NHS
Cambridgeshire and Peterborough
Clinical Commissioning Group

CAMBRIDGESHIRE AND PETERBOROUGH JOINT PRESCRIBING GROUP

Date:16/11/2020

What are we bringing to C&PCCG.

A discussion paper on the use of subcutaneous infliximab (Remsima ®) for licensed indications

Why is this being brought to C&PCCG?

- Infliximab intravenous (IV) infusion is licensed and is recommended by NICE and is in use locally as a biologic treatment for a range of immune-mediated inflammatory diseases. Recently lower cost biosimilar versions have become available.
- The most common use for infliximab is in inflammatory bowel disease (IBD: Crohn's disease
- (CD) and ulcerative colitis (UC)). Infliximab is rarely used in new patients for other indications but there is some use in existing patients for rheumatology indications.
- The first subcutaneous (SC) preparation of infliximab (Remsima® 120mg solution for injection) was authorised for use earlier in the year for rheumatoid arthritis (RA) in adults. The marketing authorisation has recently been extended to the treatment of adults with Crohn's disease, ulcerative colitis, ankylosing spondylitis (AS), psoriatic arthritis (PsA) and psoriasis.
- (Ps) (same indications as for intravenous infliximab). Remsima is the only brand of SC
- infliximab currently available.
- Local specialists expressed an interest in using infliximab SC including switching existing patients, to avoid attendance at hospital during the COVID-19 pandemic.
- Following a request from CUH specialists, C&PCCG supported CUH undertaking restricted temporary switching of infliximab intravenous to subcutaneous in line with specified criteria. This was as an exception during the COVID-19 pandemic, with support for CUH claims for reimbursement from NHS England & NHS Improvement (NHSE/I) against the national COVID-19 funds.
- The evidence for SC use is not substantial. Limited trial data suggests that in the short term, efficacy, and safety for the two formulations are similar in the studied cohort for RA and IBD.
- Efficacy outcomes are not available for all indications and use in practice, and extrapolation was used as part of marketing authorisation.
- Drug costs for Remsima SC are higher than for IV infliximab. Maintenance infliximab is given as IV infusions so there are both drug and administration activity costs. If administered via SC form, there will be no administration activity costs. The use of SC infliximab will result in a drug cost pressure but the overall costs including drug and activity need to be considered to estimate the overall cost impact to the health economy.
- If the desire to treat patients in their homes continues to be a priority for NHSE, then Remsima SC remains the most cost-effective option.

Background Information

- IV infliximab is given as infusions (3mg/kg RA or 5mg/kg other indications) at weeks 0, 2, 6 and then every 8 weeks.
- For new patients, following two IV infusions 2 weeks apart, the recommended dose for SC Remsima is 120 mg once every 2 weeks starting 4 weeks after the 2nd IV dose. For RA it must be given concomitantly with methotrexate.
- When switching from IV maintenance infliximab to SC Remsima, the 1st dose may be administered 8 weeks after the last administration of the IV infusion.
- The only licensed dose for SC infliximab is 120mg every 2 weeks. However, there are times when patients required a limited decrease in interval of treatment to reduce a flare and bring a patient back into remission. If this is the case, the company have agreed to provide the extra doses free of charge and as such the treatment cost will be an annual charge regardless of the number of doses given,
- Switching suitable patients to SC infliximab (Remsima) and starting in new patients who can self-inject could help
- reduce unnecessary hospital attendances
- support capacity problems at providers
- protect vulnerable individuals from the risk of infection during COVID pandemic (patients on infliximab may have been classified as shielders or recommended to self- isolate as a clinically vulnerable group)
- reduce the risk of infection transmission between people attending clinical facilities.

Proposed Recommendation Options

1. To recommend the use of infliximab SC as an option when infliximab is indicated in new patients and to support switching of existing patients
2. Not to recommend the use of infliximab SC as an option when infliximab is indicated in new patients and not to support switching of existing patients
3. To recommend the use of infliximab SC as an option when infliximab is indicated in new patients and to support switching of existing patients with restrictions e.g., only during COVID-19 pandemic in patients who consent to use/switch to SC infliximab also consent to switch to IV in the future.

Evidence of Clinical Effectiveness

Comparability studies have been undertaken to compare safety and efficacy of the intravenous (i.v.) biosimilar Remsima® (CT-P13) with the originator Remicade®, the outcome of which informed the decision to authorise the i.v. preparation.

