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COVID-19
Questions, Answers and Actions
Switching from intravenous to subcutaneous infliximab

Question: "Is a switch from Intravenous (IV) infliximab to subcutaneous (SC) infliximab an option as a part of a management strategy to reduce hospital day case admissions, and keep immunosuppressed people out of hospital during the COVID-19 pandemic?"

Answer:

- Remsima SC® was originally only licensed for Rheumatoid arthritis (RA) in adults. A license extension for the treatment of adult patients with ankylosing spondylitis, Crohn's disease, ulcerative colitis, psoriatic arthritis and psoriasis was granted on the 24th July 2020, in line with the adult indications of the IV formulation.
- Hospital Trusts may wish to consider a switch from IV infliximab to SC infliximab during the COVID - 19 pandemic as part of their management strategy to reduce hospital day case admissions, keep immunosuppressed people out of hospital, and to enable social distancing within the day case units plus shielding of high risk patients. However, it should be noted that infliximab-naive patients still require two infusions of infliximab IV before starting maintenance therapy with infliximab SC.
- There are currently constraints around homecare capacity nationally, so the preferred supply route at this time is through hospital pharmacy departments dispensing on an outpatient basis. If supplied via the hospital pharmacy, ancillaries and sharps bins should be supplied where required.
- Patients switched to subcutaneous formulations may need educating on how to self-administer the injection, and relevant specialities will need to consider how they do this e.g. virtually or via face to face outpatient appointment. For new patients who need two IV doses prior to moving to SC it could be done when patients attend for the IV doses. The manufacturer has a leaflet for patients on how to self-administer available at: https://www.medicines.org.uk/emc/product/11102/usermanual
- If localities are considering a managed therapeutic switch programme from infliximab IV to infliximab SC this should be done in agreement with Trusts and Commissioners, coordinated via regional procurement to ensure consistency across regions, and to support national constraints around homecare capacity at this time.
- Commissioners should be fully involved in discussions to move to this temporary arrangement, and Providers and patients should be aware that post COVID-19 pandemic this service provision may be revised.

Actions:

- Trusts and commissioners should consider the points raised in this document regarding the possible use of infliximab SC in place of infliximab IV during the COVID-19 pandemic. A collaborative approach between commissioner, Trust, regional procurement pharmacy specialist and patient is advised.

Clinical information

Remsima® subcutaneous (Celltrion Healthcare UK Limited) is available as a 120mg solution in pre-filled pens or syringes, alongside the existing 100mg powder for concentrate for solution for intravenous infusion. The subcutaneous product was made available in the UK on 1st March 2020

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Infliximab SC has not been studied in patients with renal and/or hepatic impairment so no dose recommendations can be made in these patient groups. Safety and efficacy in children aged below 18 years have not yet been established, therefore it is recommended for use only in adults.

Specific studies of infliximab SC in elderly patients have not been conducted. No major age-related differences in clearance or volume of distribution were observed in clinical studies with infliximab intravenous formulations and the same is expected for the subcutaneous formulation. No dose adjustment of infliximab SC is currently recommended by the manufacturer.

Remsima SC® is latex free and citrate free.

NICE regard Remsima SC® as a biosimilar, so no individual technology appraisal (TA) is required or planned. NICE has decided that normally all relevant published guidance that includes the originator molecule will apply to the biosimilar medicinal product at the time it is made available for use in the NHS.

Information regarding switching patients from the subcutaneous formulation to the intravenous formulations of infliximab is not available.

There is no data available on switching from a different brand of intravenous Infliximab other than Remsima® to Remsima SC®.

Remsima SC® should be dosed as follows:

- Infliximab-naive patients: IV formulation of Infliximab is recommend at 3mg per kg/body weight in RA and at 5mg per kg/body weight for the other licensed indications and normally given as an infusion over two hours. Remsima SC® is administered via a pre-filled pen (auto-injector) or prefilled syringe with Needle Guard and initiated as 120mg once every 2 weeks as maintenance therapy 4 weeks after the last administration of two intravenous infusions of infliximab.
- When switching from maintenance therapy with infliximab IV to the subcutaneous formulation of Remsima®, the subcutaneous formulation may be administered 8 weeks after the last administration of IV infliximab.

