NHS England

Evidence review: Vedolizumab for children and young people with refractory ulcerative colitis

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The content of this evidence review was up-to-date in month year. See summaries of product characteristics (SmPCs), British national formulary (BNF), the British national formulary for children (BNFc) or the MHRA or NICE websites for up-to-date information.

Key points

Regulatory status: Vedolizumab (Entyvio, Takeda UK Ltd) is licensed in adults for treating moderately to severely active ulcerative colitis in people who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour necrosis factor-alpha (TNF-alpha) inhibitor. It is administered as an intravenous infusion. Vedolizumab is not licensed for treating ulcerative colitis in children and young people under 18 years and use for this indication is off-label.

Overview

This review considers the best available evidence for the use of vedolizumab (alone or in combination with other medicines) in children and young people with refractory ulcerative colitis. For the purpose of this evidence review refractory ulcerative colitis is defined as ulcerative colitis 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.

Ulcerative colitis is a chronic, inflammatory condition which affects the bowel. Symptoms of active disease can include bloody diarrhoea, an urgent need to defaecate and abdominal pain. Ulcerative colitis is a lifelong disease that is associated with significant morbidity. It can also affect a person's social and psychological wellbeing, particularly if poorly controlled. Typically, it has a relapsing–remitting pattern and the aim of treatment is to manage symptoms and induce and maintain remission.

The evidence review focuses on a multi-centre retrospective, uncontrolled observational study in Europe and Israel (Ledder et al. 2017). The study included 64 children and young people aged 2 to 18 years, mean age 14.5 years, with a diagnosis of ulcerative colitis (n=33), unclassified inflammatory bowel disease (n=8), or Crohn's disease (n=23). Results were presented for the combined group of 41 children and young people with ulcerative colitis and unclassified inflammatory bowel disease.

The results of the study, alongside the evidence for the effectiveness of this treatment in adults, suggests that vedolizumab may be clinically effective in some children and young people with ulcerative colitis in whom conventional pharmacological treatment and TNF-alpha inhibitors have been ineffective. Fifteen (37%) children and young people with ulcerative colitis or unclassified inflammatory bowel disease were in steroid-free remission at week 14 and 12 of these were still in steroid-free remission at week 22. Steroid use decreased from 69% (27/39) of children and young people at baseline to 26% (9/34) at week 14. The authors also reported a reduction in median dose of corticosteroid at week 14 compared with baseline, 12.5 mg at week 14 compared with 25 mg at baseline.

There were no serious adverse events and 3 non-serious adverse events. One non-serious adverse event, intractable itch, resulted in vedolizumab being discontinued and the itch resolved upon discontinuation. It is difficult to draw firm conclusions on the safety of vedolizumab in children and young people because of the limited data reported and small size of the study.

The optimal treatment regimen for vedolizumab for children and young people with ulcerative colitis is unclear because there were no studies identified that compared different treatment regimens. Following an induction course, most children and young people in the included study received the adult dose of 300 mg as maintenance infusions every 8 weeks. A small number received infusions every 4 weeks and some received a lower dose of 150 to 250 mg. Some children and young people in the study also took steroids or thiopurines or methotrexate in combination with vedolizumab and it is not possible to say whether this affected the outcomes.

There was no comparator arm in this study therefore it is not possible to say how vedolizumab compares to other treatments. Children and young people with ulcerative colitis and unclassified inflammatory bowel disease were not reported separately, therefore it is not possible to distinguish between the role of vedolizumab in ulcerative colitis and in unclassified inflammatory bowel disease which may affect the applicability of the findings. The results of the study should be interpreted with caution because it was small, uncontrolled and subject to bias and confounding. No studies were identified which evaluated the cost-effectiveness of vedolizumab for the management of ulcerative colitis in children and young people.

Contents

1. Introduction

Background and current guidance

Ulcerative colitis is a chronic, inflammatory condition which affects the bowel. The cause of ulcerative colitis is unknown and it can develop at any age, although peak incidence is between the ages of 15 and 25 years. Ulcerative colitis usually affects the rectum and the colon proximal to the rectum. Symptoms of active disease can include bloody diarrhoea, an urgent need to defaecate and abdominal pain. Ulcerative colitis is a lifelong disease that is associated with significant morbidity. It can also affect a person's social and psychological wellbeing, particularly if poorly controlled. Typically, it has a relapsing–remitting pattern and the aim of treatment is to manage symptoms and induce and maintain remission (NICE clinical guideline: ulcerative colitis management).

The NICE guideline includes advice on pharmacological treatment to induce remission in children, young people and adults with ulcerative colitis. Topical or oral aminosalicylates should be considered first line, followed by topical or oral corticosteroids for those in whom aminosalicylates are not suitable or do not work. Topical and oral aminosalicylates and oral corticosteroids can be given in combination depending on the severity and location of the inflammation. If there is an inadequate response to oral prednisolone after 2 to 4 weeks, oral tacrolimus can be considered. This guideline, including the recommendations on pharmacological treatment, is currently being updated.

