Guidance Update

Management of Crohn’s disease

An update on the management of Crohn’s disease—the positioning of Stelara® (ustekinumab)
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Crohn’s disease is a chronic inflammatory disease that mainly affects the gastrointestinal tract. It can occur at any age, with peak incidence between the second to fourth decade of life; a smaller peak of incidence has also been observed in the latter decades of life. Whilst the cause remains unknown, the disease arises in genetically predisposed individuals with an aberrant immune response to gastrointestinal microbes. It is estimated that there are at least 115,000 people in the UK with Crohn’s disease.

Crohn’s disease often has a relapsing and remitting course. Some patients might experience mild symptoms during a relapse followed by long periods of clinical remission, whereas others might have a more severe disease with frequent relapses. The impact on a patient’s life depends on disease extent and severity as well as disease progression; it is wide ranging, affecting their self-esteem and personal relationships, potentially leading to a perception of isolation.

The cost of Crohn’s disease to the NHS is significant with an estimated annual cost for any patient with Crohn’s disease of £6156 (£1800 for patients in remission; £10,513 for patients in relapse).

Management of Crohn’s disease: escalation of therapy*

Conventional therapy in Crohn’s disease includes the use of a glucocorticosteroid, typically prednisolone, methylprednisolone, or intravenous hydrocortisone, to induce clinical remission in newly diagnosed patients or for a single inflammatory exacerbation in a 12-month period. Budesonide is an alternative steroid indicated for patients with distal ileal, ileocaecal, or right-sided colonic disease who decline, are intolerant to, or contraindicated for a conventional glucocorticosteroid. Treatment with 5-aminosalicylate (5-ASA) may be considered for those who decline, cannot tolerate, or in whom glucocorticosteroids are contraindicated.

In steroid-refractory or steroid-dependant patients, escalation of therapy to immunosuppressant or biologic drugs is recommended. The most commonly used immunosuppressants are thiopurines (azathioprine or mercaptopurine) and methotrexate. Thiopurines play a role in maintaining rather than inducing clinical remission as onset of action for thiopurines may take up to 17 weeks. Methotrexate may induce and maintain remission, as clinical efficacy in patients on steroids may be evident as early as 6 weeks after starting therapy.

For patients whose disease has not responded to conventional therapy, there is a choice of biologic drugs with different mechanisms of action. The decision to prescribe a specific biologic drug is based on efficacy, safety, and costs, taking patient preferences into consideration.

The first group of biologic drugs to be introduced for Crohn’s disease were the tumour necrosis factor (TNF)-alpha inhibitors, infliximab and adalimumab. They are recommended as treatment option for patients with severe active Crohn’s disease whose disease has not responded to conventional therapy, or who are intolerant of or have contraindications to conventional therapy. There is a wealth of real world data for their efficacy and safety in patients with inflammatory bowel disease. The replacement of the originator drugs with biosimilar drugs has reduced the cost of therapy. NICE also recommends vedolizumab, a monoclonal antibody, as an option for moderate to severe Crohn’s disease if there has been treatment failure to a TNF-alpha inhibitor or if a TNF-alpha inhibitor cannot be tolerated or is contraindicated.

*Refer to the NICE guidance and the individual summaries of product characteristics for further information and recommendations regarding the use of pharmacological therapies. Some of the drugs recommended in NICE Clinical guideline 152 (at the time of its publication, May 2016), did not have UK marketing authorisation for the indications discussed. For off-licence use of medicines, the prescriber should follow relevant professional guidance, taking full responsibility for the decision. Informed consent should be obtained and documented. See the General Medical Council’s Good practice in prescribing and managing medicines and devices for further information.
Ustekinumab, a monoclonal antibody targeting interleukin-12 and interleukin-23 is recommended as an option for treating moderately to severely active Crohn’s disease in adults who have failed to respond to, lost response to, or were intolerant to conventional therapy or a TNF-alpha inhibitor. It can also be considered in patients who have contraindications to conventional or TNF-alpha inhibitor therapies. This means that ustekinumab can be used early on in the course of disease as a first-line biologic therapy.

**The evidence for ustekinumab as a first-line biologic**

The NICE guidance supporting the use of ustekinumab in patients with Crohn’s disease is based on evidence from the UNITI clinical trials. The UNITI-1 induction study enrolled patients who had failed one or more TNF-alpha inhibitor treatment (did not respond, lost response, or were intolerant). The primary outcome measure was clinical remission at week six and ustekinumab showed superior clinical remission rates compared with placebo.