The evidence for the use of infliximab SC compared to IV is not substantial (do not appear to be any fully published trials) but it has been licensed. Trials referenced in the Summary of product Characteristics (SPC) and European Public Assessment Report (EPAR) suggest that in the short-term efficacy and safety are similar for RA and IBD. Study details are available in the EPAR.

Rheumatoid Arthritis (RA)

Initial marketing authorisation for the s.c. formulation was granted based on the data from an initial (part 1) 54-week phase 1 / phase 3 study and the subsequent randomised controlled trial (part 2), aimed at demonstrating non-inferiority of the s.c. preparation of CT-P13 (following an i.v. loading dose) compared to the i.v. preparation over a period of 30 weeks in patients with active RA, and with a similar safety profile.

In part 2 of the study, patients with active RA received two infusions of infliximab (3mg/kg) two weeks apart, followed from week six onwards by either a maintenance dose of 120mg infliximab every two weeks via s.c. injection or a 3mg/kg dose every eight weeks via infusion. Patients who received the infusion up until week 30 were then switched to the s.c. preparation at week 30 for further analysis up to week 54. In both treatment arms methotrexate was given concomitantly.

Of the 357 patients enrolled in the trial, 343 went on to receive either the infusions or s.c. injections. The s.c. formulation was found to be non-inferior to the i.v. formulation, demonstrating similar efficacy scores (DAS28, ACR20/50/70 and EULAR-CRP responses) at week 22 as well as a similar safety profile. Efficacy profile was generally comparable up to Week 54.

Outcome data, design and further information on these studies have been published in the EPAR and SPC. Relevant extract from EPAR:
2.7.4. Conclusions on clinical efficacy
Therefore, the Committee for Medicinal Products for Human Use (CHMP) concluded that the efficacy profile of Remsima subcutaneous formulation compared to Remsima intravenous formulation in RA patients was generally comparable in terms of disease activity measured by DAS28 (CRP and ESR) and ACR response up to week 54.

2.8.2. Conclusions on clinical safety
In general, the safety profile of intravenous infliximab is well established. However, safety data for SC infliximab is still relatively limited.

Inflammatory Bowel Disease
The efficacy of subcutaneous infliximab in active Crohn's disease and active ulcerative colitis patients was assessed in an open-label, randomised, parallel-group, Phase I study consisting of two parts: Part 1 to determine the optimal dose of subcutaneous infliximab and Part 2 to demonstrate non-inferiority in terms of PK of subcutaneous infliximab compared to intravenous infliximab treatment. Efficacy was only considered as secondary descriptive outcomes.

In Part 1 of this study, 45 patients with active Crohn's disease were enrolled to receive 2 doses of Remsima 5 mg/kg intravenously at Weeks 0 and 2 and subsequently 44 patients were randomised into four cohorts to receive Remsima 5 mg/kg intravenously (n=13) at Week 6 and every 8 weeks up to Week 54, Remsima 120 mg subcutaneously (n=11), Remsima 180 mg subcutaneously (n=12) or Remsima 240 mg subcutaneously (n=8) at Week 6 and every 2 weeks up to Week 54.

In Part 2 of this study, among 136 patients (57 patients with active Crohn's disease (not fistulising) and 79 patients with active ulcerative colitis) who were enrolled to receive 2 doses of Remsima 5 mg/kg intravenously at Weeks 0 and 2, 66 patients (28 patients with active Crohn's disease and 38 patients with active ulcerative colitis) were randomised to receive Remsima 120/240 mg subcutaneously at Week 6 and every 2 weeks up to Week 54, while 65 patients (25 patients with active Crohn's disease and 40 patients with active ulcerative colitis) were randomised to receive Remsima 5 mg/kg intravenously at Week 6, 14 and 22 and then switched to Remsima 120/ 240 mg subcutaneous formulation at Week 30 once-every 2 weeks up to Week 54. The dosage of Remsima 120/ 240 mg subcutaneous formulation was determined based on the patient's body weight at Week 6 for those who received Remsima subcutaneously and at week 30 for those who switched to Remsima subcutaneous formulation (Remsima subcutaneous 120 mg for patients <80 kg; 240 mg for patients ≥80 kg).

In active Crohn's disease patients, the primary endpoint was the observed serum infliximab pre- dose level at Week 22 (Ctrough - trough concentration) and results indicated non-inferiority of Remsima SC 120/240 mg compared to Remsima IV 5 mg/kg. The descriptive efficacy results following Remsima 120 mg subcutaneous formulation were generally comparable to Remsima 5 mg/kg intravenous formulation in terms of clinical response (Crohn’s disease activity index (CDAI)-70 response defined as a decrease in CDAI by ≥70 points and CDAI-100 response defined as ≥100 points from baseline) and clinical remission (defined as an absolute CDAI score of <150 points). Response remained comparable between treatment arms up to week 54, also after switching all patients to SC treatment at week 30.