NICE has also published technology appraisal guidance on infliximab, adalimumab and golimumab for treating moderately to severely active ulcerative colitis after the failure of conventional therapy. This includes recommendations on the use of infliximab in children and young people aged 6 to 17 years.

A NICE technology appraisal guidance was published for the use of vedolizumab in adults with moderately to severely active ulcerative colitis who have had an inadequate response with, or lost response to, or were intolerant to either conventional therapy or a tumour necrosis factor (TNF)‑alpha inhibitor.

This evidence review considers the best available evidence for vedolizumab for treating children and young people with refractory ulcerative colitis. For the purpose of this evidence review refractory ulcerative colitis is defined as ulcerative colitis 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.

Product overview

Mode of action

Vedolizumab is a monoclonal antibody that reduces gastrointestinal inflammation in people with ulcerative colitis. Vedolizumab is a gut-selective immunosuppressive biologic that binds specifically to the α4β7 integrin. The α4β7 integrin is expressed on a subset of memory T helper lymphocytes which move into the gastrointestinal (GI) tract and cause inflammation that is characteristic of ulcerative colitis (vedolizumab [Entyvio]: summary of product characteristics).

Regulatory status

Vedolizumab is licensed for:

- Adults with moderately to severely active ulcerative colitis who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a TNF-alpha inhibitor.
- Adults with moderately to severely active Crohn's disease who have had an inadequate response with, lost response to, or are intolerant to either conventional therapy or a tumour TNF-alpha inhibitor.

Vedolizumab is not licensed for the treatment of ulcerative colitis in children and young people under 18 years, therefore use of vedolizumab in this age group is off-label.

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 vedolizumab is appropriate outside its authorised indications. Supporting information and advice is also available from the GMC.

Dosing information

The recommended adult dose of vedolizumab is 300 mg administered by intravenous infusion at 0, 2 and 6 weeks and then every 8 weeks thereafter. People who have experienced a decrease in their response may increase the dosing frequency to every 4 weeks (summary of product characteristics [SmPC]).

There is no recommended dose for vedolizumab in children and young people in the SmPC as this is an off-label use of the medicine. A range of doses have been used in the study; these are outlined in the summary of included studies section of this evidence summary.

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 vedolizumab as a fourth line treatment compared with treatment without vedolizumab for children and young people with refractory ulcerative colitis
2. What is the safety of vedolizumab as a fourth line treatment compared with treatment without vedolizumab for children and young people with refractory ulcerative colitis?
3. What is the cost-effectiveness of vedolizumab as a fourth line treatment compared with treatment without vedolizumab for children and young people with refractory ulcerative colitis?

The searches for evidence to support the use of vedolizumab in children and young people with refractory ulcerative colitis 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 the included study

This evidence review includes 1 retrospective observational study (Ledder et al. 2017).

A summary of the included study is shown in table 1 (see the evidence summary tables for full details).

Table 1 Summary of the included study

Study	Population	Intervention and comparison	Primary outcome(s)
Ledder et al. 2017 Retrospective, uncontrolled observational study from 19 centres in Europe and Israel. Median follow-up (of those with ulcerative colitis or unclassified inflammatory bowel disease): 24 weeks (range 6 to 116 weeks).	Children and young people aged 2 to 18 years, mean age 14.5 years, diagnosed with ulcerative colitis (n=33), Crohn's disease (n=23), or unclassified inflammatory bowel disease (n=8) and started on vedolizumab for any reason. At baseline[1]: 54% (22/51) were female, mean (SD) age at diagnosis was 11.4 (±3.5) years and median (inter-quartile range [IQR]) PUCAI was 45 (30 to 65). Ulcerative colitis was classed as	Vedolizumab (with standard treatment), 81% (52/64) received a dose of 300 mg by intravenous infusion and 19% (12/64) received a lower dose of 150 to 250 mg or 3.6 to 10.3 mg/kg. Four of the 12 who had the lower dose subsequently had their dose increased. Following a 6 week induction course, 88% (56/64) of children and young people received infusions every 8 weeks, and 12% (8/64) received infusions every 4 weeks from the outset. Seven of those receiving infusions every 8 weeks increased to infusions every 4 to 6 weeks because of poor response. Three of these had ulcerative colitis.	Steroid-free remission at 14 weeks.

	severe in 37 (90%) and 8 (20%) had extra-intestinal manifestations. All children and young people had previously had TNF-alpha inhibitors before starting vedolizumab.	No comparator.	