The study population in the UNITI-2 induction study was different. Here, patients had failed to respond to conventional therapy or had unacceptable side-effects. They may still have had treatment with a TNF-alpha inhibitor, but would not have met the criteria for treatment failure. Similar to the UNITI-1 study, UNITI-2 demonstrated higher efficacy for ustekinumab compared with placebo at inducing clinical remission at week six. Remission rates with ustekinumab for the UNITI-2 population were higher than for UNITI-1, indicating better outcomes when used as a first-line biologic rather than after TNF-alpha inhibitor failure.

The effectiveness of ustekinumab in maintaining clinical remission data comes from the IM-UNITI study with a 44-week follow-up period and long-term extension study. In the IM-UNITI maintenance trial, the proportion of patients in clinical remission was significantly greater with the ustekinumab groups (receiving maintenance doses every 8 or 12 weeks) than in the placebo group. Clinical remission rates from the IM-UNITI long-term extension study have been reported for 621 out of 718 patients who completed a 96-week follow up. The proportion of patients in clinical remission was generally maintained from week 44 through to week 92 in the ustekinumab maintenance therapy groups (77.4% to 72.6% for the group receiving doses every 12 weeks; 84.1% to 74.4% for the group receiving doses every 8 weeks). The 92-week remission data shows that patients from the UNITI-2 conventional therapy failure population had slightly higher remission rates than the UNITI-1 population who had previously failed TNF-alpha inhibitor treatment. This data indicates that the benefits of higher induction remission rates can be maintained over a 92-week period encouraging the use of this drug as a first-line biologic. The long-term IM-UNITI extension study has continued for 3 years, and recent data show that remission rates were maintained at week 152. In the randomised patient group (only those patients randomised in the maintenance trial who continued into the long-term extension study) clinical remission was maintained in 74.3% of patients on 12-weekly dosing (N=70) and 82.6% of patients on 8-weekly dosing of ustekinumab (N=69). Initially in clinical practice ustekinumab has been used very late in the Crohn’s pathway. However, the UNITI studies suggest that there is an additional clinical benefit when used as a first-line biologic. Furthermore, NICE permits its use as a first-line biologic agent in Crohn’s disease. In the absence of comparative effectiveness studies between biologic drugs, the key considerations to guide clinicians, patients, and policy makers towards ustekinumab are the safety profile and costs.

The safety profile for ustekinumab comes from its use in clinical studies with around 6000 patients with psoriasis and/or psoriatic arthritis, or Crohn’s disease. There does not seem to be an increased risk of infections with ustekinumab, which could be seen as a key advantage over TNF-alpha inhibitors. The IM-UNITI study evaluated safety of ustekinumab through 156 weeks of therapy including 1544.8 total patient-years of follow up. It found that rates of serious infection and malignancy remained low and the rates of adverse events and serious adverse events were comparable to placebo.

The first dose of ustekinumab is administered intravenously for Crohn’s disease. The following doses are administered subcutaneously, the first at 8 weeks after the intravenous dose and then subsequent doses every 12 weeks are recommended. Patients who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks. Loss of response is defined as a Crohn’s Disease Activity Index (CDAI) score ≥ 220 points and a ≥ 100 point increase from the CDAI score at baseline. With the NHS discounted scheme, the costs are likely to be comparable to the other biologics considering the drug is recommended to be given every 12 weeks (three times per year after induction) instead of 8-weekly for infliximab or vedolizumab and 2-weekly for adalimumab.

**Clinical practice at a specialist inflammatory bowel disease (IBD) centre**

At our centre, the drug was available through a patient access scheme early on for patients who had failed several drugs previously. This explains why in the majority of our patients it was used as a second and third biologic. Other reasons included a lack of awareness that it is endorsed by NICE as a first-line biologic, concerns about the cost, and lack of experience with the drug. As more evidence emerges for the use of ustekinumab and through greater awareness via education, we are seeing ustekinumab used increasingly as first-line biologic.

There are several attributes of the drug that should encourage its use as first-line biologic, including:

- the convenience of administration compared to other...
biologics; 8- or 12-weekly dosing given subcutaneously by injection (aside from the initial intravenous dose), which limits the interruption of patients’ lives.