In active ulcerative colitis patients, the descriptive efficacy results following Remsima 120 mg subcutaneous formulation were generally comparable to Remsima 5 mg/kg intravenous formulation in terms of clinical response (defined as a decrease from baseline in total Mayo score (UC disease severity score)

of at least 3 points and at least 30% or a decrease from baseline in partial Mayo score at least 2 points, with an accompanying decrease from baseline in the sub score for rectal bleeding of at least 1 point, or an absolute sub score for rectal bleeding of 0 or
1), clinical remission (defined as a total Mayo score of ≤2 points with no individual sub score exceeding 1 point, or partial Mayo score of ≤1 point) and mucosal healing (defined as absolute endoscopic sub score of 0 or 1 from Mayo Scoring System). Response remained similar between treatment arms up to week 54, also after switching all patients to SC treatment at week 30.

Although a 180mg/240mg dose was used in these studies only 120mg dose is licensed. EPAR states:

- As it is believed that Ctrough is the most important parameter in relation to effect, maintaining a Ctrough above > 5 µg/mL (and above the concentration seen with approved posology of Remsima IV) should be enough to ensure efficacy of Remsima SC 120mg in all IBD patients.
- The initial proposal to recommend a dose escalation in case of loss of response, and thus allowing a dose of 240 mg to be administered to all patients, including those with a body weight <80 kg, is not supported by sufficient evidence. Additional efficacy and sufficient safety of 240mg SC, especially for patients weighing <80 kg, have not been confirmed. Therefore, it is not possible to include such an option for Remsima SC in this indication without robust clinical data. The proposal for dose escalation was withdrawn.

Relevant Extracts from EPAR
2.4.4. Conclusions on the clinical efficacy
It is known that the IV infliximab dose of 5mg/kg is efficacious in the RA/ IBD/ AS/ PsA/ Ps- indications. It is also known that Ctrough-levels above the threshold of 3-5 ug/mL correlate with efficacy in these indications. Ctrough was shown to remain clearly higher than 5 ug/mL with the 120mg SC infliximab dosing in patients with RA (in the earlier line extension) and now in IBD, even in patients without concomitant immunosuppressive medication (CIM) and with positive Neutralising antibody (Nab) status and also in the heaviest patients. Further, efficacy of SC infliximab was shown to be non-inferior to that of IV infliximab in RA in a properly powered randomized comparative trial.
The currently provided descriptive clinical efficacy data from a small, randomized, open label, mainly pharmacokinetic(s) (PK)-study supports that Remsima SC 120mg is clinically non-inferior to Remsima IV 5mg/kg also in CD and UC patients. There is no clinical data in AS/ PsA/ Ps- patients treated with SC-infliximab. However, based on the above, it is expected that the proposed posology for AS, PsA, AS would result in similar Ctrough levels and hence similar clinical effect as seen with IV infliximab.

2.5.2. Conclusions on clinical safety
In the study CT-P13 1.6 part 2 the overall safety of the IBD study sample treated with Remsima SC was largely comparable to the safety of treatment with the IV formulation, excepting a higher incidence of localised injection site reaction (ISR). This finding was expected with SC administration. Apart from this, the safety profile appeared consistent with the previously described safety profile of Remsima SC and with available extensive safety data for the infliximab IV formulation. Some uncertainties, also relevant for the extrapolation, of the Remsima SC safety data remain.

Ankylosing spondylitis (AS), psoriatic arthritis (PsA) and psoriasis (Ps)
The marketing authorisation application did not include any clinical data for patients with AS, Ps or PsA. The assessment of efficacy and approval in these indications is based on extrapolation (see above). The proposed clinical Remsima SC database was seen as sufficient to justify extrapolations for all indications currently approved for Remsima IV. The manufacturer has proposed to further evaluate the safety of Remsima SC in patients with AS, Ps and PsA in a planned post-authorisation safety study. In addition, two other placebo-controlled long-term maintenance studies, one in CD and one in UC patients have been planned.