Abbreviations: SD, standard deviation; IQR, inter-quartile range; PUCAI, paediatric ulcerative colitis activity index; UCEIS, ulcerative colitis endoscopic index of severity; TNF, tumour necrosis factor.

[1] Baseline population characteristics are reported for children and young people with ulcerative colitis or unclassified inflammatory bowel disease only. Results are reported for children and young people with ulcerative colitis or unclassified inflammatory bowel disease only unless stated otherwise.

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 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 review does not provide any data comparing the clinical effectiveness and safety of vedolizumab with any other treatment for the management of ulcerative colitis in children and young people. All outcomes in this evidence review are graded C.

Clinical effectiveness

This section considers whether vedolizumab is clinically effective in children and young people with refractory ulcerative colitis. Results are presented for the combined group of 41 children and young people with ulcerative colitis (33 participants) and unclassified inflammatory bowel disease (8 participants). The results for stool calprotectin and endoscopy were for a subgroup of children and young people with ulcerative colitis or inflammatory bowel disease.

Remission and clinical response

In the retrospective observational study by Ledder et al. (2017), steroid-free remission was observed in 37% (15/41) children and young people at 14 weeks. At 22 weeks steroid-free remission was seen in 34% (14/41). Three children and young people who were in remission

at week 14 were not in remission at week 22. Two children and young people who were not in remission at week 14 were in remission at week 22.

Steroid use

Ledder et al. (2017) reported that 69% (27/39) of children and young people used corticosteroids at baseline compared with 26% (9/34) at week 14. The authors also reported a reduction in median dose of corticosteroid at week 14 compared with baseline, 12.5 mg (IQR 10 to 20 mg) at week 14 compared with 25 mg (IQR 20 to 40 mg) at baseline. No statistical analysis was reported.

Surgery

Ledder et al. (2017) found that 15% (6/41) of children and young people needed colectomy during the follow-up period (median 24 months). Only one participant had had surgery before starting vedolizumab.

Stool calprotectin

Stool calprotectin was measured in 20/41 children and young people at baseline and follow-up. There was a median decrease in calprotectin levels of 518 micrograms/g (IQR 202 to 2,327 mcg/g). Deep remission, defined as clinical remission with stool calprotectin <100 micrograms/g, was seen in 30% (6/20) of children and young people in whom stool calprotectin was measured.

Endoscopic assessment

Colonoscopic assessment was carried out for 13/41 children and young people at baseline and follow-up. Two of 13 (15%) achieved mucosal healing at follow-up (defined as an ulcerative colitis endoscopic index of severity [UCEIS] score of zero).

Safety and tolerability

This section considers whether vedolizumab is safe in children and young people with refractory ulcerative colitis. Results are presented for the combined group of 64 children and young people with ulcerative colitis (n=33), Crohn's disease (n=23) or unclassified inflammatory bowel disease (n=8).

No serious medicines-related adverse events were reported and 3 minor adverse events were reported (n=64). These were: otitis externa with periorbital oedema, intractable itch, and mild shortness of breath. Discontinuation of vedolizumab was only necessary in the young person who developed intractable itch. It is not possible to say if these adverse events were in children and young people with ulcerative colitis or Crohn's disease because the safety results were not reported separately.

Vedolizumab was discontinued in 22% (14/64) of children and young people in the follow-up period. Most discontinuations (13/14) were because of poor response. As described above 1 participant discontinued treatment because of intractable itch, which resolved when vedolizumab was stopped. It is not possible to say how many discontinuations were in children and young people with ulcerative colitis because the results for ulcerative colitis and Crohn's disease were not reported separately.

Adverse effect information from the summary of product characteristics (SmPC) derived from use in adults can also be used to predict the type of adverse effects likely to be seen in children. Vedolizumab is contraindicated in people with active severe infections for example, active tuberculosis. The SmPC on vedolizumab also includes special warnings and precautions for use including: potential increased risk of infection and malignancy, hypersensitivity reactions, administration of vaccines, and prior use of biologics.

Based on clinical studies and post-marketing experience with vedolizumab, the following adverse reactions are listed as being very common (incidence greater than 1 in 10): nasopharyngitis, headache and arthralgia. Other adverse effects seen commonly (incidence between 1 in 10 and 1 in 100) include upper respiratory tract infections, paraesthesia, hypertension, cough, gastrointestinal effects such as dyspepsia and nausea, as well as pyrexia, fatigue and muscle pain. For more information on these see the SmPC.

Cost-effectiveness

This section considers whether vedolizumab is cost effective in children and young people with refractory ulcerative colitis.

No studies were identified during literature searches (see search strategy for full details) that compared the cost-effectiveness of vedolizumab with no treatment or standard treatment in children or young people with ulcerative colitis. The study included in this evidence review does not include an outcome investigating cost-effectiveness.