There is insufficient information regarding the switching of patients who received the intravenous infusions of infliximab higher than 3 mg/kg for rheumatoid arthritis or 5 mg/kg for Crohn's disease every 8 weeks to the subcutaneous formulation of Remsima®.

Available data suggest that the clinical response is usually achieved with infliximab within the following timeframes for each indication:

- RA: after 12 weeks of treatment with infliximab. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within the first 12 weeks of treatment infliximab.
- Moderately to severely active Crohn's disease: If a patient does not respond after 2 doses of intravenous infusions, no additional treatment with infliximab should be given. Available data do not support further infliximab treatment, in patients not responding within 6 weeks of the initial infusion.

- Fistulising, active Crohn's disease: If a patient does not respond after 6 doses (i.e. 2 intravenous infusions and 4 subcutaneous injections), no additional treatment with infliximab should be given.
- Ulcerative colitis: within 14 weeks of treatment, i.e. 2 intravenous infusions and 4 subcutaneous injections. Continued therapy should be carefully reconsidered in patients who show no evidence of therapeutic benefit within this time period.
- Ankylosing spondylitis: If a patient does not respond by 6 weeks (i.e. after 2 intravenous infusions), no additional treatment with infliximab should be given.
- Psoriasis: If a patient shows no response after 14 weeks (i.e. 2 intravenous infusions and 5 subcutaneous injections), no additional treatment with infliximab should be given.

Evidence

Marketing authorisation for the subcutaneous 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), demonstrating non-inferiority of the subcutaneous preparation of CT-P13 compared to the intravenous preparation over a period of 30 weeks in patients with active RA. The license extension is based on data from a pivotal study comparing the pharmacokinetics, efficacy and safety of the subcutaneous (SC) and intravenous (IV) formulations of Remsima® in people with active Crohn's disease and ulcerative colitis, throughout a 1-year treatment period.

To gain approval in the EU, biosimilar medicines must demonstrate that they are as safe and as effective as the reference medicine, and have the same quality characteristics. The license for infliximab SC in rheumatoid arthritis was based on a phase I/III study to evaluate the pharmacokinetics, efficacy and safety of infliximab SC versus infliximab IV in people with active RA. The efficacy and safety profile of the two administration routes was found to be comparable.

The pivotal phase I/III trial was a randomised, parallel-group study with two parts: Part 1 to determine the optimal dose of subcutaneous infliximab and Part 2 to demonstrate non-inferiority of infliximab SC compared to intravenous treatment. In Part 2 all participants received 2 doses of Remsima® 3 mg/kg intravenously at weeks 0 and 2. Subsequently 167 patients were randomised to receive Remsima® 120 mg subcutaneously at week 6 and every 2 weeks up to week 54, and the remaining 176 patients were randomised to receive Remsima® 3 mg/kg intravenously at weeks 6, 14 and 22. The IV arm were then switched at week 30 to receive Remsima® 120 mg subcutaneous once every 2 weeks up to week 54. Methotrexate was given concomitantly in both arms. The primary endpoint was the estimated treatment difference in terms of the change from baseline in DAS28 (CRP) at week 22, which was 0.27 (95% CI: 0.02, 0.52). The lower limit of the confidence interval did not exceed the pre-specified non-inferiority margin of -0.6, indicating non-inferiority of Remsima SC® to Remsima® IV. The analysis of other efficacy endpoints showed that the efficacy profile of Remsima SC® was generally comparable to Remsima® IV in terms of disease activity measured by DAS28 (CRP and ESR) and ACR response up to week 54. The mean scores for DAS28 (CRP) and DAS28 (ESR) gradually decreased from baseline at each time point until week 54 in each treatment arm.

