Evidence Status Report: ustekinumab (Stelara®▼) for the treatment of inflammatory bowel disease in children and young people aged 6 to 17 years: for ulcerative colitis following loss of response, non-response or intolerance to anti-TNF therapies and vedolizumab; for Crohn's disease following loss of response, non-response or intolerance to anti-TNF therapies **(OW25)**

Report prepared by the All Wales Therapeutics and Toxicology Centre
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Key findings

License status
Ustekinumab is not licensed for the treatment of inflammatory bowel disease in children and young people aged less than 18 years. Its use for the treatment of both ulcerative colitis following loss of response, non-response or intolerance to anti-TNF therapies and vedolizumab; and Crohn's disease following loss of response, non-response or intolerance to anti-TNF therapies is off-label for children and young people aged 6 to 17 years.

Clinical evidence
The evidence of clinical efficacy of ustekinumab in this setting comes mainly from a phase III open-label prospective study, a phase I randomised study, two retrospective studies and an observational study. All studies identified in this report concluded ustekinumab demonstrated efficacy in children and young people (CYP) with otherwise treatment-refractory inflammatory bowel disease.

Safety
No new safety signals have been observed for ustekinumab for this indication.

Patient factors
Ustekinumab treatment is to be initiated with a single intravenous dose based on body weight over a period of 30 minutes. Patients should be monitored during the infusion as hypersensitivity reactions, including anaphylaxis and angioedema can develop. Maintenance treatment is given as a subcutaneous injection every 8 weeks or every 12 weeks according to clinical judgement and may be administered by the patient or a carer at home.

Cost-effectiveness
No cost-effectiveness analyses have been undertaken in the paediatric population. The cost-effectiveness of ustekinumab has been assessed in adults: NICE TA633 and TA456.

Budget impact
Based on consultation with clinicians in Wales, 22 CYP are estimated to start treatment with ustekinumab each year at an annual cost per patient of [commercial in confidence text removed] and a total cost of [commercial in confidence text removed] in year one rising to [commercial in confidence text removed] in year 3. It has been assumed that all patients receive treatment for 12 months with one third subsequently discontinuing treatment at year 2 and year 3. However, the budget impact is subject to uncertainty due to lack of longer-term discontinuation rate data. Additionally, the budget impact is anticipated to be lower in year 1 as over half of estimated patients are currently accessing treatment through IPFR. Adverse event and monitoring costs are not included.

Impact on health and social care services
Minimal increased use of existing services.

Innovation and/or advantages
Welsh clinical experts indicate an unmet need in this population. For CYP who have failed all the current treatments in the pathway, there is no alternative licensed therapy and these patients may be dependent on steroids to control the disease. Patients are at risk of complications and repeated surgical interventions if inflammatory bowel disease is poorly controlled.

Background

Clinicians in Wales consider there is an unmet need and have identified a cohort of patients who could benefit from this treatment. Ustekinumab was therefore considered suitable for assessment though the One Wales Medicines process.

Ustekinumab (Stelara®) is a humanised IgG1 monoclonal antibody that is targeted against the p40 subunit of interleukin-12 (IL-12) and interleukin-23 (IL-23), which is expressed in certain white blood cells causing bowel tissue inflammation. It is available for administration by intravenous infusion for induction and subcutaneously for maintenance therapy[1].

Target group

The indication under consideration is the treatment of inflammatory bowel disease in children and young people (CYP) aged 6 to 17 years: ulcerative colitis following loss of response, non-response, or intolerance to anti-TNF therapy and vedolizumab; Crohn's disease following loss of response, non-response or intolerance to anti-TNF therapy. The age range in the indication under consideration aligns with that defined in the licensed indication for the use of anti-TNF inhibitors for ulcerative colitis and Crohn's disease in the paediatric population[2,3]. Individual patient funding request (IPFR) will remain a route of access for children under 6 years.

Marketing authorisation date: Not applicable, off-label

Ustekinumab is not licensed for the treatment of inflammatory bowel disease in CYP.

Ustekinumab is licenced for the treatment of[4]:

- Moderately to severely active Crohn's disease in adults who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or an anti-TNF or have medical contraindications to such therapies.