5. Discussion

Evidence strengths and limitations

The evidence presented in this review is based on data from 1 retrospective, uncontrolled observational study in 64 children and young people with Crohn's disease, ulcerative colitis or unclassified inflammatory bowel disease from 19 centres in Europe and Israel. The most important limitation of the evidence is that there are no comparative studies that have investigated the role of vedolizumab in treating ulcerative colitis in children and young people. The included study was small, did not include a control group and its retrospective, observational design makes it subject to a higher risk of bias and confounding. Because of this the results should be interpreted with caution.

Another limitation of the evidence is that children and young people with ulcerative colitis and unclassified inflammatory bowel disease were not reported separately in the study by Ledder et al. (2017). Although most children and young people had a diagnosis of ulcerative colitis in this group (33/41, 80%), it is not possible to distinguish between the role of vedolizumab in ulcerative colitis and in unclassified inflammatory bowel disease which may affect the applicability of the findings to a population with ulcerative colitis only. In addition, adverse events and treatment discontinuations were provided for the whole study group which also included children and young people with Crohn's disease.

The mean age of the entire cohort was 14.5 years at baseline. However, the age range was not reported and the mean age in the ulcerative colitis group was not reported separately.

Therefore it is not possible to know whether the findings are generalisable to children and young people of other ages between 2 and 17 years with refractory ulcerative colitis.

Colonoscopic assessment and stool calprotectin were only measured for a subset of participants. Although there is no reason to believe that these participants differ from the rest of the cohort, it is not possible to know as the baseline characteristics were not reported separately.

6. Conclusion

Ulcerative colitis is a lifelong disease that is associated with significant morbidity. It can also affect a person's social and psychological wellbeing, particularly if poorly controlled. Typically, it has a relapsing–remitting pattern and the aim of treatment is to manage symptoms and induce and maintain remission.

The study included in this evidence review, although being small, uncontrolled and of relatively poor quality, suggests that vedolizumab may improve outcomes for some children and young people with refractory ulcerative colitis. Over a third of participants were in steroid-free remission after a 14 week period. A similar number maintained remission at 22 weeks with 3 participants losing remission and 2 gaining remission between weeks 14 and 22. The study also suggests that vedolizumab may reduce steroid use and steroid dose.

No serious adverse events were reported and few non-serious adverse events were reported. Only one adverse event resulted in vedolizumab being discontinued. However, because of the small size of the study and the limited follow-up period, it is not possible to draw firm conclusions on the safety of vedolizumab in children and young people with refractory ulcerative colitis.

The optimal treatment regimen for vedolizumab for children and young people with ulcerative colitis is unclear because there were no studies that compared different treatment regimens. In the study included, most children and young people received the adult dose of 300 mg and the rest received 150 mg to 250 mg. The number of children and young people in each group were small and the outcomes for these groups were not reported separately. Some children and young people in the study also took steroids, thiopurines or methotrexate in combination with vedolizumab and, although use of these decreased over the follow-up period, it is not possible to say whether this affected the outcomes.

This study, alongside the evidence for the effectiveness of this treatment in adults, provides some promising evidence for the clinical effectiveness and safety of vedolizumab in children and young people with refractory ulcerative colitis. However, it provides no comparison with other treatments and the study size and design leave it open to bias and confounding. The study also includes children and young people with unclassified inflammatory bowel disease which may affect the applicability of the findings to a population with ulcerative colitis only.

7. Evidence summary table

Use of vedolizumab plus standard treatment to treat children and young people with refractory ulcerative colitis – no comparator in study							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
Study reference 1: Ledder et al. 2017							
P1, retrospective non-comparative observational study from 19 centres in Europe and Israel. Median follow-up (of those with ulcerative colitis or unclassified inflammatory bowel disease): 24 weeks (range 6 to 116 weeks).	Children and young people aged 2 to 18 years, mean age 14.5 years, diagnosed with Crohn's disease (n=23), ulcerative colitis (n=33) or unclassified inflammatory bowel disease (n=8) and started on vedolizumab for any reason. Baseline population characteristics are reported for children and young people with ulcerative colitis and unclassified inflammatory bowel disease together. At baseline: 54% (22/51) were female, mean (SD) age at diagnosis was 11.4 (±3.5) years and median (IQR) PUCAI 45 (30 to 65). All children and young people had previously had	Vedolizumab (with standard treatment), 81% (52/64) received a dose of 300 mg by intravenous infusion and 19% (12/64) received a lower dose of 150 to 250 mg or 3.6 to 10.3 mg/kg. Four of the 12 who had the lower dose subsequently had their dose increased. Following a 6 week induction course, 88% (56/64) of children and young people received infusions every 8 weeks, and 12% (8/64) received infusions every 4 weeks from the outset. Seven of those receiving infusions every 8 weeks increased to infusions every 4 to 6 weeks because of poor response. Three of these had ulcerative colitis.	Primary Clinical effectiveness	Steroid-free remission at 14 weeks	Steroid-free remission (defined as a PUCAI < 10) at 14 weeks was observed in 37% (15/41) children and young people.	6/10 The research questions are stated but, as the study is an observational, uncontrolled study it is insufficient to reliably answer the questions. The results can only be considered hypothesis generating and cannot support any definitive conclusions.	Direct study focusing on people with the indication and characteristics of interest.
			Secondary Clinical effectiveness	Steroid-free remission at 22 weeks	Steroid-free remission at 22 weeks was observed in 34% (14/41) children and young people. Three children and young people who were in remission at week 14 were not in remission at week 22, 2 children and young people who were not in remission at week 14 were in remission at week 22.		
			Secondary Clinical effectiveness	Steroid-free remission at last follow-up (median 24 weeks)	Steroid-free remission at last follow-up was observed in 39% (16/41) children and young people		
			Secondary Clinical effectiveness	Surgical resection	Fifteen percent (6/41) children and young people needed surgical resection during the follow-up period.		
			Secondary	Steroid use at 14 weeks	Steroid use was 26% (9/34) at week 14 compared with 69% (27/39) at baseline.		