- real world evidence that patients on ustekinumab have a low risk of serious infections:
  - a study concluded that patients receiving ustekinumab had fewer infections compared with patients on TNF-alpha inhibitors, however this data comes from patients with psoriasis not Crohn’s disease.
  - a caveat of the psoriasis study is that the doses of ustekinumab used are lower than those used with Crohn’s disease — further long-term real world data on safety with the drug in Crohn’s disease is needed to confirm this but, nonetheless, the psoriasis findings are promising.

- low immunogenicity — at 3 years only 4.8% of patients receiving ustekinumab tested positive for antibodies at any time during maintenance.

- contraindications to TNF-alpha inhibitor use.

There remain a few barriers to implementation related to comparative efficacy, patient groups, and costs:

- uncertainty about the efficacy of the drug compared with established biological therapy.

- to date, there are limited head-to-head comparisons of ustekinumab with other biologics and there is a gap in knowledge about response to TNF-alpha inhibitors if given second-line after ustekinumab.

- although ustekinumab can be considered a cost-effective option in the NHS, this may be challenged by the increasing number of TNF-alpha inhibitor biosimilar drugs.

- clinical experience with other biologics is larger, thus clinicians may be more likely to opt to use drugs they have experience with.

- this is particularly relevant for certain patient groups such as those planning a pregnancy or those who are already pregnant; there is a substantial body of evidence for the safety of TNF-alpha inhibitors in pregnancy and methods of mitigating exposure of the newborn.

- in contrast to TNF-alpha inhibitors, the clinical efficacy in perianal disease with ustekinumab remains unknown.

- until further evidence comes to light, it is likely that infliximab will remain first-line based on clinical trials showing its efficacy.

**Clinical outcomes in practice**

We currently have 94 patients who were prescribed ustekinumab. We have seen a gradual shift from ustekinumab as a second-line biologic to first-line biologic. Our experience with ustekinumab as a first-line biologic is limited and to date we have had four patients who started ustekinumab as a first-line biologic. One patient reported a history of recurrent infections hence the reluctance to start on TNF-alpha inhibitors with the associated increased risk of infections. One patient had experienced side-effects to all previous immunosuppressant drugs and was reluctant to consider dual therapy and drugs with possible risk of infections. The remaining two patients opted for ustekinumab due to the convenience of subcutaneous delivery and lower frequency of administration. We anticipate this number to increase in the coming months and years.

Twenty-two percent (21/94) of our patient cohort were prescribed ustekinumab as a fourth-line biologic drug. Only four of these patients discontinued therapy, three due to lack of response and one due to possible adverse effects (dizziness and memory loss). Five of these patients needed rescue therapy with steroids and the majority (n=12) responded with ongoing therapy.

**How to decide on a biologic drug in Crohn’s disease**

The decision to start any biologic drug depends on pre-agreed treatment goals of induction of remission and mucosal healing. However, the decision defining the choice of biologic drug presents more difficulty: there is equipoise in the options, that is, the best option is not clear, and the ‘stakes’ are not minimal (there are significant consequences associated with the choice) and the decision is preference sensitive. Such situations are recognised as appropriate for a shared decision-making process, whereby clinicians inform and recommend treatment to patients, and the process of deciding on how to act is shared. The choice of biologic drug qualifies as a preference-sensitive decision since there is more than one appropriate option and patients will decide based on what is right for them, depending on the balance of benefits and risks.

To help decide between the different groups of biologic drugs many factors should be considered including:

- safety
- evidence supporting the use of the drugs
- ease of administration
- frequency of administration
- patient age
- patient family planning
- use of immunomodulators
- number of years of experience prescribing the drug
- population sizes of studies reporting safety data.

**Ustekinumab as first-line biologic within the NHS**

The NHS Long Term Plan advocates more personalised care as well as out of hospital care harnessing digital technologies to deliver care. Ustekinumab offers benefits over other biologic drugs pertaining to:

- patient preference for route of administration subcutaneous (homecare) versus intravenous (hospital)
- patient preference for frequency of drug administration – every 2 weeks versus every 8 or 12 weeks
- patient empowerment with understanding of positive safety profile
- patient understanding of efficacy of biologics.
A patient case study for using ustekinumab as a first-line biologic