- Moderately to severely active ulcerative colitis in adults who have had an inadequate response with, lost response to, or were intolerant to either conventional therapy or a biologic or have medical contraindications to such therapies

Subcutaneous use of ustekinumab is licenced for the treatment of moderate to severe plaque psoriasis in children and adolescent patients from the age of 6 years

and older, who are inadequately controlled by, or are intolerant to, other systemic therapies or phototherapies[5].

Dosing

Induction treatment is administered intravenously as a weight-based dose of about 6 mg per kg (maximum 520 mg)[4]. Maintenance treatment is administered as a subcutaneous injection, with the dose adjusted to body surface area, given at week 8 after induction. After this, dosing every 12 weeks is recommended. Patients who have not had an adequate response 8 weeks after the first subcutaneous dose (week 16) may have a second subcutaneous dose at this time, to allow for delayed response. Patients who lose response on 12-weekly dosing may benefit from an increase in dosing frequency to every 8 weeks. Patients may subsequently have ustekinumab every 8 weeks or every 12 weeks according to clinical judgement. Consideration should be given to discontinuing treatment in patients who show no evidence of therapeutic benefit 16 weeks after the IV induction dose or 16 weeks after switching to the 8-weekly maintenance dose[4,5].

Clinical background

Ulcerative colitis (UC) and Crohn's disease (CD) are the two main forms of inflammatory bowel disease (IBD). They are lifelong, chronic conditions that follow an unpredictable relapsing and remitting course and can cause significant morbidity. They can affect a person's social and psychological wellbeing, particularly if poorly controlled[1,6].

Ulcerative colitis usually affects the rectum, and a variable extent of the colon proximal to the rectum[7]. The inflammation is continuous in extent. Hereditary, infectious and immunological factors have been proposed as possible causes. It can develop at any age, but peak incidence is between the ages of 15 and 25 years. UC in CYP has several distinct features from the disease seen in adults. Common presenting symptoms of paediatric UC include diarrhoea, haematochezia, abdominal pain, and weight loss; constipation can also be an early symptom. Adults often have disease that is limited to the rectosigmoid area of the colon, but more than 80% of CYP have pancolitis[8]. An estimated 50% of people with UC will have at least one relapse per year; 80% of these are mild to moderate and about 20% are severe. Complications of UC may include haemorrhage, perforation, stricture formation, abscess formation and anorectal disease. People with long-standing disease have an increased risk of bowel cancer[9].

Crohn's disease is an incurable chronic inflammatory bowel disease with 25% of patients being diagnosed under the age of 20 years[10]. Any part of the gut may be affected from the mouth to the anus. People with CD have recurrent attacks, with acute exacerbations ('flares') in between periods of remission or less active disease. The clinical features of CD are variable and are determined partly by the site of the disease. The symptoms include diarrhoea, abdominal pain and weight loss. Constitutional symptoms include malaise, lethargy, anorexia, nausea, vomiting and low-grade fever. CD can be complicated by the development of strictures (a narrowing of the intestine), obstructions, fistulae and perianal disease. Other complications include acute dilation, perforation and massive haemorrhage, and carcinoma of the small bowel or colon[10]. It is estimated 50% of CD patients relapse and between 50 and 80% of people with CD will eventually need surgery for

strictures causing symptoms of obstruction, other complications such as fistula formation, perforation or failure of medical therapy[11,12].

Delayed puberty frequently complicates the clinical course of young patients with IBD, more often in CD than UC. Undernutrition has been thought to be the main reason for delayed puberty in these patients. However, puberty may be delayed despite a normal nutritional status[13]. Steroid-free remission, whether clinically or endoscopically is an important treatment goal for paediatric IBD, as corticosteroids have potentially serious side effects associated with long term use including linear growth restriction, and osteopenia amongst many others[14].

Incidence/prevalence

A UK prevalence study conducted in 2020 calculated an IBD prevalence of 0.8% equating to over 500,000 people in the UK living with the condition[15]. Ulcerative colitis has a higher prevalence (0.4%) compared with Crohn's disease (0.3%) and unclassified IBD (0.07%) in the UK population[15].

