

Clinical Effectiveness

Pouchitis is defined in the European Crohn's and Colitis Organisation (ECCO) publication[1] as non-specific inflammation of the ileal reservoir (pouch). It affects up to 50% of people 10 years after ileal pouch-anal anastomosis (IPAA) for ulcerative colitis, although the cumulative incidence of pouchitis in people with an IPAA for familial adenomatous polyposis is much lower. Symptoms of pouchitis include pelvic discomfort, abdominal cramps and urgency, tenesmus, increased stool frequency and liquidity, and faecal incontinence. There may also be rectal bleeding, fever or other systemic symptoms.

The ECCO document states that single antibiotic treatment with a 2-week course of either metronidazole or ciprofloxacin is the first-line treatment of choice for acute pouchitis, and combination therapy may also be used. Up to 10% of people develop chronic pouchitis with symptoms lasting longer than 4 weeks. Chronic pouchitis is often treated with combined antibiotic treatment or budesonide. If these interventions do not work, infliximab may be effective.

European Crohns and Colitis Organisation (ECCO) have published an algorithm for pouchitis

treatment. (http://www.e-guide.ecco-ibd.eu/algorithm/pouchitis)

There is limited good quality evidence on the use of infliximab for chronic refractory pouchitis. Most of the studies are observational and with small study populations.

How much improvement in quality and/or length of life is the intervention likely to produce? i.e. what are the improvements in patient orientated outcomes

Complete resolution of pouchitis can occur, preventing the development of complications secondary to pouchitis (abscesses, fistulae, anastomotic stenosis).

Patients treated successfully for pouchitis will have an improved quality of life as patients with chronic pouchitis have symptoms that include: increased stool frequency and consistency, cramping, tenesmus, incontinence and urgency.

Infliximab (if effective) can reduce the need to recurrent long courses of antibiotics which can lead to resistance and associated complications e.g. C. Diff.

How likely is it that the improvement will happen? Include ARR and number needed to treat (NNT) if possible

In patients with chronic pouchitis, 80% respond to first line treatment of combination antibiotics or steroids (according to the ECCO guidelines for pouchitis).
However in the population that do not respond to first line treatment: More than 80% respond to infliximab, with just over 50% those treated still responding at 20 months.

SORT level 3

Safety

Infusion related side-effects are managed by pre-medication (hydrocortisone, chlorphenamine and paracetamol).

The most common side effect is an increased risk of bacterial and viral infections.

As per the SPC[2], the most serious ADRs associated with its use include HBV reactivation, CHF (congestive heart failure), serious infections (including sepsis, opportunistic infections and TB), serum sickness (delayed hypersensitivity reactions), haematologic reactions, systemic lupus erythematosus/lupus-like syndrome, demyelinating disorders, hepatobiliary events, lymphoma, HSTCL, leukaemia, Merkel cell carcinoma, melanoma, paediatric malignancy, sarcoidosis/sarcoid-like reaction, intestinal or perianal abscess (in Crohn's disease), and serious infusion reactions.

Patient factors

This is a new indication, for a well established medicine, now available as a biosimilar biologic and as a sub-cutaneous injection for home care.
Infliximab is currently used for inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) treatment in secondary care. There are already systems in place for the procurement, supply and administration to patients. Staff are familiar with its use.
This will provide a very useful treatment option for patients who currently require chronic, repeated treatments of antibiotics and steroids, and should prevent further surgery: pouchectomy and ileostomy formation
It reflects the wishes of patients with refractory chronic pouchitis as if offers the chance of

complete resolution of pouchitis who are not sufficiently responding to other therapies, which in themselves have significant adverse effects and consequences.