A 61-year-old woman with a 34-year history of ileocolonic Crohn’s disease and a previous right hemicolecction, presented with a Harvey-Bradshaw index (HBI) score of 8. Her quality of life was poor with an Inflammatory Bowel Disease Questionnaire (IBDQ) score of 37. Colonoscopy showed inflammation of the neoterminal ileum, distal ileum and mid-transverse colon. She had tried several immunosuppressants over the years and experienced side effects to azathioprine, mercaptopurine, methotrexate, and mesalazine preparations. The clinician established that she would be on monotherapy as she was intolerant to immunosuppressant drugs. Both TNF-alpha inhibitor drugs, infliximab and adalimumab, show greater efficacy and less immunogenicity when prescribed as combination therapy. Patients over 60 years of age are also more susceptible to risk of infections with TNF-alpha inhibitor therapy and also combination therapy. The clinician was also aware that the patient resided a long way from the hospital and it was inconvenient for her to attend for intravenous administration. After discussing these issues and the safety profile of the drugs, a shared decision was reached to start ustekinumab as first-line biologic therapy. She received 390 mg of ustekinumab as the first intravenous dose followed by a 90 mg subcutaneous dose after 8 weeks. By week 12, her HBI score was 1 and her IBDQ improved to 41. She was scheduled for a further 90 mg subcutaneous dose of ustekinumab 12 weeks after her first subcutaneous dose.

Personal perspective on the first-line use of ustekinumab

Our rationale for including ustekinumab as first-line biologic, is:

- its efficacy in inducing clinical remission
- cost effectiveness from the perspective of the number of injections and home administration
- the convenience of subcutaneous and relatively infrequent administration.

Practical tips and advice for clinicians when counselling regarding biological therapy

- When patients fail immunosuppressant therapy, consider and discuss both pharmacological and surgical options
- When counselling patients about biologic drugs, discuss all options in terms of efficacy (they seem comparable)
- To help decide between the different groups of biologic drugs, consider safety and ease of administration and discuss with patients the clinical factors that may favour one drug over another such as patient family planning, use of immunomodulators, and patient age
- Inform patients about biologics and how this might affect family planning
- Give patients relevant information about each drug
- Involve your pharmacist with regards to drug costing
- Patients who have not previously responded to anti-TNF and anti-integrin drugs may respond to ustekinumab even as a fourth biologic drug.


STEELARA® 45 mg and 90 mg solution for injection and 130 mg concentrate for solution for infusion PRESCRIBING INFORMATION

ACTIVE INGREDIENT(S): Ustekinumab

Please refer to Summary of Product Characteristics (SmPC) before prescribing.

INDICATION(S): Plaque psoriasis adults: Treatment of moderate to severe plaque psoriasis in adults who failed to respond to, or who have a contraindication to, or are intolerant to other systemic therapies including ciclosporin, methotrexate or PUVA.

Plaque psoriasis paediatrics: Moderate to severe plaque psoriasis in adolescent patients from 12 years of age, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies.

Psoriatic arthritis: Alone or in combination with methotrexate for treatment of active psoriatic arthritis in adult patients when response to previous non-biological disease-modifying anti-rheumatic drug (DMARD) therapy has been inadequate.

Crohn's Disease: Treatment of adult patients with moderately to severely active Crohn's disease who had inadequate response with/without response to/with intolerance to either conventional therapy or TNFα antagonist or have contraindications to such therapies.

DOSE & ADMINISTRATION: Adults: Under guidance and supervision of a physician experienced in diagnosis and treatment of psoriasis/psoriatic arthritis/Crohn's disease. Psoriasis or protective arthritis: Subcutaneous (s.c.) injection. Avoid areas with psoriasis. Self-injecting patients or caregivers ensure appropriate training. Physicians are required to follow-up and monitor patients.

Plaque psoriasis, adults & elderly: Patients ≤100 kg, 45 mg at week 0 followed by a 45 mg dose at week 4, then every 12 weeks. Patients >100 kg, 90 mg at week 0 followed by a 90 mg dose at week 4, then every 12 weeks (45 mg was less effective in these patients).

Plaque psoriasis paediatrics (12 years and older): Patients <60 kg, 0.75 mg/kg at week 0, followed by 0.75 mg/kg at week 4 then every 12 weeks thereafter. Patients 60 ≤ <100 kg, 45 mg at week 0 followed by 45 mg at week 4, then every 12 weeks. Patients >100 kg, 90 mg at week 0, followed by 90 mg at week 4, then every 12 weeks.