Crohn's & Colitis UK estimate that around 25,000 people are diagnosed with IBD each year in the UK[15]. While incidence rates have remained stable for the last 15 years, due to population growth it is likely the number of people diagnosed with IBD in the UK will increase further[15]. IBD UK estimates there are at least 8000 CYP living with IBD in the UK[16], this would suggest there are around 400 CYP with IBD in Wales.

Current treatment options and relevant guidance

The National Institute for Health and Care Excellence (NICE) has published guidelines which covers managing ulcerative colitis in children, young people and adults (NG130) and Crohn's disease in children, young people and adults (NG129)[7,11]. Current medical approaches focus on treating active disease to address symptoms, to improve quality of life, and thereafter to maintain remission[7,17]. 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, adding a second line therapy such as azathioprine is recommended; 5-aminosalicylate (5-ASA) drugs, budesonide, mercaptopurine and methotrexate have also been used off-label as second line treatments. Infliximab is recommended as a third line agent for people aged 6 to 17 years for CD and as a treatment option for acute exacerbations of severely active UC but only when ciclosporin is contraindicated or clinically inappropriate[7,11]. Anti-TNF agents are now standard of care for the treatment of IBD, however approximately 10%-40% patients do not improve after anti-TNF therapy (primary non response), and 20%-40% may lose response to therapy over time (second loss of response)[14]. However, unlike for adults, no licensed medicinal therapies are available for CYP with IBD following loss of response or non-response to infliximab. Off-label biologics may be used and would be accessed through individual patient funding request (IPFR) in Wales. More severely affected 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[17].

Clinical practice recommendations for the medical management of paediatric CD were published in 2020 as an evidence-based guideline by the European Crohn's and Colitis Organisation (ECCO) and the Paediatric IBD Porto group of the European

Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)[18]. They recommend that for patients who fail to achieve or maintain clinical remission on anti-TNF agents, despite anti-TNF dose optimisation and immunomodulator use, treatment with ustekinumab or vedolizumab can be considered[18].

NICE recommends ustekinumab for treating moderately to severely active ulcerative colitis in adults (TA633) and for moderately to severely active Crohn's disease in adults after previous treatment (TA456)[1,6]. Access to ustekinumab for CYP in England may be considered in line with the criteria in NHS England's Commissioning Medicines for Children in Specialised Services policy apart for the treatment of refractory CD in pre-pubescent children[19]. In 2020, NHS England reviewed the evidence for use in this sub-population and issued a non-recommendation for the routine commissioning of this treatment option as the evidence base was considered sparse with no standard treatment pathways or monitoring[17]. NHS England will review the evidence base again on release of the findings of a randomised controlled trial due to be reported in 2023[17,20].

Summary of evidence on clinical effectiveness

AWTTC conducted a literature search and identified a number of studies with the main ones of interest highlighted below. The evidence presented in this review does not provide any data comparing the clinical effectiveness and safety of ustekinumab with any other treatment for the management of IBD in CYP. There are currently five clinical trials underway in the paediatric population with estimated completion dates between 2022 and 2027[20-24].

Crohn's disease (CD)

Clinical trial

Rosh et al (2021) conducted a phase I, multicentre, 16-week, randomised, double-blind, dose-ranging study of intravenous (IV) ustekinumab induction followed by subcutaneous (SC) ustekinumab maintenance in paediatric patients with moderately to severely active CD[25]. A total of 44 patients with a median age of 13 years (interquartile range [IQR] 11-16 years) were randomised and treated with ustekinumab; 23 in the lower induction dose group (ustekinumab 3 mg/kg IV or 130 mg IV) and 21 in the higher induction dose group (ustekinumab 9 mg/kg IV or 390 mg IV). Of the total, 91% (40) had received a biologic previously and around half had failed at least one anti-TNF agent and a third two anti-TNF agents. Clinical response (reduction from baseline in Paediatric Crohn's Disease Activity Index [PCDAI][26] score of ≥15 points) and remission (defined as a PCDAI score ≤10 points) at week 16 was assessed. Through week 6 in the overall paediatric population (combined doses), serum ustekinumab concentrations were generally comparable to those in the reference adult phase III CD studies. At week 8, 48% of patients in the lower and higher dose groups were in clinical response; these rates were similar at week 16. The percentage of patients in clinical remission was greater in the higher than in the lower dose group at week 16 (29% versus 22%); at week 8, remission rates were similar. The proportions of patients achieving clinical response or clinical remission were generally consistent across baseline age and weight subgroups. Based on pharmacokinetic data, the authors noted that the dose for children weighing less than 40kg may need to be different to that used in the study to obtain a comparable exposure to ustekinumab in an adult. Further studies are needed in this group[25].