Although the IBD trial used 240mg Remsima SC® in Crohn's disease and ulcerative colitis patients over 80kg, the approved licensed dose is 120 mg for all patients due to the pharmacokinetic (PK) profile. Based on the PK data, the EMA decided that 120 mg SC provides sufficient blood levels for patients of higher weights - who were given 240 mg SC in the pivotal data. The SC route PK profile is also flatter, which means the high peaks and troughs of IV administration are avoided.

The efficacy and safety profile of infliximab IV is well established. The clearly higher drug concentrations during SC administration did not seem to translate into a higher risk for infections or other adverse events, although the number of patients and duration of follow-up is still limited. Some uncertainty remains regarding the effect of higher C_{trough} levels of infliximab on the potential risk of some rare

adverse events (e.g. cardiac AEs); long-term safety will be further studied in a post-approval programme (including a non-interventional study in patients with RA). The only new unfavourable effect identified after SC dosing were injection site reactions, which are common for SC dosing in general, and were all mild or moderate in severity and manageable.

National guidance

NICE have published NG167 - COVID-19 rapid guideline: rheumatological autoimmune, inflammatory and metabolic bone disorders on 3rd April 2020 and updated on the 2nd July 2020. This recommends assessing whether patients having intravenous treatment can be switched to the same treatment in subcutaneous form. If this is not possible, discuss with the patient an alternative subcutaneous treatment.

NICE have published an evidence summary ES29: Remsima (infliximab biosimilar) for subcutaneous injection for managing rheumatoid arthritis on the 21st July 2020. This suggests that Remsima SC® is most likely to be used in patients who are already established on intravenous infliximab with stable disease but who have difficulty attending hospital appointments, and in whom the risk of attending hospital for intravenous infusions outweighs the benefits. The evidence summary also suggests that Remisima SC® may be beneficial for patients who are starting on infliximab who have not used a biologic before or who are switching from a biologic with a different mechanism of action to the tumour necrosis factor (TNF)-alpha inhibitors.

There is currently no formal guidance from The British Society of Rheumatology on the use of infliximab SC during the current COVID -19 pandemic.

The British Society of Gastroenterology (BSG) guidance currently for anti-TNF therapy during COVID -19 is that enforced IV to SC switching is not recommended and to consider initiation with monotherapy (therefore to consider use of adalimumab to promote home care and its lower risk of immunogenicity relative to infliximab).

There is currently no formal guidance from The British Society of Dermatology on the use of infliximab SC during the current COVID -19 pandemic.

In informal guidance the European Crohn's and Colitis Organisation suggest that an elective switch in Crohn's disease from infliximab to adalimumab can lead to increased risk loss of response, so switching to subcutaneous drugs should be limited to centres where use of IV infusions is no longer available. In centres able to schedule infusions in order to avoid crowding and with appropriate sanitation done between each infusion, patients can continue their IV biologics. A different approach can be considered for those who start a new biologic. In this case, subcutaneous drugs may be preferred, together with a program of remote patient education, and home delivery service. Because of the lack of any data to support an elective switch in ulcerative colitis patients, infliximab should not be switched to adalimumab or golimumab.

Cost

Remsima SC® has an NHS list price of £377.66 per 120mg pre-filled syringe or pen. For comparison IV infliximab biosimilars all have an NHS list price of £377.66 per 100 mg vial, which is 10% lower than the list price of the originator product Remicade® (£419.62 per 100 mg vial). However, the actual cost of Remicade® and the biosimilar products (including Remsima SC®) may differ from list prices due to locally negotiated procurement discounts.

Based on a 75kg adult, and using NHS list prices (excl VAT), the cost of SC vs. IV infliximab is as follows:

- Remsima SC® (all indications) 120mg maintenance dose every 2 weeks = £1,510.64 over 8 week period (not including homecare costs)

- Infliximab IV (biosimilar) for RA 3mg/kg every 8 weeks maintenance dose = £1,132.98 (not including administration and day case attendance costs)
- Infliximab IV (biosimilar) for all other indications 5mg/kg every 8 weeks maintenance dose = £1,510.64 (not including administration and day case attendance costs)

(N.B. VAT will have to be applied to items dispensed by hospital inpatient pharmacies)

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