Cost implications

Based on weight: 70kg @ 5mg/kg=350mg at £400.57 per dose. Dose at 0,2,6weeks then 8 weekly- total 9 infusions £3605.13. Dose is weight based and determines whether a pre-made batch is used (supplied by Baxters® for certain doses) or if it is reconstituted in the pharmacy aseptic suite. (These are list prices, there are confidential NHS discounts)

After two IV infusions, the patients can be switched to the sub-cut injection, to be administered every two weeks (all formulations are off license for this indication)

For the administration of the IV infusions there are procurement and day case costs

Successful treatment will mean less hospital inpatient stays/investigations/alternative treatments. Savings related to not having to resort to a surgical intervention e.g. pouch excision.

A full evaluation of the cost effectiveness of this treatment has not been carried out, but the expenditure is expected to be limited as it is expected that there will not be more than 2-3 patients per year in Surrey Heatlands who fit into this subset.

Relevant guidance / reviews

ECCO treatment algorithm for Pouchitis (see page 1).
No NICE guidelines for infliximab use in this indication.

Likely place in therapy relative to current treatments

Describe likely place in therapy and which patient's it should be used in.
Current treatment pathway:
Acute pouchitis is treated with antibiotic therapy
When symptoms persist for > 4 weeks it is classified as chronic pouchitis.
This is initially treated with a combination of antibiotics and/or steroids (effective in 80% of patients)
If recurrent courses of antibiotics are not effective and the patient is steroid dependent (symptoms flare when steroids are weaned) the next step should be considered.
For the patients that have chronic antibiotic-refractory pouchitis an anti-TNF agent (infliximab) should be considered.
Once all medical interventions have been trialled, the last line option is surgery (pouch failure) for a pouch resection/ileostomy.

This treatment is unlikely to be used beyond the described place in therapy - 30% of patients with UC progress to a colectomy. Most have a ileo-anal pouch formation and 10-15% of that population progress to chronic antibiotic-refractory pouchitis.

This is a high cost drug, to be give a RED traffic light classification for treatment by gastroenterologists only

Recommendation to APC

The APC is asked to approve the use of: Infliximab infusion and then sub-cut for the treatment of Chronic pouchitis (When symptoms persist for > 4 weeks)

- For patients who are refractory to dietary management
- AND who are refractory to repeated antibiotic and steroid courses

Please note for the above bullet points: ALL must be met.
It is hoped that the infliximab will reduce the need for repeated surgeries, and should be used before surgery whenever possible.

For use by gastroenterologists with a RED classification on the traffic light system

Medicine details	
Name and brand name	Infliximab (inflectra)
Licensed indication, formulation and usual dosage	Licensed indications: Rheumatoid arthritis, Adult Crohn's disease, Paediatric Crohn's disease, Ulcerative colitis, Paediatric ulcerative colitis, Ankylosing spondylitis, Psoriatic arthritis, Psoriasis. Dose= Varies based on weight- Based on 70kg @ 5mg/kg=350mg at £400.57 per dose. Dose at 0,2,6weeks then 8 weekly- total 9 infusions £3605.13 for IV infusions (day cases) or can be prescribed for sub-cut administration at home (unlicensed for both indications) These are list prices and there are additional NHS agreed discounts
Summary of mechanism of action, and relevant pharmacokinetics	Infliximab is a chimeric human-murine monoclonal antibody that binds with high affinity to both soluble and transmembrane forms of TNF_{α} but not to lymphotoxin α (TNF_{β}). Single intravenous infusions of 1, 3, 5, 10 or 20 mg/kg of infliximab yielded dose proportional increases in the maximum serum concentration (C_{max}) and area under the concentration-time curve (AUC). The volume of distribution at steady state (median $V_d$of 3.0 to 4.1 litres) was not dependent on the administered dose and indicated that infliximab is predominantly distributed within the vascular compartment. No time-dependency of the Pharmacokinetics was observed. The elimination pathways for infliximab have not been characterised. Unchanged infliximab was not detected in urine. At single doses of 3, 5, or 10 mg/kg, the median C_{max} values were 77, 118 and 277 micrograms/mL, respectively. The median terminal half-life at these doses ranged from 8 to 9.5 days. In most patients, infliximab could be detected in the serum for at least 8 weeks after the recommended single dose of 5 mg/kg for Crohn's disease and the rheumatoid arthritis maintenance dose of 3 mg/kg every 8 weeks. Repeated administration of infliximab (5 mg/kg at 0, 2 and 6 weeks in fistulising Crohn's disease, 3 or 10 mg/kg every 4 or 8 weeks in rheumatoid arthritis) resulted in a slight accumulation of infliximab in serum after the second dose. No further clinically relevant accumulation was observed. In most fistulising Crohn's disease patients, infliximab was detected in serum for 12 weeks (range 4-28 weeks) after administration of the regimen.
Important drug interactions	The combination of infliximab with other biological therapeutics used to treat the same conditions as infliximab, including anakinra and abatacept, is not recommended. It is recommended that live vaccines not be given concurrently with infliximab. It is recommended that therapeutic infectious agents not be given

