Clinical Commissioning Policy
Ustekinumab for refractory Crohn's disease in pre-pubescent children [200404P]

Commissioning Position

Summary

Ustekinumab is not recommended to be available as a routinely commissioned treatment option for refractory Crohn's disease in pre-pubescent children.

The policy is restricted to certain age groups as there is insufficient evidence to confirm safety and it is not recommended to be used in those age groups included in this policy.

Executive Summary

Equality statement

Promoting equality and addressing health inequalities are at the heart of NHS England's values. Throughout the development of the policies and processes cited in this document, we have:

- Given due regard to the need to eliminate discrimination, harassment and victimisation, to advance equality of opportunity, and to foster good relations between people who share a relevant protected characteristic (as cited under the Equality Act 2010) and those who do not share it; and
- Given regard to the need to reduce inequalities between patients in access to, and outcomes from healthcare services and to ensure services are provided in an integrated way where this might reduce health inequalities.

Plain language summary

About Crohn's disease

Crohn's disease (CD) is a long-term condition that mainly affects the bowel. Some people may develop symptoms that affect other body parts as well. There are currently at least 115,000 people in the UK with CD. Up to a third of people with CD are diagnosed before the age of 21 years. Common symptoms of CD in children include bloody diarrhoea, weight loss, abdominal (tummy) pain and delayed puberty.

CD has two basic phases: the active phase and the remission (inactive) phase. The active phase involves frequent flares (sudden occurrences of severe symptoms). There are two different treatments depending on the phase of the disease; treatment of active phase of the disease (inducing remission) or prevention of relapse during the remission phase. For this policy, refractory CD is defined as patients whose active disease does not respond or has stopped responding to standard treatment.

About current treatment

Treatment is largely to relieve symptoms rather than cure. For mild disease, two types of therapies are generally used: enteral nutrition or steroids. For severe disease, add on therapy

with stronger immunosuppressive medications such as azathioprine and methotrexate are used. Infliximab, a tumour necrosis factor (TNF) alpha inhibitor can be used in severe, active CD.

For children who have failed all the treatment as stated above, there is no alternative licensed therapy. These patients may be dependent on steroids to control the disease. Patients are at risk of complications and repeated surgical interventions if the disease is poorly controlled.

About the new treatment

Ustekinumab is a biological medicine which inhibits molecules involved in the immune system functions and reduces disease activity. It is licensed for the treatment of adults with moderate to severely active CD as the fourth line treatment. Ustekinumab is not licensed for this indication in children.

For adults, the first dose (weight dependent dosing) is given intravenously. Subsequent doses are given subcutaneously at week 8 followed by every 12 weeks.

What we have decided

Ustekinumab is licensed for use in adult patients with moderately to severely active Crohn's Disease and access is defined in NICE Technology Appraisal 456 Ustekinumab for moderately to severely active Crohn's disease after previous treatment. Ustekinumab is not licensed for this indication in children. As such, access for post pubescent children may be considered in line with the criteria in NHS England's Commissioning Medicines for Children in Specialised Services policy (NHS England 170001/P, 2017). NHS England has carefully reviewed the evidence to treat refractory Crohn's disease with ustekinumab in pre-pubescent children in this policy. We have concluded that there is not enough evidence to make the treatment available at this time.

Committee discussion

Clinical Panel recommended progressing as a not for routine policy proposition, as proposed. The evidence base was considered to be sparse in pre-pubertal children with no standard treatment pathways or monitoring. It was agreed that NHS England should await the radndomised controlled trial report in 2023 and then review the evidence base.

Clinical Priorities Advisory Group considered the documentation presented.

See the committee papers (link) for full details of the evidence.

The condition

CD is a chronic inflammatory disease that mainly affects the gastrointestinal system. The disease may be progressive in some people, and a proportion may develop extra-intestinal manifestations. There are currently at least 115,000 people in the UK with CD. Up to a third of people with CD are diagnosed before the age of 21 years (NICE, 2016).

Typically, CD has a relapsing-remitting pattern. Common symptoms of CD in children and young people (CYP) include bloody diarrhoea, weight loss, abdominal pain and delayed puberty.

Current treatments

The aim of treatment is to manage symptoms rather than to cure the disease, and active treatment of acute disease (inducing remission) should be distinguished from preventing relapse (maintaining remission) (NICE, 2016). NICE have published a clinical guideline on the management of CD in adults, children and young people.