Safety

From the SPC

- The safety profile of Remsima subcutaneous formulation from active rheumatoid arthritis (evaluated in 168 and 175 patients for the subcutaneous infliximab group and the intravenous infliximab group, respectively), active Crohn's disease (evaluated in 59 and 38 patients for the subcutaneous infliximab group and the intravenous infliximab group, respectively) and active ulcerative colitis patients (evaluated in 38 and 40 patients for the subcutaneous infliximab group and the intravenous infliximab group, respectively) was overall similar to the safety profile of the intravenous formulation.
- Remsima subcutaneous is associated with systemic and localised injection reactions (usually mild to moderate)
- In RA patients on maintenance treatment, the incidence of anti-infliximab antibodies following the subcutaneous infliximab was demonstrated to be not higher than that of the intravenous infliximab and anti-infliximab antibodies had no significant impact on efficacy/safety profile.
- In Crohn's disease and ulcerative colitis patients on maintenance treatment, the incidence of anti-infliximab antibodies was not higher in patients who received subcutaneous infliximab in comparison to those who received intravenous infliximab and anti-infliximab antibodies had no significant impact on efficacy/safety profile.

From EPAR (also see above):

- In general, unfavourable effects associated with the use of TNF-blockers that have been reported for infliximab (Remsima SmPC), also apply for Remsima SC with the exception of acute infusion reactions (as no infusion is given).
- The present data, while limited, does not raise concerns regarding immunogenicity and safety in patients without concomitant methotrexate or other immunosuppressive medication. This supports the possibility of extrapolation of the data to the indications where patients use less
- methotrexate.
- Overall, no unexpected findings were seen, and the overall safety profile of the patients treated with SC was no worse compared to the IV arm, even after switching, and was overall comparable with the known safety profile of infliximab. The single notable finding among otherwise comparable safety data between treatment arms was the higher proportion of patients that reported localised ISR in the SC group.
- Uncertainties and limitations about unfavourable effects:

- no post-marketing experience on the treatment of patient with the SC formulation exists.
- Up to tenfold higher Ctrough levels, compared to IV, are achieved when on the proposed Remsima SC 120 mg 2 weekly posology. This is a safety concern, especially in long-term, beyond the current 54 weeks.
- The overall exposure of the entire Remsima SC database is not extensive, especially considering the various indications applied for.
- Data on treatment with the Remsima SC without immunosuppressive co-medication appears scarce, and thus calls for post-approval safety data.

To summarise, the uncertainties with regards to the unfavourable effects pertain mainly to the fact that there is still relatively limited safety data, especially considering the several applied for indications without any clinical data, and to the sufficiency of the overall data for current extrapolation purposes. To address these uncertainties, a robust post approval strategy has been proposed which is considered adequate by CHMP.

Cost of treatment and Cost Effectiveness

- Currently maintenance infliximab is given as IV infusions every 8 weeks so there are both drug and administration activity costs. If administered via SC form then patients will be able to receive supplies via homecare arrangements and self-administer, so there will be no administration activity costs. However, the use of IV infliximab biosimilars has decreased previous costs substantially.
- The cost of SC infliximab is substantially higher than the SC TNF inhibitor alternatives available as biosimilars: adalimumab and etanercept.
- Remsima SC is lower cost than alternative biologic treatments for IBD: vedolizumab and ustekinumab which are available as SC maintenance treatment. Specialists may prefer use of SC options so availability of Remsima SC may prevent/delay progression to higher cost treatments.
- There are a few variables concerning costs for the use of IV infliximab: brand used, dose is weight dependent so number of vials used, number of infusions per year may vary and the associated activity costs may also vary.

Current IV infliximab brand choices at local providers:

- Remsima and Inflectra at CUH
- Inflectra, Flixabi and Zessly at NWAFT

There is some minimal ongoing prescribing of the high cost originator brand Remicade (estimated CUH 10 patients)

- Use of infliximab SC will increase drug costs but total costs will be offset by a reduction in the activity costs associated with IV administration.
- For any patients switching, additional patient contact (and activity costs) would likely be required in the interim to train on use and monitor tolerance effectiveness.
- It is possible that patient reviews are currently undertaken while patients are having IV infliximab administered. There may be some costs associated with additional outpatient appointments to undertake reviews of patients on SC treatment.

The needs of the population

- The needs of the population may be high as use of a SC formulation will avoid regular attendance at hospital for repeat infusions and the associated risks during the COVID-19 pandemic (patients on infliximab may have been classified as shielders or recommended to self-isolate as a clinically vulnerable group) and reduce the risk of infection transmission between people attending clinical facilities.
- Some patients may prefer self-administering a SC version. Other TNF inhibitors are available as SC formulations. Some patients may not be able to administer SC injections
- Some stable patients may have reservations concerning the risk of switching and potential for destabilising disease control and the limited efficacy and safety data.
- Switching would only occur with the consent of the patient.