	concurrently with infliximab
Monitoring requirements	Monitor of efficacy: infection markers, symptoms. Monitor for toxicity: closely monitoring for development of opportunistic infections.
Prescribing considerations	• Likely traffic light status (see attached guidelines) Red for gastroenterologists only  Colour classification guidelines
Other considerations	Staff in the Medical Day Unit are trained on administration (currently in use for RA and IBD) Subcutaneous infliximab has not yet been implemented at the Royal Surrey Foundation Trust, however the clinicians are happy to use this route of administration to avoid hospital (day case) interventions There are no existing guidelines for this condition in Surrey Heartlands, but this could be developed in line with the described place in therapy. Patients will be monitored via biologics IBD MDT

Potential patient group (if appropriate to include)	
Brief description of disease	Pouchitis is non-specific inflammation of the ileal reservoir (pouch). Chronic pouchitis is defined as when symptoms last > 4 weeks.
Potential patient numbers per 100,000	Chronic pouchitis develops in 10% patients with pouch. Most respond to intermittent courses of antibiotics and dietary interventions. A small proportion of these patients progress to refractoy pouchitis, that requires steroids and trials of biologics. Finally they may may progress to require pouch excision and ileostomy formation. Not likely to be more than 1 patient/year for the Royal Surrey Hospitals, up to 3 in Surrey Heartlands
Outcomes required	Resolution of pouchitis, avoidance of surgical interventions. Steroid-free symptom control and improved endoscopic features would be used to assess response (no standardised scoring available). Treatment will be needed for at least induction, and could continue for up to 1 year (depending on response) before reassessing (similar to use in IBD).

Summary of current treatment pathway
Acute pouchitis is treated with antibiotic therapy When symptoms persist for > 4 weeks it is classified as chronic pouchitis. This is initially treated with a combination of antibiotics (e.g. ciprofloxacin, metronidazole, rifaxamin) and/or steroids (e.g. budesonide, prednisolone) (effective in 80% of patients) Ongoing management with St marks solution, dietetic support, probiotics and loperamide is also used. If recurrent courses of antibiotics are not effective and the patient is steroid dependent

(symptoms flare when steroids are weaned) the next step should be considered.
Once all medical interventions have been trialled, the last line option is surgery (pouch failure) for a pouch resection/ileostomy.

For the patients that have chronic antibiotic-refractory pouchitis an anti-TNF agent (infliximab) should be considered prior to the last line option of surgery (pouch failure).

Evidence review

See ECCO guidelines (page 2)[1].

The results from a systematic review[3] with meta-analysis for infliximab use in pouchitis can be seen in the table below:

Study	Year	Intervention	Study design	n	Summary outcomes
Viscido	2004	Infliximab 5 mg/kg (week 0, 2, 6 then every 8 weeks for a year)	Observational	7	6/7 (86%) achieved remission
Gionchetti	2010	Infliximab 5 mg/kg (week 0, 2, 6) for 10 weeks or Adalimumab 160/80 mg induction then 40 mg alternate weeks	Observational	12	9/12 (75%) achieved remission in infliximab group 5/7 (72%) achieved remission in adalimumab group
Ferrante	2010	Infliximab 5 mg/kg (week 0, 2, 6) for 10 weeks	Observational	11	3/11 (27%) achieved remission
Viazis	2012	Infliximab 5 mg/kg (week 0, 2, 6 then every 8 weeks for a year)	Observational	7	5/7 (72%) achieved remission
Barreiro-de Acosta	2012	Infliximab 5 mg/kg (week 0, 2, 6) Followed by 5 mg/kg every 8 weeks or 10 mg/kg every 10 weeks based on clinical	Observational	33	7/33 (21%) achieved remission at week 8 11/33(34%) achieved