To induce remission in mild to moderate disease, first line treatment includes enteral nutrition and steroids. If this does not control the disease or the disease is severe, second line therapy is, azathioprine. The following drugs have been used off label as second line treatment: 5-aminosalicylate (5-ASA) drugs, budesonide, mercaptopurine and methotrexate.

Third line treatment is with TNF-alpha inhibitors, such as infliximab, in line with NICE guidance (NICE, 2010).

Proposed treatments

Ustekinumab is a biological human monoclonal antibody, which inhibits human cytokine interleukins 12 and 23 (which are involved in immune system functions), thereby reducing disease activity (ustekinumab, summaries of product characteristics).

Ustekinumab is licensed for the treatment of moderately to severely active CD in adults and access is defined as per NICE Technology Appraisal 456 Ustekinumab for moderately to severely active Crohn's disease after previous treatment.

Ustekinumab is not licensed for this indication in children under 18 years.
The subcutaneous injections are licensed for the treatment of moderate to severe plaque psoriasis in young people from the age of 12 years and older. Access for post pubescent children may be considered in line with the criteria in NHS England's Commissioning Medicines for Children in Specialised Services policy (NHS England 170001/P, 2017). This policy therefore considers the use of ustekinumab to treat refractory Crohn's disease in pre-pubescent children.

Epidemiology and Needs Assessment

The incidence of CD in CYP is increasing worldwide, ranging from 2.5 to 11.4 per 100,000 population, with an estimated prevalence of 43/100,000 (Benchimol EI et al 2011; Kappelman MD et al, 2007). It is estimated that 8,000 CYP are affected by IBD nationally. It is anticipated that around 30% CYP will require escalation to TNF alpha inhibitor treatment, out of which, 10% will fail the treatment or not maintain a response and require ustekinumab. This approximates to 250 CYP nationally, and 10-15 CYP annually within a large paediatric IBD centre.

In paediatric-onset CD, the genetic component is more dominant and recurrence within the family is more prevalent than in adults (Polito II JM et al, 1996; Griffiths AM, 2004). Childhood is a time of dynamic physical changes, bone accrual and growth along with emotional maturation. Paediatric IBD is also more often extensive and is associated with a more aggressive disease course, including a greater propensity for disease extension and early immunomodulation (Van Limbergen J, 2008; Vernier-Massouille G et al, 2008; Pigneur B et al 2010).

Evidence summary

NHS England has concluded that there is not sufficient evidence to support a policy for the routine commissioning of this treatment for the indication for pre-pubescent children.

An evidence review was undertaken to establish the clinical effectiveness, safety and cost-effectiveness of ustekinumab compared to standard care in the treatment of refractory Crohn's disease in CYP of 3-18 years. However, the policy provides a commissioning position for pre-pubescent children only, as access for older children will be provided in line with the NHS England's Commissioning Medicines for Children in Specialised Services Policy (NHS England 170001/P, 2017).

This evidence summary focuses on a multi-centre retrospective cohort study (Chavannes et al. 2018, n=44), which was published after the searches for this evidence review were conducted. This study is included in the evidence summary tables. The evidence review also gives a brief

overview of 1 retrospective chart review in 4 children and young people (Bishop et al. 2016) identified from the search. However, this study has not been included in the main evidence tables because of its poor quality and high risk of bias. There is also a manufacturer-sponsored randomised double-blind controlled trial, currently ongoing, comparing 2 different dosage regimens of ustekinumab in children and young people aged from 2 to 17 years with moderately to severely active Crohn's disease. The study has enrolled 45 participants and the estimated study completion date is March 21, 2023. For details see NCT02968108.

An overview of the results for clinical effectiveness and safety and tolerability for the retrospective cohort study (Chavannes et al. 2018) can be found in the evidence summary table. The research questions for the evidence review and the key outcomes identified in the scope are discussed in this section.

The evidence presented in this evidence review does not provide any data comparing the clinical effectiveness and safety of ustekinumab with any other treatment for the management of Crohn's disease in children and young people. No studies were identified which evaluated the cost effectiveness of ustekinumab for the management of Crohn's disease in children and young people. All outcomes presented in this evidence review are based on a grade of evidence score of C.