Psoriatic arthritis, adults & elderly: 45 mg at week 0 followed by a 45 mg dose at week 4, then every 12 weeks. Alternatively, 90 mg may be used in patients with a body weight >100 kg.

Consider discontinuation if no response after 28 weeks.

Crohn's Disease: Initial single intravenous infusion dose based on body weight (260 mg or 390 mg or 520 mg) diluted in sodium chloride solution and given over at least one hour. At week 8 after intravenous dose, 90 mg s.c. dose is given; followed by every 12 weeks (or 8 weeks based on clinical judgement). Consider discontinuation if no response at 16 weeks. Immunomodulators and/or corticosteroids may be continued but consider reducing/discontinuing corticosteroids if responding to Stelara. If therapy interrupted, resume s.c. every 8 weeks if safe/effective.

Children: <12 years - Not recommended for psoriasis. <18 years - Not recommended for psoriatic arthritis and Crohn's disease. Renal & Hepatic impairment: Not studied.

CONTRAINDICATIONS: Hypersensitivity to product; clinically important, active infection.

SPECIAL WARNINGS & PRECAUTIONS: Infections: Potential to increase risk of infections and reactivate latent infections. Caution in patients with a chronic infection or history of recurrent infection, particularly TB. Patients should be evaluated for tuberculosis prior to initiation of STELARA. Consider anti-tuberculosis therapy prior to initiation of STELARA in patients with past history of latent or active tuberculosis. Patients should seek medical advice if signs or symptoms suggestive of an infection occur. If a serious infection develops, closely monitor and STELARA should not be administered until infection resolves.

Malignancies: Potential to increase risk of malignancy. No studies in patients with history of malignancy or in patients who develop malignancy while receiving STELARA. Monitor all patients, in particular those older than 60, patients with a medical history of prolonged immunosuppressant therapy (in particular, with a history of PUVA treatment for non-melanoma skin cancer. Concomitant immunosuppressive therapy: Caution, including when changing immunosuppressive biologic agents. Hypersensitivity reactions: Serious hypersensitivity reactions (anaphylaxis and angioedema) reported, in some cases several days after treatment. If these occur appropriate therapy should be instituted and STELARA discontinued. Latent sensitivity: Needle cover contains natural rubber (latex), may cause allergic reactions. Immune reconstitution: Not known whether STELARA affects allergy immunotherapy. Serious skin conditions: Exfoliative dermatitis reported following treatment. Discontinue STELARA if drug reaction is suspected.

SIDE EFFECTS: Common: upper respiratory tract infection, nasopharyngitis, dizziness, headache, ophthalmogical pain, diarrhoea, nausea, vomiting, pruritus, back pain, myalgia, arthralgia, fatigue, injection site erythema, injection site pain. Other side effects: cellulitis, serious hypersensitivity reactions (including anaphylaxis, angioedema), skin exfoliation, exfoliative dermatitis, lower respiratory tract infection. Studies show adverse events reported in ≥2 year olds with plaque psoriasis were similar to those seen in previous studies in adults with plaque psoriasis.

Refer to SmPC for other side effects.

FERTILITY: The effect of ustekinumab has not been evaluated.


LACTATION: Limited data in humans.

INTERACTIONS: In vitro, STELARA had no effect on CYP50 activities. Vaccinations: Live vaccines should not be given concurrently with STELARA, and should be withheld for at least 15 weeks after last dose of STELARA. STELARA can resume at least 2 weeks after such vaccinations. No data on secondary transmission of infection by live vaccines in patients receiving STELARA. Concomitant immunosuppressive therapy: Psoriasis: Safety and efficacy of STELARA in combination with other immunosuppressants, including biologics, or phototherapy have not been evaluated. Psoriatic arthritis: concomitant MTX did not appear to affect STELARA. Crohn’s disease: concomitant immunosuppressive or corticosteroid therapy did not appear to affect STELARA.

Refer to SmPC for full details of interactions.

LEGAL CATEGORY: POM

PRESEN TATIONS, PACK SIZES, MARKETING AUTHORISATION NUMBERS & BASIC NHS COSTS:

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MARKETING AUTHORISATION HOLDER: JANSSEN-CILAG INTERNATIONAL NV, Turnhoutseweg 30, B-2340 Beerse, Belgium.

FURTHER INFORMATION IS AVAILABLE FROM: Janssen-Cilag Limited, 50 – 100 Holmers Farm Way, High Wycombe, Buckinghamshire, HP12 4EG UK.

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