		need			remission at 26 weeks 9/33 (27%) achieved remission at 52 weeks
Iizuka	2014	Infliximab 5 mg/kg (week 0, 2, 6 then every 8 weeks for a year)	Observational	1	1/1 (100%) achieved remission

Pardi et al (2009) Clinical Guidelines for the Management of Pouchitis:

“infliximab was reported to be effective in a small group of patients with chronic active pouchitis not responding to antibiotic treatment or oral budesonide. Similarly, patients with chronic pouchitis complicated by fistulae were successfully treated with infliximab.”

Equity / Stakeholder views (if relevant)	
Decisions of local Trusts DTCs and neighbouring APCs	Nil
Recommendations from national / regional decision making groups	Nil
Stakeholder views	Use the enclosed proforma to obtain views from clinicians Summarise who has been consulted e.g. secondary care consultants, what their views are and any declared conflict of interest Have views of patient groups been sought?
CCG priorities	Does this treatment fit with existing national, regional or local priorities, policies or activity?

Health economic considerations	
Cost per year per patient	Varies based on weight- Based on 70kg @ 5mg/kg=350mg at £400.57 per dose. Dose at 0,2,6weeks then 8 weekly- total 9 infusions £3605.13 for IV infusions (day cases) or can be prescribed for sub-cut administration at home (unlicensed for both indications) For Remsima s/c: 120mg = £377.66 (BNF price). 120mg x 3 = £1132.98. These are list prices and there are additional NHS agreed discounts
Alternative treatments cost per patient per year	Include comparable costs of alternative treatments at patient and per 100,000 population if relevant Not calculated. This would be antibiotics, steroids and surgery.

Other financial considerations (if relevant)	Potential off-set costs include reduction of in-patient admissions and reduced incidence of need for ileostomy/pouchectomy
Health economic data (if available)	Not available

References

1) European Crohn's and Colitis Organisation (ECCO): Pouchitis algorithm [online]. Available at: http://www.e-guide.ecco-ibd.eu/algorithm/pouchitis
2) Inflectra 100 mg powder for concentrate for solution for infusion- Summary of Product Characteristics (SPC). eMC, [online]. Last updated June 2018. Available at: https://www.medicines.org.uk/emc/medicine/29980
3) Segal JP, Ding NS, Worley G, Mclaughlin S, Preston S, Faiz OD, Clark SK, Hart AL. Systematic review with meta-analysis: the management of chronic refractory pouchitis with an evidence-based treatment algorithm. Aliment Pharmacol Ther. 2017 Mar;45(5):581-592.
4) Pardi DS, D'Haens G, Shen B, Campbell S, Gionchetti P. Clinical guidelines for the management of pouchitis. Inflamm Bowel Dis. 2009 Sep;15(9):1424-31

Which cites the following 2 papers in relation to this topic:

Calabrese C Gionchetti P, Rizzello F et al. Short-term treatment with infliximab in chronic refractory pouchitis and ileitis. *Aliment Pharmacol Ther.* 2008;27: 759-764.

Viscido A, Habib FI, Kohn A, Papi C, Marcheggiano A, Pimpo MT, Vernia P, Cadau G, Caprilli R. Infliximab in refractory pouchitis complicated by fistulae following ileo-anal pouch for ulcerative colitis. Aliment Pharmacol Ther. 2003 May 15;17(10):1263-71.

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Declaration of Interest:

None

Date: 15.06.21 (revised 20.7.21)

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Declaration of Interest:

Nil

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