Clinical effectiveness

This section considers whether ustekinumab is clinically effective when used to treat refractory Crohn's disease in children and young people.

Clinical remission and clinical response:
In Chavannes et al. 2018 and Bishop et al. 2016, the abbreviated Paediatric Crohn disease Activity Index (PCDAI) was used to measure clinical remission and clinical response. A score on the scale of less than 10 indicates clinical remission, a score of 10 to 15 indicates mild disease, 16 to 25 moderate disease and greater than 25 severe disease.

In Chavannes et al. 2018, clinical remission was seen in 36.4% (16/44) children and young people at 3 months (p= 0.006, statistically significant) and 38.6% (17/44) at 12 months (p=0.006, statistically significant). It is unclear from the study whether the 16 participants in clinical remission at 3 months were all still in remission at 12 months. Four participants were in clinical remission (based on the abbreviated PCDAI score) at baseline before ustekinumab was started. Ustekinumab was started in these 4 participants because of active disease on colonoscopy in 1 participant, raised faecal calprotectin in 2 participants and persistent growth failure in another participant. It is unclear from the study if these 4 participants were still in remission at 3 and 12 months.

The median (interquartile range, IQR) abbreviated PCDAI at baseline was 27.5 (20 to 40), indicating severe disease. Clinical response (defined as a decrease in the abbreviated PCDAI score of 15 or more) was seen in 47.8% (21/44) participants at both 3 and 12 months (no statistical analysis presented). The data analysis was conducted for the intention-to-treat population; only 32 participants continued ustekinumab for at least 12 months.

The study evaluated which factors may be associated with failure of ustekinumab treatment (stopping treatment was used as a measure of treatment failure). A higher ustekinumab induction dose per body weight was associated with a lower risk of stopping treatment (odds ratio 0.53, 95% confidence interval 0.28 to 0.84, p=0.0211). Other factors including disease duration, use of combination treatment with an immunomodulator, a complicated disease phenotype, ileocolonic disease, age at diagnosis, high C reactive protein at baseline and disease activity were not associated with stopping treatment. However, these results should be

interpreted with caution because of the small size of the study, number of different induction regimens and methodological limitations.

In Bishop et al. 2016, 2 of the 4 participants (case 2, a 16 year old female and case 4, a 17 year old male) were reported to have responded to ustekinumab. At the time of writing the report they were still receiving treatment, case 2 had received 10 doses and case four 9 doses of ustekinumab. In case 2, at the last follow-up no active symptoms were reported and the abbreviated PCDAI had reduced to 0 (remission), from a score of 35 (severe disease) before starting ustekinumab. In case 4, there was an improvement in symptoms of pain and non-bloody diarrhoea, but mild diarrhoea remained. The abbreviated PCDAI reduced to 5 (remission), from a score of 20 (moderate disease). The other 2 participants (case 1, a 12 year old male and case 3, a 13 year old female) were reported not to have responded to ustekinumab. Case 1 had 5 doses of ustekinumab and case 3 had 6 doses before it was stopped.

Steroid free clinical remission:
In Chavannes et al. 2018, 27.3% (12/44) participants were in steroid free clinical remission (defined as being off systemic steroids and with an abbreviated PCDAI less than 10) at 12 months (no statistical analysis presented). Steroid exposure was only measured in the 32 participants who remained on treatment for at least 12 months. At baseline, 40.6% (13/32) were taking steroids and 15.6% (5/32) were taking steroids at 12 months (p=0.06, not statistically significant). However, given the small size of the study it may not have been sufficiently powered to detect a difference between the number taking steroids at baseline and 12 months.

In Bishop et al. 2016 the 2 participants who responded to ustekinumab treatment were receiving prednisone before ustekinumab was started. Both were able to have their prednisone dose reduced and eventually stopped and neither received further steroids. It was not reported what dose of prednisone they were taking before ustekinumab was started or how long it took for the prednisone dose to be reduced and stopped.

Surgical interventions and complications from disease progression and exacerbation:
In Chavannes et al. 2018, 9.1% (4/44) required surgery during the follow-up period. It was not reported what the surgery was. It is also not clear from the study whether the reason for surgery was because of the Crohn’s disease or a complication related to this. Two of the 4 participants continued ustekinumab treatment post-operatively.