The needs of the community

- The impact on the health economy appears uncertain as there are many variables but from estimates appears likely to be a cost pressure which may affect available funding for other treatments/services.

- Cost pressure is dependent on infliximab IV brand and number of vials used. In general infliximab SC is similar cost to IV Remsima but higher cost than Inflectra. There are also alternative lower cost IV biosimilar infliximab products some of which are currently in use at local providers.
- Not all existing patients may be appropriate for, or consent to, a switch and/or patients/carers may be unable to self-administer which will affect cost impact.
- Patients on higher cost originator brand may not consent to switching especially if they have had an unsuccessful trial switch to an IV biosimilar.
- The availability of a SC formulation may allow for reduced staffing and healthcare resources associated with infusion clinics and support any capacity problems at providers. This may be particularly relevant during the COVID pandemic. However, providers would also no longer receive activity costs associated with IV administration.
- For any patients switching, additional patient contact (and activity costs) would likely be required in the interim to train on use and monitor tolerance / effectiveness.
- There may be some costs associated with additional outpatient appointments to undertake reviews of patients on SC treatment.

Equity and Equality

No impact anticipated. Treatment recommendations apply to all adult patients. No differential impact on people with protected characteristics is anticipated. A switch to a SC formulation could be an option for all patients. Some patients could be considered to be disabled and therefore members of a protected equality group under the Equality Act 2010. Approval of infliximab SC as an option may have a positive impact for this group. However, some patients/carers may not be able to self-inject due to disability. Appropriateness of medicines for individual patients is a clinical decision by the prescribing clinician. There are many considerations concerning appropriate and safe drug use in pregnancy / breast feeding and standard drug choices may need to be amended depending on the risk/benefit and safety information available. NHS England is the responsible commissioner for children.

Policy Drivers

- All areas considered introducing SC infliximab at the start of the pandemic and this has been revisited due to recent price reduction of Remsima SC.
- Some areas in East of England supported restricted switching during the COVID pandemic but with the requirement to switch back to IV. Business cases are being submitted for continuation following the price reduction of Remsima SC.

COVID-19 rapid guideline: Rheumatological autoimmune, inflammatory, and metabolic bone disorders - NG167 supports switching patients and states:
Assess whether patients having intravenous treatment can be switched to the same treatment in subcutaneous form

- NHS England Specialty guide: management of Rheumatology patients during the coronavirus pandemic includes the following:
  - The threat to those with reduced immune responses from being infected with coronavirus may require the NHS to do three things: 1. protect vulnerable individuals from the risk of infection; 2. reduce the risk of transmission between people attending clinical facilities; 3. free up capacity for inpatient and high-dependency care.
    The vulnerable population will include rheumatology patients who are receiving conventional disease-modifying drugs, JAK inhibitors and biologics. Many patients have multisystem disease including heart, lung and/or renal involvement which puts them at an additional risk.
  - If prevalence of COVID-19 infection and associated available hospital resources is Medium (ITU beds start to be in short supply, still reasonable number of hospital beds): Switch IV infusions to subcutaneous injections where available.
- NICE COVID-19 rapid guideline: gastrointestinal and liver conditions treated with drugs affecting the immune response - NICE guideline NG172 includes the following:
  - When deciding whether to start a new treatment with a drug that affects the immune response, discuss the risks and benefits with the patient or their parents or carers, and consider the following in the context of COVID-19:
    - Is it essential to start this drug immediately?

- If treatment is needed, is there an alternative with a better risk profile?
- Is the required monitoring and review feasible?
- Can monitoring be done remotely or at a frequency that minimises the risk to the
    - patient's safety and wellbeing?
- Is there a route of administration that could make hospital attendance or admission less likely?

- For patients who are already taking drugs that affect the immune response, continue with existing courses of treatment to minimise the risk of a flare-up. Think about whether any changes are needed to minimise face-to-face contact during the COVID-19 pandemic, including:
    - dosage
    - route of administration
    - mode of delivery.

Implementation

Switching would need to be undertaken by the specialist team in consultation with the patient. Implementation would be dependent on adequate homecare capacity

Comments Received

This paper has been prepared by a collaboration of clinical staff from the Medicines Optimisation Team C&PCCG, the clinicians and pharmacy staff at Addenbrookes Hospital and the clinicians and pharmacy team at NWAFT.

The Medicines Optimisation Team would like to thank both Trusts for their support and scrutiny throughout the process.

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With thanks to Colin Sach, Lead Pharmacist – Commissioning, ENHCCG PMOT