Use of vedolizumab plus standard treatment to treat children and young people with refractory ulcerative colitis – no comparator in study							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
	TNF-alpha inhibitors before starting vedolizumab. All results are reported for the ulcerative colitis and unclassified inflammatory bowel disease cohort only as a combined group (41 participants in total) with the exception of some safety results which are reported for the whole cohort. This includes children and young people with Crohn's disease as outcomes were not reported separately in the paper.		Clinical effectiveness		No statistical analysis was reported. The median steroid dose at baseline was 25 mg (IQR 20 to 40 mg) compared with 12.5 mg (10 to 20 mg) at week 14.		
			Secondary Clinical effectiveness	Mucosal healing	Thirteen children and young people with ulcerative colitis or unclassified inflammatory bowel disease had baseline and follow-up colonoscopic assessment, of these 15% (2/13) achieved mucosal healing (defined as a UCEIS score of zero).		
			Secondary Clinical effectiveness	Stool calprotectin levels	Stool calprotectin was measured in 20 children and young people with ulcerative colitis or unclassified inflammatory bowel disease at baseline and follow-up. There was a median (IQR) decrease in calprotectin levels of 518 micrograms/g (202 to 2,327 mcg/g). Deep remission, defined as clinical remission with stool calprotectin <100 mcg/g, was achieved by 30% (6/20) of children and young people in whom stool calprotectin was measured.		
			Secondary Safety	Discontinuation of vedolizumab	Vedolizumab was discontinued in 22% (14/64) of children and young people in the follow-up period. Most discontinuations (13/14) were because of poor response and 1 young person		

Use of vedolizumab plus standard treatment to treat children and young people with refractory ulcerative colitis – no comparator in study							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
					discontinued treatment because of intractable itch, which resolved when vedolizumab was stopped. These findings include children and young people with Crohn's disease.		
			Secondary Safety	Serious adverse events	No serious drug related adverse events were reported		
			Secondary Safety	Mild adverse events	Three mild adverse events were reported out of the entire cohort which included children and young people with Crohn's disease. These included: • one 13 year old female who developed otitis externa and periorbital oedema after the first and second infusions which resolved and she remained on treatment, • one 17 year old female who developed intractable itch after the 1st infusion and vedolizumab was stopped, • one 17 year old female who developed mild shortness of breath during the 4th infusion which improved with antihistamine medication and a slower infusion rate. Vedolizumab was continued,		

Use of vedolizumab plus standard treatment to treat children and young people with refractory ulcerative colitis – no comparator in study							
Study Design	**Population characteristics**	**Intervention**	**Outcome measure type**	**Outcome measures**	**Results**	**Quality of Evidence Score**	**Applicability**
					but stopped later because of poor efficacy.		
Critical appraisal summary: This is a retrospective non-comparative observational study, which is susceptible to bias, confounding and other methodological problems. Outcome assessment was not blinded. The focus of the study was to investigate the short-term effectiveness and safety of vedolizumab in children and young people with inflammatory bowel disease.							

8. Grade of evidence table

Use of vedolizumab plus standard treatment to treat children and young people with refractory ulcerative colitis – no comparator in study					
Outcome Measure	**Reference**	**Quality of Evidence Score**	**Applicability**	**Grade of Evidence**	**Interpretation of Evidence**
Steroid-free remission at 14 weeks	Ledder et al. 2017	6/10	Direct study	C	This outcome looks at the steroid-free remission rates 14 weeks after starting vedolizumab. Steroid-free remission at 14 weeks was observed in 37% (15/41) children and young people with ulcerative colitis or unclassified inflammatory bowel disease. These results suggest that vedolizumab may be effective at inducing remission at 14 weeks in some children and young people with refractory ulcerative colitis or unclassified inflammatory bowel disease. 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 confounding, is difficult to interpret and cannot support firm conclusions. The results also included children with unclassified inflammatory bowel disease which may affect the applicability of the findings.