In Bishop et al. 2016, the 2 participants who did not respond to ustekinumab treatment had several hospital admissions within 1 to 5 months of starting ustekinumab. Case 1 had 4 hospital admissions because of an acute exacerbation of Crohn’s disease, Clostridium difficile infection and 2 recurrences of perianal abscess. The perianal abscess was surgically managed and ustekinumab treatment was stopped. The participant had an ileocaecal resection for a stricture. Case 3 had 5 hospital admissions. The first hospital admission was to start total parenteral nutrition because of ongoing weight loss, 3 hospital admissions were for fever because of an upper respiratory tract infection, urinary tract infection and culture positive central line infection. The last hospital admission was because of an acute exacerbation of Crohn’s disease, after which the participant received steroids.

Weight and height:
In Chavannes et al. 2018, change in height, weight and BMI (based on WHO growth chart standard z-scores) was measured between baseline and 12 months. A z-score expresses deviation from a mean (for height, weight or BMI for a child or young person at a specific age and gender). A z-score of 0 is equal to the mean. A z-score of −1 is equal to 1 standard deviation below the mean, and a z-score of +1 is equal to 1 standard deviation above the mean.

At baseline, the median (IQR) z-score for height was −0.68 (−1.95 to 0.23), for weight it was −0.61 (−2.16 to 0.31) and for BMI it was −0.66 (−1.61 to 0.38). At 12 months, the median z-score for height was −0.82 (−1.95 to 0.27), for weight it was −0.05 (−1.48 to 0.69) and for BMI it was 0.18 (−0.63 to 1.04). The mean increase in height z-score was 0.072 (p= 0.2441, not statistically significant). The mean increase in weight z-score was 0.48 (p=0.0008, statistically significant) and the mean increase in BMI z-score was 0.66 (p=0.0003, statistically significant).

In Bishop et al. 2016, for the 2 participants who responded to ustekinumab and continued treatment, BMI increased from 20.0 to 21.8 kg/m2 in 1 participant (case 2). However, in the other participant (case 4), the BMI which was 17.2 kg/m2 before starting ustekinumab, did not increase.

Biochemical markers:
In Chavannes et al. 2018, 68.2% (30/44) had a raised C reactive protein at baseline. In this group, the C reactive protein return to normal in 33.3% (10/30) at 3 months (p=0.004) and 26.7% (8/30) at 12 months (p=0.01, statistically significant). The clinical significance of this outcome is unclear, 31.8% (14/44) of the population had a normal C reactive protein before ustekinumab was started. The median (IQR) albumin level was 34.5 (32.0 to 38.9) g/litre at baseline, 36.7 (34.2 to 41.1) g/litre at 3 months and 40.2 (38.0 to 43.0) g/litre at 12 months. There was a statistically significant increase in albumin levels of 2.7 g/litre (standard error: 0.94, p=0.0147) at 3 months and 5.3 g/litre (0.99, p<0.0001) at 12 months. The clinical significance of this increase is unclear.

In Bishop et al. 2016, for the 2 participants who responded to ustekinumab treatment; albumin levels improved from 2.9 g/100 ml to 4.7 g/100 ml (normal range 3.8 to 5.4 g/100 ml in this study) in case 2. Also, C reactive protein reduced to normal levels. In case 4, albumin levels improved from 3.5 g/100 ml to 3.8 g/100 ml. However, C reactive protein levels remained high.

Safety and tolerability
In Chavannes et al. 2018 the rate of adverse events was 12.4 per 1000 patient-months follow-up. Two participants who only received 1 induction dose of ustekinumab had serious adverse events: one had a perianal abscess and the other had worsening of chronic recurrent multifocal osteomyelitis (bone infection) and cutaneous psoriasis. For the 42 participants who continued treatment after the induction phase, 6 (14.3%) had mild adverse events during the maintenance phase. Two participants reported migraine after 1 and 3 months on treatment, 2 participants reported flares of scalp psoriasis, 1 participant reported non-persistent bilateral feet paraesthesia (a burning or prickling sensation) after 3 months on treatment and 1 participant reported chronic rhinitis symptoms. During the study, 30.9% (13/42) had their ustekinumab treatment stopped during the maintenance phase. Median (IQR) time to stopping treatment was 13 (10.3 to 21.3) months. The reason for stopping treatment during the maintenance phase in all cases was poor clinical response not adverse events.

