Guideline for the use of infliximab in pyoderma gangrenosum

Aim

The aim of this guideline is to provide guidance on the use of infliximab for pyoderma gangrenosum (PG) as this is not a licensed indication for infliximab. Consequently, there is no national commissioning guidance to support its use and so funding will need to be provided by GHT.

Rationale

PG is a rare ulcerative skin condition which can cause significant morbidity. It belongs to a group of related conditions called neutrophilic dermatoses and is characterised by deep skin ulcers with undermined edges that occur most often on the lower limbs but may affect any skin surface. 50% patients have no known cause for it. In some cases, it may start after trauma to the skin but other cases are associated with an underlying inflammatory condition such as arthritis or more commonly, inflammatory bowel disease (IBD). PG is difficult to treat and can take time to heal. Mild cases can be treated with topical agents, such as corticosteroids and calcineurin inhibitors but more severe cases require systemic treatments such as prednisolone or immunosuppression with azathioprine, ciclosporin or mycophenolate. Some patients can become refractory to these treatments[1,2]. Patients suffering from PG often have to cope with side effects caused by long term steroids, frequent dressing changes and poor mental health. They also need frequent follow-up appointments from both practice nurses for dressings and the dermatology team. Therefore, some patients could benefit from using infliximab to manage this condition.

Indications

- Patients with severe PG refractory to azathioprine, mycophenolate and ciclosporin

Evidence

The evidence for infliximab for PG is limited to one small randomised controlled trial as low-evidence studies and lack of validated diagnostic and response criteria have affected the discovery of new treatments for PG[3]. In this multicentre, randomised, double blind placebo-controlled study 30 patients with PG were randomised to receive 5mg/kg infliximab infusion or placebo at week 0. At week 2, patients were assessed and non-responders were offered open-label infliximab. The primary end point was clinical improvement at week 2 and secondary end points were remission and improvement at week 6. 46% patients in the infliximab arm showed improvement within 2 weeks compared to 6% of patients in the placebo arm. The study showed no different in outcomes between patients with and without IBD[2]. This was a very small and short study, as it was undertaken when induction dosing for infliximab was not common place and this is its main limitation.

In addition, a semi-systematic review of 275 patient experiences found that 87% patients had a response to infliximab and 68% had a complete response. These figures are higher than found in the initial study discussed above as patients had a longer treatment duration so the former response rate may have been underestimated[4].

The review was semi-systematic because the literature lacked high-quality studies and consisted predominantly of case reports and case series. This study concluded that to date, infliximab remains the sole anti-TNF agent that has demonstrated efficacy in classical PG[3]. Recently, there has been a phase 3 open-label multicentre study in 22 patients to evaluate the safety and efficacy of adalimumab in refractory PG. 55% participants experienced complete healing after 26 weeks[5]. The semi-systematic review concluded that anti-TNF, especially infliximab and adalimumab, represent the best options for patients who have PG refractory to systemic corticosteroids, ciclosporin or a combination of both[3].

Contraindications

Hypersensitivity to the active substance, any murine proteins or excipients

Patients with tuberculosis or other severe infections such as sepsis, abscesses and opportunistic infections

Patients with moderate or severe heart failure (NHYA class III/IV)[6]

Practicalities

Remsima® is available as IV and SC infusions, dermatology patients receiving SC maintenance treatment do still require two IV loading doses given at the Medical Day Unit, CGH. SC maintenance will be used in preference to IV dosing as it is more cost effective and results in higher serum infliximab levels which can reduce the risk of immunogenicity and associated loss of response. SC dosing is provided via Homecare. Patients who decline or who are considered unsuitable for Homecare will be offered maintenance treatment with IV dosing.

Formulation	Year One cost (VAT and tariffs included)
IV loading and maintenance	£6,795
IV loading and SC maintenance	£5,137

Patients will be treated for 1 year and if in remission at that time, treatment may be stopped. If patients later relapse treatment may be re-started.

Patient numbers

It is estimated that approximately 5 patients per year will require treatment with infliximab

References

1. British Association of Dermatologists (2020); Patient Information Leaflet: Pyoderma Gangrenosum; available from British Association of Dermatologists (bad.org.uk)
2. Brooklyn TN, Dunnill MGS et al (2006); Infliximab for the treatment of pyoderma gangrenosum: a randomised, double blind, placebo-controlled trial; *Gut*; 55 (4); 505-509

3. Maronese CA, Pimentel M et al (2022); Pyoderma Gangrenosum: An Updated Literature Review on Established and Emerging Pharmacological Treatments; *American Journal of Clinical Dermatology*; 23; 615-634
4. 4. Abdallah HB et al (2018); Pyoderma gangrenosum and tumour necrosis factor alpha inhibitors: A semi-synthetic review; *International Wound Journal;* 16(2); 511-521
5. Yamamoto T (2021); An update on adalimumab for pyoderma gangrenosum. *Drugs Today;* 57(9); 535-42
6. Summary of Product Characteristics for Remsima SC 120mg pre-filled pen (Infliximab). DORT 21/7/22; Available from Remsima 120 mg solution for injection in pre-filled pen - Summary of Product Characteristics (SmPC) - (emc) (medicines.org.uk)