Steroid-free remission at 22 weeks	Ledder et al. 2017	6/10	Direct study	C	This outcome looks at the steroid-free remission rates 22 weeks after starting vedolizumab. Steroid-free remission at 22 weeks was observed in 34% (14/41) children and young people. Three children and young people who were in remission at week 14 were not in remission at week 22, 2 children and young people who were not in remission at week 14 were in remission at week 22. These results suggest that for most children and young people whose ulcerative colitis or unclassified inflammatory bowel disease was in remission by week 14, vedolizumab was effective in maintaining remission to week 22. However, 3 children and young people did not remain in remission. Vedolizumab was effective in inducing remission after 22 weeks in a small number of children and young people who were not in remission by week 14. See above for limitations of the study.
Steroid-free remission at last follow-up (median 24 weeks)	Ledder et al. 2017	6/10	Direct study	C	This outcome looks at the steroid-free remission rates at the last follow-up date. Steroid-free remission at last follow-up was observed in 39% (16/41) children and young people. These results suggest that, after a median follow-up of 24 weeks, vedolizumab was effective in maintaining remission in the same proportion of children and young people who achieved remission at week 14. The authors did not report whether these were the same participants so it is not possible to say whether those who initially achieved remission were still in remission at the last follow-up date. See above for limitations of the study.
Surgical resection	Ledder et al. 2017	6/10	Direct study	C	This outcome looks at the number of children and young people who needed surgical resection over the follow-up period (median 24 months). Fifteen percent (6/41) children and young people needed surgical resection during the follow-up period. These results suggest that despite vedolizumab treatment, some children and young people will still need surgery. The non-comparative study design means it is not possible to say whether this is more or less than the number who would need surgery without vedolizumab treatment. See above for limitations of the study.

Steroid use at 14 weeks	Ledder et al. 2017	6/10	Direct study	C	This outcome looks at the number of children and young people using corticosteroids 14 weeks after starting vedolizumab. Steroid use was 26% (9/34) at week 14 compared with 69% (27/39) at baseline. These results suggest that vedolizumab use reduces steroid use. No statistical analysis was reported. See above for limitations of the study. In addition, steroid use was only reported for 34 of the 41 participants at week 14. The authors did not report any missing data analysis.
Mucosal healing	Ledder et al. 2017	6/10	Direct study	C	This outcome looks at mucosal healing in a subgroup of participants. This was defined using an endoscopy score called the UCEIS. Thirteen children and young people had both baseline and follow-up colonoscopic assessment. Two of 13 (15%) achieved mucosal healing at follow-up. These results suggest that vedolizumab use led to mucosal healing in a small number of children and young people in whom this outcome was measured. See above for limitations of the study.
Stool calprotectin levels	Ledder et al. 2017	6/10	Direct study	C	This outcome looks at stool calprotectin levels at baseline and at follow-up. Stool calprotectin was measured in 20 children and young people at baseline and follow-up. There was a median decrease in calprotectin. Deep remission, defined as clinical remission with stool calprotectin <100 micrograms/g, was achieved by 30% (6/20) of children and young people in whom stool calprotectin levels were measured. These results suggest that vedolizumab may decrease stool calprotectin levels, a marker of intestinal inflammation. See above for limitations of the study.

Discontinuation of vedolizumab	Ledder et al. 2017	6/10	Direct study	C	This outcome looks at the number and reasons for discontinuation of vedolizumab in children and young people with ulcerative colitis, unclassified inflammatory bowel disease or Crohn's disease. Vedolizumab was discontinued in 22% (14/64) of children and young people throughout the follow-up period. The median (average) discontinuation time was 14 weeks. All but one discontinuation was because of poor response and 1 discontinuation was because of chronic itch which stopped when vedolizumab was stopped. These results suggest that the main reason for discontinuing vedolizumab was because of poor response and that vedolizumab had to be discontinued in at least a fifth of participants. See above for limitations of the study.
Serious adverse events	Ledder et al. 2017	6/10	Direct study	C	This outcome looks at the number of serious adverse events over the follow-up period (median 24 months) in both children and young people with ulcerative colitis, unclassified inflammatory bowel disease or Crohn's disease. There were no reported serious drug related adverse events. See above for limitations of the study. In addition, it is not possible to know how the reduction in concomitant medicine use may affect this outcome and it is not possible to know what adverse events would present over a longer time period or in a larger group.
Mild adverse events	Ledder et al. 2017	6/10	Direct study	C	This outcome looks at the number and type of non-serious adverse events over the follow-up period (median 24 months) in both children and young people with ulcerative colitis, unclassified inflammatory bowel disease or Crohn's disease. In total, 3 participants out of 64 reported non-serious adverse events. These were: otitis externa with periorbital oedema, intractable itch, and mild shortness of breath. Discontinuation of vedolizumab was only necessary in the young person who developed intractable itch. It is not possible to say if these adverse events were in children and young people with ulcerative colitis or Crohn's disease because the safety results were not reported separately. The adverse events reported in the study are similar to those listed in the summary of product characteristics (SmPC) for the licensed indication in adults with infusion-related reactions and hypersensitivity reactions, such as bronchospasm, being reported and skin and subcutaneous tissue disorders being common. See above for limitations of the study. In particular it is not possible to know how concomitant medicine use may affect this outcome and it is not possible to know what adverse events would present over a longer time period.