Bishop et al. 2016 reported that any adverse events or complications during ustekinumab treatment would be noted. However, no safety and tolerability data were provided in this study, other than reporting that the ustekinumab injections were well tolerated. Two of the 4 study participants did not respond to ustekinumab treatment and had several hospital admissions because of acute exacerbations, other complications and infections. The study authors comment that ustekinumab cannot be ruled out as a contributing factor to these complications.

Summary of product characteristics:
Ustekinumab is contraindicated in people with clinically important active infections for example, active tuberculosis. The summary of product characteristics for ustekinumab also includes several special warnings and precautions for use including: potential increase in risk of infection and malignancy, hypersensitivity reactions, serious skin reactions (in people with psoriasis) and

warnings and precautions on vaccinations, immunotherapy and concomitant use with immunosuppressants. For more information on these see the summary of product characteristics (SPC).

Based on clinical studies for the licensed indications in adults, the SPC lists upper respiratory tract infection, nasopharyngitis, dizziness, headache, oropharyngeal pain, diarrhoea, nausea, vomiting, pruritus, back pain, myalgia (muscle pain), arthralgia (joint pain), fatigue, injection site erythema and injection site pain as common adverse reactions (occurring in between 1 in 10 and 1 in 100 people).

The subcutaneous formulations of ustekinumab are licensed for the treatment of moderate to severe plaque psoriasis in young people aged 12 and over whose disease is inadequately controlled by, or who are intolerant to, other systemic therapies or phototherapies. The SPC says that the safety of ustekinumab has been studied in 110 young people from 12 to 17 years with plaque psoriasis for up to 60 weeks. The SPC states that, in this study, the adverse events reported were similar to those seen in previous studies in adults with plaque psoriasis. However, it should be noted that the licensed subcutaneous injection dose for plaque psoriasis (for young people aged 12 and over and adults under 100 kg body weight) is lower than the licensed dose for Crohn's disease in adults. In addition, for Crohn's disease in adults the licensed dosage regimen includes an intravenous infusion for the first dose. Ustekinumab is not licensed for any indication in children under 12 years.

The MHRA issued a Drug Safety Update on ustekinumab in January 2015 highlighting the risk of exfoliative dermatitis with ustekinumab.

Policy review date

This document will be reviewed when information is received which indicates that the policy requires revision. If a review is needed due to a new evidence base then a new Preliminary Policy Proposal needs to be submitted by contacting england.CET@nhs.net.

Our policies provide access on the basis that the prices of therapies will be at or below the prices and commercial terms submitted for consideration at the time evaluated. NHS England reserves the right to review policies where the supplier of an intervention is no longer willing to supply the treatment to the NHS at or below this price and to review policies where the supplier is unable or unwilling to match price reductions in alternative therapies.

Definitions

Abbreviated paediatric Crohn's disease activity index (PCDAI)	An abbreviated scoring system that evaluates CD disease activity. A score of 0 to 70 with 0 to 10: remission, 10 to 15: mild disease, 16 to 25: moderate disease and greater than 25: severe disease.
Children and young people (CYP)	This refers to children and young people aged 3-18 years.
Pre-pubescent children	A child or young person in the years prior to puberty, as determined by clinical judgement.

Enteral nutrition	This refers to a method of feeding that delivers nutrition and medication directly to the gastrointestinal tract.
Ileocaecal resection	This surgery involves removing the junction of the small and large intestine. The healthy end of the small intestine is then joined directly to the colon.
Immunosuppressive medications	This is a group of medication that acts by suppressing the immune system. Examples are aminosalicylates (5- aminosalicylic acid, 5-ASA) and methotrexate.
Inflammatory bowel disease (IBD)	This refers to Crohn's disease and ulcerative colitis. Both causes inflammation in the bowels.
Refractory Crohn's disease (CD)	This means there is high Crohn's disease activity despite conventional pharmacological treatment, including inadequate response to or loss of response to TNF alpha inhibitor treatment.
Steroids	This includes prednisolone, methylprednisolone or intravenous hydrocortisone.
Stricture	Narrowing of the intestine.
Stool/ faecal calprotectin	A substance that is found in the intestines when there is inflammation present.
Tumour necrosis factor alpha (TNF alpha) inhibitors	This refers to a group of biological medication that blocks a pro-inflammatory molecule, TNF alpha in the body. An example of this is infliximab.

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