Retrospective study

Chavannes et al (2019) conducted an open-label multicentre retrospective cohort study to assess the effectiveness and safety of ustekinumab in paediatric patients with refractory (intolerant of, had failed or lost response to at least one biologic) CD and to identify risk factors predicting discontinuation of ustekinumab[27]. The study included 44 patients with a median interquartile range (IQR) age of 16 years at initiation of ustekinumab (IQR 13–17 years). Overall, six different induction regimens were used, induction and maintenance doses were administered subcutaneously in all patients. The primary outcome was defined as the percentage of patients achieving clinical remission over the first 12 months of therapy. Clinical remission was achieved in 16/44 patients (36.4%, p = 0.006) at 3 months and 17/44 patients (38.6%, p = 0.006) at 12 months. At 12 months, 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 (no statistical analysis presented). Weight but not height scores improved significantly during the 12 months. The probability of remaining on ustekinumab by 12 months was 76.9% (95% confidence interval: 65.3–90.6%). The study also reported that C-reactive protein and albumin significantly improved at both 3 and 12-months' follow-up in ustekinumab responders[27].

Ulcerative colitis (UC)

Clinical trial

Dhaliwal et al (2021) conducted a phase III open-label prospective study to monitor efficacy and serum concentrations of ustekinumab in children with UC refractory to infliximab[28]. In total, 25 children with a median (IQR) age of 14.8 years (range 12.3-16.2 years) and with a UC median duration of 2.3 years (range 1.1-4.2 years) received intravenous induction ustekinumab (median dose 6.4 mg/kg [range 5.5-7.5 mg/kg]). All patients had failed prior anti-TNF therapy (all infliximab, 3 also adalimumab) and 12 (48%) had additionally failed vedolizumab therapy. Two-thirds of children (n = 17) were receiving concomitant corticosteroids at ustekinumab initiation. The primary endpoint was steroid-free clinical remission at 52 weeks (Paediatric Ulcerative Colitis Activity Index [PUCAI][29] <10, no steroids ≥4 weeks) while receiving subcutaneous ustekinumab maintenance. Eleven (44%) of 25 met the primary endpoint; this included 9 (69%) of 13 who were previously treated with anti-TNF therapy only versus 2 (17%) of 12 who previously failed also on vedolizumab. Of the 11 who met the primary endpoint, longer term data for 8 were available indicating steroid-free clinical remission was maintained for 7 patients to ≥72 weeks. At week 52, overall, 16 (64%) of 25 patients continued to receive ustekinumab therapy, including 9 (69%) of 13 with only prior anti-TNF failure, and 7 (58%) of 12 with prior failure also of vedolizumab. Corticosteroids were discontinued in all after a median 19.4 weeks (range 5.5-22.5 weeks). The five non-remitters continuing ustekinumab (all with prior failure of both infliximab and vedolizumab) were off steroids but with mild to moderate disease activity (median PUCAI 20, range 12.5-35). Four of these five had improved from baseline with the median difference in PUCAI of - 25 (- 53 to 0). Five patients discontinued ustekinumab after receiving one intravenous dose, due to ongoing active colitis (n = 4) or family request (n = 1). Six (24%) of the cohort underwent colectomy by 1 year at a median time of 5.3 weeks (IQR 3.6-36.4 weeks) following intravenous ustekinumab[28].

IBD (mixed group)

Observational study

Dayan et al (2019) describes real-world experience in an ongoing observational cohort study of biologic-treated paediatric IBD patients which was initiated in October 2014[30]. The latest reported data includes analysis for 52 children and young adults initiating ustekinumab; 81% with CD, 8% with UC, and 11% with IBD-unspecified. The median (IQR) age at induction was 16.8 years (range14-18 years). Patients were followed for a minimum of 12 months. Most patients (81%) had failed >1 anti-TNF therapy, and 37% had failed anti-TNF therapy and vedolizumab; 10 patients were biologic-naïve. Ustekinumab dosing was 260 mg-390 mg IV infusion followed by SC ustekinumab 90mg every 8 weeks. At week 52, 39 (75%) were still on ustekinumab; biologic-naïve patients were found to be significantly more likely to achieve steroid-free remission than biologic-exposed patients (90% and 50% respectively, p = 0.03) [30].

Other smaller paediatric studies support the results of the above studies, with clinical response reported in all[31,32].

Clinical trials in progress

There are currently five trials ongoing in paediatric populations sponsored by Janssen Research & Development, LLC:

1. A Pharmacokinetic Study of Ustekinumab in Paediatric Subjects with Moderately to Severely Active Crohn's Disease (STELARA): NCT02968108: A randomised double-blind pharmacokinetic study of ustekinumab in paediatric subjects with moderately to severely active Crohn's disease. Study completed March 2022, results pending[20].

2. A Study of Ustekinumab Treatment in Children with Crohn's Disease (REALITI): NCT05242458: Real-world evidence for the effectiveness and safety of ustekinumab treatment in children with Crohn's disease: a retrospective cohort study using the ImproveCareNow registry data. Study completed November 2022, results pending[21].

3. A Long-term Extension Study of Ustekinumab in Pediatric Participants (UNITED): NCT05092269: A phase III, multicenter, open-label, basket, long-term extension study of ustekinumab in pediatric clinical study participants (2 to <18 Years of Age). This study is due to complete in December 2027[22].

4. A Study of Ustekinumab in Paediatric Participants with Moderately to Severely Active Crohn's Disease (UNITI Jr): NCT04673357: A phase III study of the efficacy, safety, and pharmacokinetics of ustekinumab as open-label intravenous induction treatment followed by randomised double-blind subcutaneous ustekinumab maintenance in paediatric participants with moderately to severely active crohn's disease. This study is due to complete in July 2025[23].

5. A Study of Ustekinumab in Paediatric Participants with Moderately to Severely Active Ulcerative Colitis (UC) (UNIFI Jr): NCT04630028: A phase III study of the efficacy, safety and pharmacokinetics of ustekinumab as open-label

intravenous induction treatment followed by randomised double-blind subcutaneous ustekinumab maintenance in paediatric participants with moderately to severely active ulcerative colitis The purpose of this study is to evaluate: a) the efficacy of ustekinumab dosing in inducing clinical remission, b) safety profile of ustekinumab, and c) ustekinumab exposure (pharmacokinetics) in paediatric participants with moderately to severely active UC. This study is due to complete in July 2025[24].

Safety

The Summary of Product Characteristics (SmPC) for ustekinumab (Stelara®) states the most common adverse reactions (> 5%) in controlled periods of the adult clinical studies of ustekinumab for psoriasis, psoriatic arthritis, CD and UC were nasopharyngitis and headache[4]. Most were considered to be mild and did not necessitate discontinuation of study treatment. The most serious adverse reaction reported for ustekinumab (Stelara®) is serious hypersensitivity reactions including anaphylaxis. Ustekinumab may have the potential to increase the risk of infections and reactivate latent infections. Prior to initiating treatment, patients should be evaluated for tuberculosis infection. Immunosuppressants such as ustekinumab have the potential to increase the risk of malignancy[4].

The safety of subcutaneous ustekinumab has been studied in two phase III studies of paediatric patients with moderate to severe plaque psoriasis[5]. The first study was in 110 patients from 12 to 17 years of age treated for up to 60 weeks and the second study was in 44 patients aged from 6 to 11 years treated for up to 56 weeks. In general, the adverse events reported in these two studies with safety data up to 1 year were similar to those seen in previous studies of adults with plaque psoriasis[5].

In a dose escalation study by Yerushalmy-Feler et al, adverse events (AEs) that were potentially related to therapy were reported in six (8.7%) children, and included infections (cellulitis, external otitis), arthritis, flushing, mild leukopenia, and fever[33]. All AEs were mild, and none of the children stopped therapy due to adverse events[33].

In the Rosh et al study, 73% of patients reported one or more AEs[25]. Infections (e.g., upper respiratory tract infection, anal abscess, *clostridium difficile*, infected eczema, gastroenteritis, viral gastroenteritis, and nasopharyngitis) occurred in 39% of patients (lower dose: 39%, n = 9; higher dose: 38%, n = 8); there were no serious infections through week 16. More AEs/serious adverse events (SAEs) occurred in the lower dose group than the higher dose group at weeks 8 and 16. SAEs occurred in 26% of patients (n = 6) in the lower dose group and 5% of patients (n = 1) in the higher dose group, with CD exacerbation being the most frequent SAE (9% and 5%, respectively)[25].

The European Medicines Agency (EMA) risk management plan for ustekinumab use in children with psoriasis include the theoretical risk of malignancy, serious risks depression including suicidality, reversible posterior leukoencephalopathy syndrome and venous thromboembolism[34]. Long term effects are not known and included in post authorisation development plan. The SmPC for Stelara® states incidence of non-melanoma cancers 0.54 per 100 patient years of follow up comparable to the incidence in the general population and non-melanoma cancer 0.49 per 100 patient years[5].

Discussion

- Welsh clinical experts indicate there is an unmet medical need for CYP with IBD who have failed conventional treatments in the pathway; there is no alternative licensed therapy and patients may be dependent on steroids to control the disease. Patients are at risk of complications and repeated surgical interventions if IBD is poorly controlled. For CYP, access to ustekinumab for CD and UC would be accessible in NHS England through the Medicines for Children policy in line with TA456 and TA633, respectively, apart for pre-pubescent children with refractory CD. There is no current agreed route of access for this patient group due to sparsity of data.
- Other licenced, NICE approved medicines for use in adults for the treatment of moderately to severely active UC are: tofacitinib (TA547), filgotinib (TA792) and ozanimod (TA828)[35-37]. There are currently two medicines being appraised by NICE for UC: mirikizumab (ID3973, date tbc) and upadacitinib (ID3953, due January 2023)[38,39]. A medicine currently being appraised by NICE for moderately to severely active CD is risankizumab (ID3986, due March 2023)[40]. These medicines are placed after the use of ustekinumab in the treatment pathways for both diseases and are also not licenced in CYP so would be used off-label. Use of these medicines in CYP would be subject to IPFR.
- In the absence of pharmacokinetic dosing data for children, extrapolation of adult dosing to the paediatric population was used in the published studies identified. Results of these showed either improvement in both clinical and biological markers comparable to adult study findings or a slightly lower response rate than seen in the real-world use of subcutaneous ustekinumab in the management of IBD in adults[25,27,30,33].
- There have been no comparative effectiveness studies carried out in children. Several phase III clinical trials in the paediatric cohort are ongoing but completion dates are up to five years away.
- There are limited safety data available. Paediatric psoriasis trial data indicate a similar safety profile for ustekinumab in children as for adults. There have been no new safety signals reported in the small cohort paediatric IBD studies, although they have relatively short follow up. Janssen Pharmaceuticals have highlighted two ongoing clinical trials examining safety which are due to complete in 2025[23,24].
- The SmPC states adults who lose response on dosing every 12 weeks may benefit from an increase in dosing frequency to eight-weekly. In Dayan et al 57% of patients received a dose escalation with increasing frequency of maintenance injections because of inadequate clinical response from the standard 8-weekly dosing interval[30]. In the report by Chavannes et al, 30% of patients had their dose escalated to every four weeks [27]. In a dose escalation study by Yerushalmy-Feler et al, reducing the interval between dosing to less than 8 weeks was associated with higher clinical response and remission rates (67% and 42%, respectively) at 3 months. However, no association was found between dose escalation and steroid-free or clinical remission in Dayan et al[27,30,33].
- Studies included in this report have limitations including heterogeneous populations largely due to small sample size and mostly retrospective designs. There are also varying dosing regimens, differing levels of exposure to other agents and not all patients were refractory to prior treatment, including anti-TNF therapy.

- Due to the lack of placebo-controlled trials it is difficult to assess the true effectiveness of ustekinumab in this population. Studies have been relatively short term and given the relapsing-remitting nature of IBD, its effectiveness in treating these conditions and long-term outcomes are subject to uncertainty.
- Studies conducted in adults indicate that ustekimumab may be more effective in treating CD than UC [41,42]. However, there is not enough data to conclude the same trend in CYP.
  The literature acknowledges the significant burden IBD has on patients' health and health-related quality of life, and on the NHS in terms of the resource use associated with the clinical manifestations of the disease[43]. The symptoms of CD and UC, and their unpredictable nature, can be detrimental to both the physical and mental health of CYP and negatively impact on educational attainment and social interaction.

Cost-effectiveness evidence

No studies on the cost-effectiveness of ustekinumab were identified for the paediatric populations. Cost-effectiveness has been assessed for ustekimumab in adult patients with CD and UC by NICE[1,6]. The relevance of these studies to the paediatric population is uncertain as variables informing the cost-effectiveness models such as disease severity definitions, the presentation of the disease and dosing regimens are likely to be different in comparison to adults.

Crohn's disease

The company presented a model to the NICE committee consisting of a short-term induction phase (a decision tree) and a long-term maintenance phase (a Markov state transition model) comparing ustekinumab with conventional non-biological care and other biological therapies (infliximab, adalimumab and vedolizumab) in patients with moderately to severely active CD[1,10]. The model evaluated treatments over a lifetime horizon and used the commercially agreed discounted price for ustekinumab and list price of comparators. The company's base-case analysis showed that ustekinumab dominated other biological treatments (that is, it cost less and resulted in higher quality adjusted life years [QALYs]), both in the conventional-care failure population and in the anti-TNF therapy failure population. The company considered that a cost minimisation approach was more appropriate as the ICER was subject to large differences in the sensitivity analysis due to the small QALY gains in the base-case results. The NICE committee thought it not unreasonable to assume similar efficacy between the biological therapies based on the available evidence and accepted cost minimisation was not an unreasonable approach. However, it noted that the company analysis used the confidential price for ustekinumab and so appeared to have lower total costs in year 1 than comparator treatments when considered at their list price, and therefore ustekinumab could be considered a cost-effective option. It was acknowledged that discounted prices may also be available for comparators and that the total cost of the treatments should be taken into account when deciding which one to use in clinical practice[10].

Ulcerative colitis

The company used a model with a hybrid structure; the induction phase was modelled using a decision tree and the maintenance phase was modelled using a Markov structure.[9] The model evaluated treatments over a lifetime horizon and used the commercially agreed discounted price for ustekinumab and list price of comparators. The company provided cost-effectiveness estimates for 2 subgroups (failed conventional therapy with or without prior exposure to a biological), but not for

the overall population which included patients whose disease was being controlled with the long-term use of corticosteroids. When ustekinumab was compared with vedolizumab, for all scenarios investigated and irrespective of the source of utilities, the ICERs were below £30,000 per QALY gained for both patient subgroups. The NICE committee agreed that ustekinumab is likely to be cost-effective in people who would otherwise have vedolizumab[9].

Budget impact

Costs are based on a required induction dose administered intravenously as a weight-based dose of approximately 6 mg per kg up to a recommended dose of 260 mg for patients weighing 55kg or less[4]. Intravenous induction dosing is assumed to be a single treatment and some vial wastage would be expected for patients with lower weights; given approximate average weights of 3kg to 64kg for a child from birth to 17 years[44], the number of vials need for induction of treatment would range from 1 to 3. The first recommended subcutaneous administration of 90 mg ustekinumab (Stelara®) should take place at week 8 after the intravenous dose. After this, dosing is recommended every 8 - 12 weeks. Based on the 8-weekly dosing from Dayan et al, this equates to six subcutaneous injections annually[5]. The commercially discounted price agreed between the company and NHS Wales for ustekinumab (Stelara®) is [commercial in confidence text removed] for 130 mg vial and [commercial in confidence text removed] for 90 mg pre-filled syringe.

Using an assumed average weight of 50kg (the average weight of a 14-year-old child which was the average in the studies used in this report), calculated treatment costs for ustekinumab (Stelara®) are presented in Table 1.

Table 1. Estimated annual costs for ustekinumab per patient in Wales*

	Treatment cost	Administration cost¶	Total annual cost per patient
Induction ustekinumab (260 mg) †	¶¶	¶¶	¶¶
Maintenance ustekinumab (90 mg) **	¶¶	¶¶	¶¶
Total annual cost per patient			¶¶

*This assumes patient weighs 50kg, average weight of a 14-year-old receiving the recommended dose of 260 mg.
†Assumes 2x130 mg vials used, confidential NHS Wales contract price plus VAT
¶2020-2021 National Schedule of Reference Costs: assumes 'Deliver Simple Parenteral Chemotherapy at first attendance' (HRG code SB12Z)
**Assumes maintenance dose every 8 weeks (annual total of 6)
¶¶ commercial in confidence figure removed

Table 2 shows the estimated annual acquisition costs. Based on consultation with clinical experts, 22 patients in Wales are estimated to start treatment each year with all assumed to have at least 12 months of treatment. A third of patients are estimated to discontinue ustekinumab per year after the initial first year of treatment.

Table 2. Estimated annual acquisition costs for ustekinumab for CYP in Wales

	Year 1	Year 2	Year 3
Number of patients	22*	37†	47¶
Total annual costs for ustekinumab	¶¶	¶¶	¶¶

*Assumes 22 patients will have 12 months of treatment
†Assumes 15 patients continue from year 1 and 22 new patients will commence treatment in year 2, all having 12 months of treatment
¶Assumes 25 patients continue from year 2 and 22 new patients will commence treatment in year 3, all having 12 months of treatment
¶¶ commercial in confidence figure removed

Discussion

- The recommended dosing interval between subcutaneous injections is 12-weekly, however, based on available study data, an 8-weekly dosing interval was used to estimate the budget impact. Therefore, a lower budget impact than predicted is plausible.
- The budget impact is likely to be lower for year one than estimated given that over half (12) of the estimated number of patients are already receiving treatment through IPFR.
- There are no data available for discontinuation rates of ustekinumab in the longer term. Budget impact calculations have been based on the assumption that all patients will receive treatment for at least 12 months after initiation with a third subsequently discontinuing treatment in year 2 and year 3. The NICE recommendation for its use in adults with Crohn's disease states that ustekinumab should be given until treatment failure (including the need for surgery) or until 12 months after the start of treatment, whichever is shorter; it is plausible that some CYP will also discontinue treatment within 12 months of initiation, reducing the budget impact. However, until further data are available, it is difficult to estimate the proportion of CYP discontinuing treatment throughout the 3-year timeframe. Hence, budget impact predictions are subject to uncertainty.
- Patient numbers do not account for those reaching the age of 18 years and moving into adult services for treatment with ustekinumab in line with NICE recommendations. However, it is reasonable to expect that the number of paediatric patients will remain relatively stable over time and, therefore, the impact this will have on estimated cost is minimal.
- Administration costs were not included except for the cost of administering ustekinumab infusion as other associated treatments are expected to be part of standard of care for the patients in this cohort. It is assumed that subcutaneous doses can be given at home by the CYP, their parent or carer.
- Additional screening and monitoring and adverse event costs are also excluded from the budget impact.

Additional factors

Prescribing unlicensed medicines

Ustekinumab is not licensed to treat this indication and is therefore prescribed ’off label’. Prescribers should consult their relevant guidelines on prescribing unlicensed medicines before any off-label medicines are prescribed.

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