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 ulcerative colitis who have failed anti- TNF α treatment
I – Intervention Which intervention, treatment or approach should be used?	Vedolizumab (with background treatment as reported)
C – Comparison What is/are the main alternative/s to compare with the intervention being considered?	No vedolizumab

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
	  o complications from disease progression and exacerbation
	• Paediatric Quality of Life, school performance, low mood, depression and emotional issues.
	• Safety of vedolizumab compared to standard treatment, including severe adverse effects of:
	  o vedolizumab
	  o standard treatment, e.g. steroids or surgery.
	• Mortality
	
	Important to decision-making:

	• Reduction in disease activity, for example:
	  o Paediatric Ulcerative Colitis Activity Index
	  o Markers of inflammation in blood, and stools such as faecal calprotectin
	  o Endoscopic findings of active disease
	• The reduction/ addition of hospital appointments, and its effect on children's social functioning, parent's work commitment
	• Cost-effectiveness of vedolizumab

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: Medline ALL including daily update. 1946 to November 26, 2018
Search date: 27th November 2018
Number of results retrieved: 23
Search strategy:

1 vedolizumab.ti,ab. (529)
2 entyvio.ti,ab. (8)
3 MLN0002.ti,ab. (9)
4 (mln adj "0002").ti,ab. (1)
5 ldp02.ti,ab. (0)
6 (ldp adj "02").ti,ab. (8)
7 or/1-6 (536)
8 Colitis, Ulcerative/ (32362)
9 colitis.ti,ab. (58088)
10 proctocolitis.ti,ab. (400)
11 colorectitis.ti,ab. (9)
12 or/8-11 (65772)
13 adolescent/ or child/ or child, preschool/ (2829924)
14 child*.ti,ab,jn. (1278255)
15 boy*.ti,ab. (142694)
16 girl*.ti,ab. (137063)
17 school*.ti,ab. (254919)
18 adolescen*.ti,ab. (246033)
19 juvenil*.ti,ab. (75165)
20 youth*.ti,ab. (63921)
21 teen*.ti,ab. (27921)
22 pubescen*.ti,ab. (2124)
23 pediatric*.ti,ab,jn. (384131)
24 paediatric*.ti,ab,jn. (69444)
25 Pediatrics/ (50207)
26 peadiatric*.ti,ab. (36)
27 "off license".ti,ab. (51)
28 "off label".ti,ab. (6417)
29 "Off-Label Use"/ (2110)
30 or/13-29 (3557313)
31 7 and 12 and 30 (23)

Database: Medline in-process
Platform: Ovid
Version: 26th November 2018
Search date: 27th November 2018
Number of results retrieved: 3
Search strategy: as per Medline

Database: Medline epubs ahead of print
Platform: Ovid
Version: November 26th 2018
Search date: 27th November 2018
Number of results retrieved: 1
Search strategy: as per Medline

Database: Embase
Platform: Ovid
Version: 1974 to November 21st 2018
Search date: 27th November 2018
Number of results retrieved: 51
Search strategy:

1 vedolizumab.ti,ab. (1524)
2 entyvio.ti,ab. (25)
3 MLN0002.ti,ab. (28)
4 (mln adj "0002").ti,ab. (1)
5 ldp02.ti,ab. (1)
6 (ldp adj "02").ti,ab. (25)
7 vedolizumab/ (2179)
8 or/1-7 (2233)
9 ulcerative colitis/ (64240)
10 colitis.ti,ab. (89160)
11 colorectitis.ti,ab. (2)
12 proctocolitis.ti,ab. (532)
13 or/9-12 (104851)
14 exp juvenile/ (3118769)
15 child*.ti,ab,jn. (1563575)
16 boy*.ti,ab. (186760)
17 girl*.ti,ab. (178977)
18 school*.ti,ab. (304304)
19 adolescen*.ti,ab. (316052)
20 juvenil*.ti,ab. (88504)
21 youth*.ti,ab. (76164)
22 teen*.ti,ab. (36977)
23 pubescen*.ti,ab. (2463)
24 pediatric*.ti,ab,jn. (537122)
25 paediatric*.ti,ab,jn. (111036)
26 Pediatrics/ (69127)
27 peadiatric*.ti,ab. (172)
28 "off license".ti,ab. (116)
29 "off label".ti,ab. (11179)
30 "off label drug use"/ (7202)
31 or/14-30 (3883955)
32 8 and 13 and 31 (113)
33 limit 32 to (conference abstract or conference paper or "conference review" or editorial or letter or tombstone) (62)
34 32 not 33 (51)

Database: Cochrane Library – incorporating Cochrane Database of Systematic Reviews (CDSR); DARE; CENTRAL; HTA database; NHS EED
Platform: Wiley
Version:
CDSR –Issue 11 of 12, November 2018
CENTRAL – Issue 11 of 12, November 2018
Search date: 27th November 2018
Number of results retrieved: CDSR – 0; CENTRAL – 6

ID	Search
#1	vedolizumab:ti,ab
#2	entyvio:ti,ab
#3	MLN0002:ti,ab
#4	(mln adj "0002"):ti,ab
#5	ldp02:ti,ab
#6	(ldp adj "02"):ti,ab
#7	{or #1-#6}
#8	MeSH descriptor: [Colitis, Ulcerative] this term only
#9	colitis:ti,ab
#10	colorectitis:ti,ab
#11	proctocolitis:ti,ab
#12	{or #8-#11}
#13	MeSH descriptor: [Adolescent] this term only
#14	MeSH descriptor: [Child] this term only
#15	MeSH descriptor: [Child, Preschool] this term only
#16	child*:ti,ab,so
#17	boy*:ti,ab
#18	girl*:ti,ab
#19	school*:ti,ab
#20	adolescen*:ti,ab
#21	juvenil*:ti,ab
#22	youth*:ti,ab
#23	teen*:ti,ab
#24	pubescen*:ti,ab
#25	pediatric*:ti,ab,so
#26	paediatric*:ti,ab,so
#27	MeSH descriptor: [Pediatrics] this term only
#28	peadiatric*:ti,ab
#29	"off license":ti,ab
#30	"off label":ti,ab
#31	MeSH descriptor: [Off-Label Use] this term only
#32	{or #13-#31}
#33	#7 AND #12 AND #32
#34	conference:so
#35	clinicaltrials:so
#36	#33 NOT (#34 OR #35)

11. Evidence selection

A literature search was conducted which identified, after removal of duplicates, 63 references (see search strategy for full details). These references were screened using their titles and abstracts, and 16 references were obtained and assessed for relevance. Of these, 1 reference is included in the evidence summary. The remaining 15 references were excluded and are listed in the following table along with reasons for exclusion.

Study reference	Reason for exclusion
Conrad M, Stein R, Maxwell E et al. (2016) Vedolizumab Therapy in Severe Pediatric Inflammatory Bowel Disease, Inflammatory bowel diseases, 22, 10, 2425-31	Case series with a small proportion of participants with ulcerative colitis for whom outcomes were not reported separately from those with unclassified inflammatory bowel disease and reporting no additional outcomes of interest.
Hamel B, Wu M, Hamel E et al. (2018) Outcome of tacrolimus and vedolizumab after corticosteroid and anti-TNF failure in paediatric severe colitis, BMJ open gastroenterology, 5, 1, e000195	Intervention – vedolizumab plus concomitant tacrolimus study.
Ledder O, Assa A, Escher J et al. (2018) Corrigendum: Vedolizumab in paediatric inflammatory Bowel Disease: A retrospective multi-centre experience from the paediatric IBD Porto Group of ESPGHAN [Journal of Crohn's and Colitis, 630 (2018)] doi:10.1093/ecco-jcc/jjx172, Journal of Crohn's and Colitis, 12, 5, 630-630	Published correction to included article. Authors name corrected only.
Lightner A, Tse C, Potter D et al. (2018) Postoperative outcomes in vedolizumab-treated pediatric patients undergoing abdominal operations for inflammatory bowel disease, Journal of Pediatric Surgery, 53, 9, 1706-1709	Outcome/ intervention - postoperative complications were not an outcome of interest.
Lopez R, Gupta N, Lemberg D et al. (2018) Vedolizumab-Associated Pancreatitis in Paediatric Ulcerative Colitis: Functional Selectivity of the alpha4beta7integrin and MAdCAM-1 Pathway?, Journal of Crohn's & colitis, 12, 4, 507-508	Study design – case study.
Mitsuya J, Gonzalez R, Thomas R et al. (2018) The Effect of Biologics on Post-Operative Complications in Children with Inflammatory Bowel Disease and Bowel Resection, