NHS England

Evidence review: Ustekinumab treatment of refractory Crohn's disease in children and young people

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The content of this evidence review was up-to-date in March 2019. See summaries of product characteristics (SPCs), British national formulary for children (BNFc) and British national formulary (BNF) or the MHRA or NICE websites for up-to-date information. For details on the date the searches for evidence were conducted see the search strategy.

Key points

Regulatory status: Off-label use of a licensed medicine.

Ustekinumab (Stelara, Janssen-Cilag Ltd) is a monoclonal antibody which inhibits human cytokine interleukins 12 and 23. Ustekinumab's licensed indications include the treatment of adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor (TNF) alpha inhibitor or have medical contraindications to such therapies. For the treatment of Crohn's disease, it is given as an intravenous infusion for the first dose, with subsequent dosages given as subcutaneous injections. Ustekinumab is not licensed for Crohn's disease in children and young people under 18 years, therefore the use of ustekinumab for this indication is off-label.

The subcutaneous formulations of ustekinumab are licensed in young people aged 12 and over for the treatment of moderate to severe plaque psoriasis that is inadequately controlled by other systemic therapies or phototherapies or when they are not tolerated. However, 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 subcutaneous dose for Crohn's disease in adults. Ustekinumab is not licensed for any indication in children under 12 years.

Overview

This evidence review considers the best available evidence on ustekinumab for the treatment of refractory Crohn's disease in children and young people aged under 18 years. In this evidence review, refractory Crohn's disease is defined as Crohn's disease that has not adequately responded to conventional pharmacological treatment and has had an inadequate response to or has lost response to TNF alpha inhibitor treatment.

NICE have published a clinical guideline on the management of Crohn's disease in adults, children and young people. NICE have also published a technology appraisal on ustekinumab for moderately to severely active Crohn's disease, which covers the licensed indication in adults.

This evidence review focuses on 1 retrospective cohort study in 44 children and young people with refractory Crohn's disease, recruited from 4 specialist centres (Chavannes et al. 2018). The median age in this study was 16 years (interquartile range 13 to 17). Additional information is provided from a retrospective chart review in 4 young people with refractory Crohn's disease aged between 12 and 17 years recruited from a single centre in the US (Bishop et al. 2016). It is unclear how generalisable the results of these studies will be to younger children.

In summary, the main study suggests that ustekinumab can induce remission in around a third and improve symptoms in around half of children and young people with refractory Crohn's disease. However, ustekinumab had to be stopped in around a third of children and young people because of a poor clinical response and adverse effects serious enough to stop treatment were seen in 2 children and young people.

In Chavannes et al. 2018, approximately 36% (16/44) were in clinical remission after 3 months treatment. Clinical remission was defined as a score of less than 10 on the abbreviated Paediatric Crohn's disease activity index (PCDAI, a validated assessment tool). After 12 months treatment, approximately 39% (17/44) were in clinical remission. 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 at baseline before ustekinumab was started. Steroid free clinical remission was seen in approximately 27% (12/44) at 12 months. Approximately 48% (21/44) had a clinical response (defined as a reduction of at least 15 points in the abbreviated PCDAI) to ustekinumab treatment. During the study, 9% (4/44) had surgery. It was not reported what the surgery was or if it was related to the Crohn's disease.

Two participants had serious adverse events after 1 induction dose. For the participants who continued treatment into the maintenance phase, 14% (6/42) had mild adverse events. Based on the limited data from the study it is difficult to draw firm conclusions on the safety and tolerability of ustekinumab for the treatment of refractory Crohn's disease in children and young people. Approximately 31% (13/42) stopped ustekinumab during the maintenance phase of treatment because of poor clinical response and not adverse events. The median time to stopping treatment was 13 months.

The optimal treatment regimen for ustekinumab for Crohn's disease in children and young people is unclear because dosage and frequency varied within and between the studies. Chavannes et al. 2018 had 6 different induction regimens. The most common (38%, 16/42 participants) induction regimen was 90 mg subcutaneously at weeks 0, 1 and 2 followed by a maintenance dose of 90 mg every 8 weeks. It is unclear from the study if the maintenance dose was 90 mg for all participants as details on the maintenance dose are only provided for the 38% of participants who had the most common induction regimen. Approximately 30% (13/44) of participants in the study had the frequency of the maintenance dose increased from every 8 weeks to every 4 weeks because of persistent symptoms. The licensed dose and maximum dosing frequency for subcutaneous ustekinumab for the treatment of Crohn's disease in adults (after the initial intravenous infusion induction dose) is 90 mg every 8 weeks. Therefore, a maintenance dose of 90 mg every 4 weeks would be higher than the maximum licensed dosage in adults.

The results of the studies should be interpreted with caution because the studies are very small, uncontrolled, non-comparative and did not use standardised treatment and monitoring protocols. Weaknesses in the studies' design and conduct mean they are subject to bias and confounding, are difficult to interpret and cannot support firm conclusions. The induction regimens used in these studies in children and young people were different to the induction regimen for the licensed indication for the treatment of Crohn's disease in adults. For the treatment of Crohn's disease in adults ustekinumab is given as an intravenous infusion for the first dose, subsequent dosages are then given as subcutaneous injections. In the studies a subcutaneous injection induction regimen was used. Therefore, these studies do not provide any information on the intravenous infusion ustekinumab formulation 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.

Contents

1. Introduction

Background and current guidance

Crohn's disease is a chronic inflammatory disease that mainly affects the gastrointestinal tract. 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 Crohn's disease. Up to a third of people with Crohn's disease are diagnosed before the age of 21 (NICE clinical guideline: Crohn's disease management).

Typically, people with Crohn's disease have recurrent attacks, with acute exacerbations interspersed with periods of remission or less active disease. Treatment is largely directed at symptom relief rather than cure, and active treatment of acute disease (inducing remission) should be distinguished from preventing relapse (maintaining remission) (NICE clinical guideline: Crohn's disease management).

Common symptoms of Crohn's disease in children include bloody diarrhoea, weight loss, abdominal pain and delayed puberty.

The NICE guideline covers the management of Crohn's disease in adults, children and young people. It includes recommendations on pharmacological treatment for inducing remission including recommendations on monotherapy with conventional glucocorticosteroids, enteral nutrition (for children and young people), budesonide or 5-aminosalicylates and recommendations on add-on treatment with azathioprine, mercaptopurine or methotrexate. For full details on these recommendations see the NICE guideline.

NICE have also published technology appraisal guidance on the tumour necrosis factor (TNF) alpha inhibitors infliximab and adalimumab for the treatment of Crohn's disease. This includes the recommendation that infliximab, within its licensed indication, is recommended for the treatment of children and young people aged 6 to 17 years with severe active Crohn's disease whose disease has not responded to conventional therapy (including corticosteroids, immunomodulators and primary nutrition therapy), or who are intolerant of or have contraindications to conventional therapy. The need to continue treatment should be reviewed at least every 12 months.

The purpose of this evidence review is to assess the effectiveness and safety of using the interleukin inhibitor ustekinumab in children and young people aged between 3 and 18 years old with refractory Crohn's disease. For the purpose of this evidence review refractory Crohn's disease is defined as Crohn's disease that has not adequately responded to conventional pharmacological treatment and has had an inadequate response to or has lost response to TNF alpha inhibitor treatment.

NICE have published a technology appraisal on ustekinumab for moderately to severely active Crohn's disease which recommends ustekinumab within its marketing authorisation, as an option for treating Crohn's disease in adults who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a TNF alpha inhibitor or have medical contraindications to such therapies.

Product overview

Mode of action

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 [Stelara] summaries of product characteristics).

Regulatory status: Off-label use of a licensed medicine***.***

Ustekinumab (Stelara) licensed indications include the treatment of adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor (TNF) alpha inhibitor or have medical contraindications to such therapies. Ustekinumab is not licensed for Crohn's disease in children and young people under 18 years, therefore the use of ustekinumab for this indication is off-label.

The subcutaneous injection formulations of ustekinumab are also licensed for the following indications:

- the 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 (psoralen and ultraviolet A)
- the treatment of moderate to severe plaque psoriasis in young people from the age of 12 years and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies
- the treatment of active psoriatic arthritis in adults (alone or in combination with methotrexate) when the response to previous non-biological disease-modifying anti-rheumatic drug therapy has been inadequate.

In line with the guidance from the General Medical Council (GMC) on prescribing unlicensed medicines, the prescriber should take full responsibility for determining the needs of the person and whether using ustekinumab is appropriate outside its authorised indications. Supporting information and advice is also available from the GMC.

Dosing information

For the licensed indication for the treatment of moderately to severely active Crohn's disease in adults, the first dose is given by intravenous infusion. The intravenous dose varies depending on body weight. Further details on dosing information can be found in the summary of product characteristics (SPC) for ustekinumab 130 mg concentrate for solution for infusion (Stelara 130 mg concentrate for solution for infusion). This ustekinumab preparation is only licensed for use in the treatment of Crohn's disease in adults for the initial intravenous induction dose. It is not licensed for use in any other indication. After the initial intravenous dose, subsequent doses are given subcutaneously. The first subcutaneous injection of 90 mg ustekinumab is given at week 8 after the intravenous dose. After this, 90 mg every 12 weeks is recommended.

In the treatment of Crohn's disease in adults, the SPC recommends that people who have not shown an adequate response at 8 weeks after the first subcutaneous dose, may receive a second subcutaneous dose at this time. In addition, people who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to every 8 weeks. People may then be dosed every 8 weeks or every 12 weeks according to clinical judgment. The

SPC recommends that consideration should be given to stopping treatment in people who show no evidence of therapeutic benefit by week 16 or 16 weeks after switching to the 8-weekly dose (ustekinumab [Stelara] summaries of product characteristics).

Dosing information for the other licensed indications of ustekinumab can be found in the SPC.

2. Methodology

A description of the relevant Population, Intervention, Comparison and Outcomes (PICO) for this review was provided by NHS England's Policy Working Group for the topic (see the literature search terms section for more information). The research questions for this evidence review are:

1. What is the clinical effectiveness of ustekinumab as a fourth line treatment compared with treatment without ustekinumab for children with refractory Crohn's disease?
2. What is the safety of ustekinumab as a fourth line treatment compared with treatment without ustekinumab for children with refractory Crohn's disease?
3. What is the cost effectiveness of ustekinumab as a fourth line treatment compared with treatment without ustekinumab for children with refractory Crohn's disease?

The searches for evidence to support the use of ustekinumab for refractory Crohn's disease in children were undertaken by the NICE Guidance Information Services' team. Results from the literature searches were screened using their titles and abstracts for relevance against the criteria from the PICO. Full text references of potentially relevant evidence were obtained and reviewed to determine whether they met the PICO inclusion criteria for this evidence review. More information can be found in the sections on search strategy and evidence selection.

The NICE evidence summary: process guide (2017) sets out the how the summaries are developed and approved for publication. The included studies are quality assessed using the National Service Framework for Long term Conditions (NSF-LTC) evidence assessment framework as set out in NHS England's Guidance on conducting evidence reviews for Specialised Services Commissioning Products (2016) (see the grade of evidence section for more information).

3. Summary of included studies

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.

Table 1 Summary of included studies

Study	Population	Intervention and comparison	Primary outcome
Key evidence from retrospective cohort study			
Chavannes et al. 2018 Open-label retrospective cohort study conducted at 4 centres (not reported in the study where the centres were, the study authors were from hospitals in Canada, the US, Australia and France)	44 children and young people (50% male) with refractory Crohn's disease. Median (IQR) age when ustekinumab started 16 (13 to 17) years. 72.7% (32/44) had disease phenotype B1 (non-stricturing, non-penetrating) using the Paris classification, 25% (11/44) had extraintestinal manifestations and 20.4% (9/44) had previous surgery. All participants had previously received at least 1 TNF alpha inhibitor. Participants were followed up for at least 12 months or until the ustekinumab was discontinued.	The intervention was ustekinumab, 6 different induction regimens[a] were used, induction and maintenance doses were administered subcutaneously in all participants. The most common (38.1%, 16/42 participants) induction dose was 90 mg at weeks 0, 1 and 2 followed by a maintenance dose of 90 mg every 8 weeks. The median (IQR) observed treatment duration on ustekinumab was 13 (10.3 to 21.3) months. By the time of last follow-up 29.5% (13/44) of participants had the frequency of the maintenance dose increased from every 8 weeks to every 4 weeks. 22.7% (10/44) had concomitant methotrexate, 6.8% (3/44) had concomitant azathioprine. There was no comparator group.	Clinical remission. Clinical remission was defined as an abbreviated PCDAI score of less than 10[b].
Supplementary evidence from retrospective chart review in 4 young people			
Bishop et al. 2016 Retrospective chart review in 4 young people conducted at 1 site in the US	4 young people (2 female and 2 male) with Crohn's disease. All 4 participants were described as having non- stricturing,	The intervention was ustekinumab. No immunomodulatory treatment was given at the same time. All study participants had 90 mg ustekinumab	No primary or secondary outcomes.

	non-penetrating Crohn's disease with colonic involvement, 1 participant also had ileal disease. Two participants had perianal disease with fistula and abscess. Ages at ustekinumab initiation were 12, 13, 16 and 17 years with a weight range of 40.5 to 57.8 kg. All 4 young people had previously received infliximab and adalimumab.	subcutaneously at week 0 and week 4, then 90 mg subcutaneously every 8 weeks as a maintenance dosage[c]. There was no comparator group. Participants received an average of 7.5 doses (SD 2.4 doses, range 5 to 10 doses). Mean therapy duration was 11 months (SD 4.9 months, range 6 to 15 months).	

Abbreviations: IQR, interquartile range; PCDAI, paediatric Crohn's disease activity index; SD, standard deviation

[a] All induction regimens were completed within 4 weeks and administered subcutaneously, 38.1% (16/42) had 90 mg at weeks 0, 1 and 2; 21.4% (9/42) had 90 mg at weeks 0, 2 and 4; 14.3% (6/42) had 90 mg at week 0 and week 4; 11.9% (5/42) had 45 mg at weeks 0, 1 and 2; 11.9% (5/42) had 270 mg at week 0 and 180 mg at weeks 1 and 2; 2.4% (1/42) had 270 mg at week 0 and 180 mg at weeks 3 and 4. Two participants who had serious adverse events only received 1 induction dose.

[b] A score on the PCDAI 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.

[c] One participant had loss of response after 14 months treatment and had the frequency of ustekinumab injections increased from every 8 weeks to every 7 weeks.

Details of the excluded studies are listed in the section on evidence selection.

4. Results

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/m^2 in 1 participant (case 2). However, in the other participant (case 4), the BMI which was 17.2 kg/m^2 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 (SPC: Stelara) 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 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.

5. Discussion

Evidence strengths and limitations

The evidence presented in this review is based on 1 retrospective cohort study in 44 children and young people. As this included study was small and has a retrospective, observational design, this makes it subject to risk of bias and confounding. Therefore the results from this study should be interpreted with caution. Participants were recruited from 4 specialist centres, but the study does not report where these centres were. The study authors were from hospitals in Canada, the US, Australia and France. The median age in the study when ustekinumab was started was 16 years (interquartile range 13 to 17). Therefore, the results of this study may not be generalisable to younger children.

Participants in the study were treated on an individual basis and treatment pathways were not standardised or dictated by the study. Ustekinumab treatment protocols were not standardised within or across the 4 centres in the study, and variability in induction protocols and use of concurrent immunotherapies could have had some influence on efficacy and safety. The induction regimens used in the study were different to the induction regimen for

the licensed indication for the treatment of Crohn's disease in adults. For the treatment of Crohn's disease in adults, ustekinumab is given as an intravenous infusion for the first dose, with subsequent dosages then given as subcutaneous injections. In the study a subcutaneous injection induction regimen was used. Clinical remission and clinical response were assessed using a validated assessment tool, but outcome assessment was not blinded.

The study provides no data comparing ustekinumab with any other treatments for Crohn's disease in children and young people.

Supplementary evidence to the main study is provided from 1 retrospective chart review in 4 young people aged between 12 and 17 years recruited from a single centre in the US. This study provides very limited evidence on the clinical effectiveness and safety of ustekinumab for the treatment of Crohn's disease in young people. It does not provide any data on the clinical effectiveness or safety of ustekinumab for the treatment of Crohn's disease in children under 12 years.

The studies in this evidence summary do not provide any data on the clinical effectiveness and safety of ustekinumab intravenous infusion in children and young people.

Other treatments

No other pharmacological treatments are generally considered at the same stage in the treatment pathway for Crohn's disease in children and young people whose disease has failed TNF alpha inhibitor treatment. The evidence presented in this evidence review does not provide any data comparing ustekinumab with any other treatment for the management of Crohn's disease in children and young people.

6. Conclusion

The studies discussed in this evidence summary suggest that ustekinumab can induce remission and improve symptoms in some children and young people with refractory Crohn's disease. However, for some children and young people ustekinumab was not effective and had to be stopped because of poor clinical response. In the main study, the median age in the study was 16 years. The retrospective chart review which supplements the main study was conducted in 4 young people aged between 12 and 17 years. It is unclear how generalisable the results are to a younger population.

In the main study discussed in this evidence summary, out of 44 children and young people with refractory Crohn's disease who started ustekinumab treatment, approximately 36% were in clinical remission after 3 months treatment. After 12 months treatment, approximately 39% were in clinical remission. Steroid free clinical remission was seen in approximately 27% at 12 months. Approximately 48% had a clinical response (defined as a reduction of at least 15 points in the abbreviated Paediatric Crohn's disease activity index) to ustekinumab treatment.

Two participants who only received 1 induction dose had a serious adverse event. For the 42 participants who continued treatment into the maintenance phase, 6 had mild adverse events. Based on the limited data from the study it is difficult to draw firm conclusions on the

safety and tolerability of ustekinumab for the treatment of refractory Crohn's disease in children and young people. Approximately 31% stopped ustekinumab treatment during the maintenance phase of treatment. The median time to stopping treatment was 13 months. In all participants treatment was stopped during the maintenance phase because of poor clinical response not adverse events.

The optimal treatment regimen for ustekinumab for Crohn's disease in children and young people is unclear because treatment regimens varied within and between the studies. The main study had 6 different induction regimens. The most common (38%, 16/42 participants) induction regimen was 90 mg subcutaneously at weeks 0, 1 and 2 followed by a maintenance dose of 90 mg every 8 weeks. It is unclear from the study if the maintenance dose was 90 mg for all participants as details on the maintenance dose are only provided for the 38% of participants who had the most common induction regimen. Approximately 30% of participants in the study had the frequency of the maintenance dose increased from every 8 weeks to every 4 weeks because of persistent symptoms. The licensed dose and maximum dosing frequency for subcutaneous ustekinumab for the treatment of Crohn's disease in adults (after the initial intravenous infusion induction dose) is 90 mg every 8 weeks. Therefore, a maintenance dose of 90 mg every 4 weeks would be higher than the maximum licensed dosage in adults.

The induction dosage regimens used in the studies were also different to the licensed dosage regimen for the treatment of Crohn's disease in adults. These studies do not provide any information on the intravenous infusion ustekinumab formulation in children and young people.

7. Evidence summary table

Ustekinumab to treat refractory Crohn's disease in children and young people – no comparator in study							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
Study reference: Chavannes et al. 2018							
P1, retrospective non-comparative cohort study	Population recruited from 4 centres. Location not reported. Study authors were from hospitals in Canada, France, the US and Australia. 44 children and young people (50% male) with Crohn's disease. Median (IQR) age at diagnosis 11 (8 to 13) years. Median (IQR) age when ustekinumab started 16 (13 to 17) years. 72.7% (32/44) had disease phenotype B1 (non- stricturing, non-penetrating) using the Paris classification, 25% (11/44) had extraintestinal manifestations and 20.4% (9/44) had previous surgery. Median (IQR) abbreviated PCDAI at baseline 27.5 (20 to 40), indicating severe disease. Median (IQR) albumin at baseline was 34.5 (32.0 to 38.9) g/litre, median (IQR) C reactive protein was 17 (9.5 to 25.5) mg/litre. All participants had previously received at least 1 TNF alpha inhibitor, 93.1% (41/44) had infliximab and 65.9% (29/44) had adalimumab. 45.5% (20/44) were taking steroids at baseline.	All participants had subcutaneous ustekinumab, 6 different induction regimens[a] were used. The most common (38.1%, 16/42 participants) induction dose was 90 mg subcutaneous at weeks 0, 1 and 2 followed by a maintenance dose of 90 mg every 8 weeks. By time of last follow-up 13/44 (29.5%)	Primary Clinical effectiveness	Clinical remission (defined as an abbreviated PCDAI of less than 10) at 3 and 12 months	36.4% (16/44) were in clinical remission at 3 months (p=0.006, statistically significant) 38.6% (17/44) were in clinical remission at 12 months (p=0.006, statistically significant) It is unclear from the study if all 16 participants in remission at 3 months were still in remission at 12 months. Four participants were in clinical remission at baseline (based on the PCDAI), ustekinumab was started in 1 participant because of active disease on colonoscopy, 2 participants because of raised faecal calprotectin and 1 participant because of persistent growth failure. It is not clear if these 4 participants were still in remission at 3 and 12 months.	6/10 The research questions are stated but, as the study is an observational study it is insufficient to reliably answer the questions, and the results can only be considered hypothesis generating and cannot support any definitive conclusions. The methods are described and the results are generalisable to the population considered in the evidence review.	Direct study focusing on children and young people with the indication and characteristics of interest.
			Secondary Clinical effectiveness	Steroid free clinical remission at 12 months (defined as an abbreviated	Steroid exposure was only measured in the 32 participants who remained on treatment for at least 12 months 40.6% (13/32) were taking steroids at baseline and 15.6% (5/32) were taking		

	40.9% (18/44) had growth failure (defined as a deceleration in weight or height velocity, as crossing of at least 1 major percentile for height or weight on the WHO growth chart). Participants were followed up for at least 12 months or until the ustekinumab was discontinued.	of participants had the frequency of the maintenance dose increased from every 8 weeks to every 4 weeks. The median (IQR) observed treatment duration on ustekinumab was 13 (10.3-21.3) months. 22.7% (10/44) had concomitant methotrexate, 6.8% (3/44) had concomitant azathioprine		PCDAI of less than 10 and not taking systemic steroids)	steroids at 12 months (p=0.06, not statistically significant) In the ITT population 27.3% (12/44) were in steroid free clinical remission at 12 months (no statistical analysis provided)		
			Secondary Clinical effectiveness	Clinical response (defined as a decrease in abbreviated PCDAI score of 15 or more)	47.8% (21/44) had a clinical response at both 3 and 12 months (no statistical analysis provided)		
			Secondary Clinical effectiveness	Number of participants who required surgery during follow-up period	9.1% (4/44) required surgery during the follow-up period. It is not reported what the surgery was or if it was related to Crohn's disease. Two of the 4 participants continued ustekinumab treatment post-operatively.		

			Secondary Clinical effectiveness	Change in height, weight and BMI (based on WHO growth chart standard z-scores) between baseline and 12 months	Baseline (Median, IQR): z-score for height −0.68 (−1.95 to 0.23) z-score for weight −0.61 (−2.16 to 0.31) z-score for BMI −0.66 (−1.61 to 0.38) 12 months (Median, IQR): z-score for height −0.82 (−1.95 to 0.27) z-score for weight −0.05 (−1.48 to 0.69) z-score for BMI 0.18 (−0.63 to 1.04) Mean increase in z-scores from baseline to 12 months: height z-score 0.072 (p=0.2441, not statistically significant) weight z-score 0.48 (p=0.0008, statistically significant) BMI z-score 0.66 (p=0.0003, statistically significant)		
			Secondary Clinical effectiveness	Proportion in whom C reactive protein returned to normal levels (a raised level was defined as a level above 5 mg/litre)	30 participants had raised C reactive protein at baseline, this returned to normal in 33.3% (10/30) at 3 months (p=0.004, statistically significant) and 26.7% (8/30) at 12 months (p=0.01, statistically significant) 22.7% (10/44) were in clinical remission and had a normal C reactive protein at 12 months		

			Secondary Clinical effectiveness	Change in albumin levels between baseline and 3 and 12 months	Median albumin levels were: 34.5 g/litre at baseline, 36.7 g/litre at 3 months and 40.2 g/litre at 12 months Mean increase in albumin was 2.7 (SE: 0.94) g/litre from baseline to 3 months (p=0.0147, statistically significant) and 5.3 (SE: 0.99) g/litre from baseline to 12 months (p<0.0001, statistically significant)		
			Safety	Adverse events	Rate of adverse events: 12.4 per 1000 patient-months of follow-up 4.5% (2/44) had a serious adverse event after receiving 1 induction dose: perianal abscess in 1 participant and worsening of chronic recurrent multifocal osteomyelitis and cutaneous psoriasis in the other participant 14.3% (6/42) participants had mild adverse events during the maintenance phase of treatment: 2 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 after 3 months on treatment and 1 participant reported chronic rhinitis symptoms		
			Safety	Discontinuation during maintenance phase	During the study 30.9% (13/42) participants stopped ustekinumab during the maintenance phase of treatment. Median (IQR) time to stopping treatment was 13 (10.3-21.3) months. Reason for stopping treatment in all cases during maintenance phase was poor clinical response.		

Critical appraisal summary: This is a retrospective non-comparative observational study, which is susceptible to bias, confounding and other methodological problems. People were treated on an individual patient basis and treatment pathways were not dictated by the study. Outcome assessment was not blinded. Analysis of data used the ITT population, for the primary outcome of clinical remission participants with missing disease activity data were reported as having active disease. Ustekinumab treatment protocols were not standardised within or across the 4 centres, and variability in induction protocols and use of concurrent immunotherapies could have had some influence on efficacy and safety. The induction dosage regimens used in the study are different to the induction regimen for the licensed indication for the treatment of Crohn's disease in adults. For the treatment of Crohn's disease in adults ustekinumab is given as an intravenous infusion for the first dose, subsequent dosages are then given as subcutaneous injections.

Abbreviations: BMI, body mass index; IQR, interquartile range; ITT, intention to treat; PCDAI, Paediatric Crohn's disease activity index; SE, standard error; TNF, tumour necrosis factor; WHO, world health organisation

[a] All induction regimens were completed within 4 weeks and administered subcutaneously, 38.1% (16/42) had 90 mg at weeks 0, 1 and 2; 21.4% (9/42) had 90 mg at weeks 0, 2 and 4; 14.3% (6/42) had 90 mg at week 0 and week 4; 11.9% (5/42) had 45 mg at weeks 0, 1 and 2; 11.9% (5/42) had 270 mg at week 0 and 180 mg at weeks 1 and 2; 2.4% (1/42) had 270 mg at week 0 and 180 mg at weeks 3 and 4. Two participants who had serious adverse events only received 1 induction dose.

8. Grade of evidence table

Ustekinumab to treat refractory Crohn's disease in children and young people – no comparator in study					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Clinical remission	All outcomes presented from the same reference Chavannes et al. 2018	6/10	Direct Study	C	This outcome looked at how many children and young people had their Crohn's disease in clinical remission (symptoms have subsided and are under control) at 3 and 12 months after starting ustekinumab treatment. Crohn's disease symptoms were measured using the same validated scale in all participants (the abbreviated paediatric Crohn's disease activity index (PCDAI), clinical remission was defined as a score of less than 10 on this scale). 36.4% (16/44) were in clinical remission at 3 months and 38.6% (17/44) were in clinical remission at 12 months (results were statistically significant). This suggests that ustekinumab was effective at bringing refractory Crohn's disease under control in approximately 36% of the children and young people after 3 months treatment. After 12 months treatment, approximately 39% had their Crohn's disease under control. It is unclear from the study if it was the same 16 participants in remission at

					3 months that were still in remission at 12 months. Four participants were in clinical remission at baseline before ustekinumab was started, it is not clear if these participants were still in remission at 3 and 12 months. These results should be interpreted with caution because the study is small, uncontrolled and retrospective. Weaknesses in the study's design and conduct mean it is subject to bias and influence of other factors in the study population, it is difficult to interpret and cannot support firm conclusions. There was no comparator in the study, so it provides no information on clinical effectiveness of ustekinumab compared with any other treatment. The ustekinumab induction regimens varied within and across the study centres. The induction regimens used in this study in children and young people were different to the induction regimen for the licensed indication for the treatment of Crohn's disease in adults. For the treatment of Crohn's disease in adults ustekinumab is given as an intravenous infusion for the first dose, subsequent dosages are then given as subcutaneous injections. In the study a subcutaneous injection induction regimen was used. Therefore, this study does not provide any information on the intravenous infusion ustekinumab formulation in children and young people.
Steroid free clinical remission at 12 months					This outcome looked at how many children and young people had their Crohn's disease in clinical remission and in addition were not taking steroids 12 months after starting ustekinumab treatment. 27.3% (12/44) were in steroid free clinical remission at 12 months (no statistical analysis provided). Steroid exposure was only measured in the 32 participants who remained on ustekinumab for at least 12 months. 40.6% (13/32) were taking steroids at baseline and 15.6% (5/32) were taking steroids at 12 months (not statistically significant). This suggests that just over a quarter of the children and young people had their Crohn's disease in remission and in addition were not taking steroids 12 months after starting treatment with ustekinumab. Among those who continued ustekinumab treatment for at least 12 months there was no statistically significant difference between the number taking steroids at baseline and the number taking steroids at 12 months. These results should be interpreted with caution because the study is small, uncontrolled, retrospective and because of weaknesses in the study design as described above under the clinical remission outcome. The small size of the group that continued ustekinumab for at least 12 months may mean that it was not sufficiently powered to detect a difference between the number taking steroids at baseline and 12 months.
Clinical response					This outcome looked at how many children and young people had an improvement in their Crohn's disease symptoms. Crohn's disease symptoms were measured using the same validated scale in all participants (clinical response was defined as a decrease in abbreviated PCDAI score of 15 or more, on this scale lower scores are better). 47.8% (21/44) had a clinical response at both 3 and 12 months (no statistical analysis provided in study). This suggests that just under half of the children and young people had some improvement in their Crohn's disease symptoms with ustekinumab treatment.

					These results should be interpreted with caution because the study is small, uncontrolled, retrospective and because of weaknesses in the study design as described above under the clinical remission outcome.
Number of participants who required surgery					This outcome looked at how many children and young people had surgery during the follow-up period. Participants in the study were followed-up for at least 12 months or until the ustekinumab was stopped. The average follow-up period in the study was not reported. 9.1% (4/44) required surgery during the follow-up period, it was not reported what the surgery was. Two of the 4 participants continued ustekinumab treatment after surgery. This suggests that some children and young people with refractory Crohn's disease treated with ustekinumab may still require surgery. These results should be interpreted with caution because the study is small, uncontrolled, retrospective and because of weaknesses in the study design as described above under the clinical remission outcome. 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.
Change in height, weight and BMI z-scores between baseline and 12 months					This outcome looked at changes in height, weight and BMI between baseline and 12 months after starting treatment with ustekinumab, using the z-score. A z-score expresses deviation from a mean (average). A z-score of 0 is equal to the mean (for height, weight or BMI for a child or young person at a specific age and gender). 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. Z-scores based on WHO growth chart standards were used. At baseline, the median z-score for height was −0.68, for weight it was −0.61 and for BMI it was −0.66. At 12 months, the median z-score for height was −0.82, for weight it was −0.05 and for BMI it was 0.18. The mean increase in height z-score was 0.072 (not statistically significant). The mean increase in weight z-score was 0.48 (statistically significant) and the mean increase in BMI z-score was 0.66 (statistically significant). This suggests that there was an increase in the average weight and BMI. However, the average height for the group remained lower than reference average heights. These results should be interpreted with caution because the study is small, uncontrolled, retrospective and because of weaknesses in the study design as described above under the clinical remission outcome.

Proportion in whom C reactive protein returned to normal levels					This outcome looked at how many children and young people with a raised C reactive protein at baseline had their C reactive protein return to normal levels with ustekinumab treatment. C reactive protein is an inflammatory marker in the blood, that is often measured to check for active inflammation. 30 participants had raised C reactive protein at baseline, this returned to normal in 33.3% (10/30) at 3 months and 26.7% (8/30) at 12 months (results were statistically significant). This suggests that for those who had a high C reactive protein at baseline, for a third this returned to normal after 3 months and for just over a quarter it returned to normal after 12 months with ustekinumab treatment. These results should be interpreted with caution because the study is small, uncontrolled, retrospective and because of weaknesses in the study design as described above under the clinical remission outcome. The clinical significance of this outcome is unclear, approximately 32% (14/44) had a normal C reactive protein level at baseline before ustekinumab was started.
Change in albumin levels between baseline and 3 and 12 months					This outcome looked at the change in albumin levels from baseline to 3 and 12 months after ustekinumab was started. Albumin is a protein in the blood. Albumin may be low in some people with Crohn's disease because of malnutrition due to poor oral intake or increased loss of protein through the gastrointestinal tract. The normal reference ranges for albumin used in the study were not provided. Median (a way of measuring the average) albumin levels were: 34.5 g/litre at baseline, 36.7 g/litre at 3 months and 40.2 g/litre at 12 months. Average increase in albumin was 2.7 g/litre from baseline to 3 months and 5.3 g/litre from baseline to 12 months (these results were statistically significant). These results should be interpreted with caution because the study is small, uncontrolled, retrospective and because of weaknesses in the study design as described above under the clinical remission outcome. The clinical significance of these changes in the albumin levels is unclear.
Adverse events					This outcome looked at how many children and young people had adverse events while they were having ustekinumab for refractory Crohn's disease. Rate of adverse events: 12.4 per 1000 patient-months of follow-up. 4.5% (2/44) had a serious adverse event after receiving 1 induction dose: perianal abscess in 1 participant and worsening of chronic recurrent osteomyelitis (bone infection) and psoriasis in the other participant. 14.3% (6/42) participants had mild adverse events during the maintenance phase of treatment: 2 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.

					These results are from a small, uncontrolled study which is at risk of bias and other influencing factors in the study population. Only 32 children and young people had ustekinumab treatment for at least 12 months. There was no comparator in the study, so it provides no information on the safety and tolerability of ustekinumab compared with other treatments. The induction regimens varied between and within the study centres and were different to the induction regimen for the licensed indication for Crohn's disease in adults. Based on the limited data from the study it is difficult to draw firm conclusions on the safety and tolerability of ustekinumab for the treatment of refractory Crohn's disease in children and young people.
Discontinuation during maintenance phase					This outcome looked at how many children and young people stopped having ustekinumab during the maintenance phase of treatment. 30.9% (13/42) stopped ustekinumab during the maintenance phase of treatment. Median time to stopping treatment was 13 months. In all participants treatment was stopped during the maintenance phase because of poor clinical response. This suggests that approximately 31% of children and young people stopped ustekinumab treatment during the maintenance phase. Treatment was stopped because it did not help to control the Crohn's disease. These results should be interpreted with caution because the study is small, uncontrolled, retrospective and because of weaknesses in the study design as described above under the adverse events outcome.

9. Literature search terms

Search strategy	
P – Patients / Population Which patients or populations of patients are we interested in? How can they be best described? Are there subgroups that need to be considered?	Children aged 3-18 years old, diagnosed with Crohn's disease who have failed anti-TNF alpha treatment. The policy working group considered whether the review should be performed in all ages, however, the availability of the NICE Technology Appraisal for Ustekinumab in adults negates the need for adults to be included in the population.
I – Intervention Which intervention, treatment or approach should be used?	Ustekinumab (with background treatment as reported)
C – Comparison	No ustekinumab

What is/are the main alternative/s to compare with the intervention being considered?	

O – Outcomes
 	
What is really important for the patient? Which outcomes should be considered? Examples include intermediate or short-term outcomes; mortality; morbidity and quality of life; treatment complications; adverse effects; rates of relapse; late morbidity and re-admission
	Critical to decision-making:
	
	• Clinical effectiveness, such as:
	  o Steroid dose reduction
	  o Rate of surgical intervention, i.e. colectomy or small bowel resection
	  o Complications from disease progression and exacerbation, such as fistulae, fissures, abscesses, strictures, repeated surgical interventions
	• Paediatric Quality of Life, school performance, low mood, depression and emotional issues.
	• Safety of Ustekinumab compare to standard treatment, including severe adverse effects of:
	  o Ustekinumab
	  o Standard treatment e.g. steroids or surgery
	• Mortality
	
	Important to decision-making:
	
	• Reduction in disease activity, for example:
	  o Measured in Paediatric Crohn's Disease Activity Index
	  o Biochemical markers in blood and stool
	  o Endoscopic evidence of persistent active disease
	  o Radiological evidence of persistent active disease
	• The reduction/ addition of hospital appointments, and its effect on children's social functioning, parent's work commitment
	• Cost effectiveness of ustekinumab

Assumptions / limits applied to search	
Inclusions • Study design: Systematic review, meta-analysis, randomised controlled trials, controlled trials, and cohort study are preferable. If no higher level quality evidence is found, case series can be considered.	

- Language: English only.
- Patients: Human studies only.
- Date limits: 2008 – 2018.

Exclusions

Publication Type: Conference abstracts, narrative reviews, commentaries, letters, editorials, and case reports will be excluded.

10. Search strategy

Database: Medline

Platform: Ovid
Version: Ovid MEDLINE(R) ALL <1946 to November 09, 2018>
Search date: 12th Nov 18
Number of results retrieved: 175
Search strategy:
1 Crohn Disease/ (36406)
2 crohn*.tw. (42368)
3 1 or 2 (50734)
4 Ustekinumab/ (710)
5 ustekinumab*.tw. (1248)
6 Stelara*.tw. (20)
7 or/4-6 (1379)
8 3 and 7 (188)
9 limit 8 to english language (175)

Database: Medline in-process
Platform: Ovid
Version: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <November 09, 2018>
Search date: 12th Nov 18
Number of results retrieved: 58
Search strategy:
1 Crohn Disease/ (0)
2 crohn*.tw. (3839)
3 1 or 2 (3839)
4 Ustekinumab/ (0)
5 ustekinumab*.tw. (273)
6 Stelara*.tw. (2)
7 or/4-6 (273)
8 3 and 7 (62)
9 limit 8 to english language (58)

Database: Medline epubs ahead of print
Platform: Ovid
Version: Ovid MEDLINE(R) Epub Ahead of Print <November 09, 2018>
Search date: 12th Nov 2018
Number of results retrieved: 11
Search strategy:
Database: Ovid MEDLINE(R) Epub Ahead of Print <November 09, 2018>
Search Strategy:
1 Crohn Disease/ (0)
2 crohn*.tw. (725)
3 1 or 2 (725)

4 Ustekinumab/ (0)
5 ustekinumab*.tw. (83)
6 Stelara*.tw. (1)
7 or/4-6 (83)
8 3 and 7 (11)
9 limit 8 to english language (11)

Database: Medline daily update
Platform: Ovid
Version: Ovid MEDLINE(R) Daily Update <November 09, 2018>
Search date: 12th Nov 18
Number of results retrieved: 3
Search strategy
1 Crohn Disease/ (29)
2 crohn*.tw. (44)
3 1 or 2 (46)
4 Ustekinumab/ (5)
5 ustekinumab*.tw. (7)
6 Stelara*.tw. (0)
7 or/4-6 (7)
8 3 and 7 (3)
9 limit 8 to english language (3)

Database: Embase
Platform: Ovid
Version: Embase <1974 to 2018 Week 46>
Search date: 12th Nov 18
Number of results retrieved: 59
Search strategy:
1 exp Crohn disease/ (81452)
2 crohn*.tw. (70184)
3 1 or 2 (90695)
4 ustekinumab/ (4921)
5 ustekinumab*.tw. (2761)
6 Stelara*.tw. (410)
7 or/4-6 (5026)
8 3 and 7 (1080)
9 limit 8 to english language (1043)
10 limit 9 to (conference abstract or conference paper or "conference review" or letter or note or tombstone) (391)
11 9 not 10 (652)
12 (Infan* or newborn* or new-born* or perinat* or neonat* or baby or baby* or babies or toddler* or minors or minors* or boy or boys or boyfriend or boyhood or girl* or kid or kids or schoolchild* or child* or adolescen* or juvenil* or youth* or teen* or under*age* or pubescen* or pediatrics or pediatric* or paediatric* or peadiatric* or school* or prematur* or preterm*).tw. (2944836)
13 exp juvenile/ (3108706)

14 12 or 13 (4136960)
15 11 and 14 (59)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR) & CENTRAL;
Platform: Wiley
Version: CDSR – Issue 11 of 12, November 2018
CENTRAL – Issue 11 of 12, November 2018
Search date: 12th Nov 2018
Number of results retrieved: CDSR – 8; CENTRAL – 96;
Search Name: Evidence summary - ustekinumab - crohns disease - LA
Date Run: 12/11/2018 14:03:04
Comment:

ID	Search	Hits
#1	MeSH descriptor: [Crohn Disease] this term only	1348
#2	crohn*	3883
#3	#1 or #2	3883
#4	MeSH descriptor: [Ustekinumab] this term only	108
#5	ustekinumab*	446
#6	Stelara*	13
#7	#4 or #5 or #6	446
#8	#3 and #7	114

CRD databases (NHS EED, DARE, HTA)
Search date*:* 26th Nov 2018
1 (ustekinumab) 33
2 (crohn*) 374
3 #1 AND #2 3

Trials registry search strategies
Clinicaltrials.gov
Search date: 12th Nov 2018
Number of relevant results retrieved: 1
Search strategy: crohn disease AND ustekinumab
Clinicaltrialsregister.eu
Search date: 12th Nov 2018
Number of results retrieved: Same relevant result as clinical trials.gov
Search strategy: crohn disease AND ustekinumab
Excluded registry results
Too many to list – all excluded results had an adult population

11. Evidence selection

A literature search was conducted which identified 302 references (see search strategy for full details). These references were screened using their titles and abstracts and 4 references were obtained and assessed for relevance. Of these, 1 reference is included in the evidence summary. The remaining 3 references were excluded and are listed in the following table. The main study (Chavannes et al. 2018) included in the evidence summary was published after the searches for this evidence review were conducted.

Study reference	Reason for exclusion
Bertrand V, El H A, Carre D (2017) Efficiency of Ustekinumab in Crohn's Disease with Severe Psoriasiform Rash Induced by Biotherapies in an Adolescent Pediatric dermatology 34: e214-15	Not a relevant study: case report in a 16 year old female
Cameron F L, Garrick V, Russell, R K (2016) Ustekinumab in Treatment of Refractory Paediatric Crohn Disease Journal of paediatric gastroenterology and nutrition 62: e30	Not a relevant study: case report in a 16 year old male
Rinawi F, Rosenbach Y, Assa A et al. (2016) Ustekinumab for Resistant Paediatric Crohn Disease Journal of paediatric gastroenterology and nutrition 62: e34-5	Not a relevant study: case report in a 7 year old boy

Three studies were identified by specialists involved in this evidence review as being clinically impactful. These are listed in the following table:

Study	Comment
Bishop C, Simon H, Suskind D et al. (2016) Ustekinumab in paediatric Crohn disease patients. Journal of Pediatric Gastroenterology and Nutrition 63: 348-51	Identified by searches and included in evidence review as supplementary evidence
Feagan B, Sandborn W, Gasink C et al. (2016) Ustekinumab as induction and maintenance therapy for Crohn's Disease. The New England Journal of Medicine 20: 1946-60	Excluded from evidence review Not identified by searches as was conducted in an adult population
Sandborn W, Gasink C, Gao L et al. (2012) Ustekinumab induction and maintenance therapy in refractory Crohn's Disease. The New England Journal of Medicine 16: 1519-28	Excluded from evidence review Not identified by searches as was conducted in an adult population

12. Related NICE guidance and NHS England clinical policies

Crohn's disease: management NICE guideline CG152

Ustekinumab for moderately to severely Active Crohn's disease after previous treatment (for use in adults). NICE Technology appraisal guidance TA456

NICE have also published a Quality standard on inflammatory bowel disease NICE Quality standard QS81

13. Terms used in this evidence summary

Abbreviations

Term	Definition
5-ASA	5-aminosalicylate
BMI	Body mass index
IQR	Interquartile range
MHRA	Medicines and Healthcare Regulatory Agency
PCDAI	Paediatric Crohn's disease activity index
SE	Standard error
SPC	Summary of product characteristics
TNF	Tumour necrosis factor
TPMT	Thiopurine methyltransferase
WHO	World Health Organisation

Medical definitions

Term	Definition
Conventional glucocorticosteroid	This includes prednisolone, methylprednisolone or intravenous hydrocortisone.
C reactive protein	An inflammatory marker in the blood. In the Chavannes et al. 2018 study an elevated C reactive protein was defined as a level above 5 mg/litre.
Faecal calprotectin	A substance that is released into the intestines in excess when there is any inflammation there.
Fistula	A fistula is an abnormal channel or passageway connecting one internal organ to another, or to the outside surface of the body. Many fistulas (or fistulae) involve the bowel or intestine. So, a fistula might connect 2 parts of the bowel to each other, or the bowel to the vagina, bladder, or skin.
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.
Penetrating disease	The occurrence of bowel perforation, intra-abdominal fistulas, inflammatory masses or abscesses at any time in the course of the disease, and not secondary postoperative intra-abdominal complication (excludes isolated perianal or rectovaginal fistulae). Characteristics of disease were defined using the Paris classification.
Abbreviated Paediatric Crohn's disease activity index (PCDAI)	This scale is a validated clinical score that excludes the blood work component of the original PCDAI. 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.
Refractory Crohn's disease	For the purpose of this evidence review refractory Crohn's disease is defined as Crohn's disease that has not adequately responded to conventional pharmacological treatment and has had an inadequate response to or has lost response to TNF alpha inhibitor treatment.
Stricture	Narrowing of the intestine.

14. References

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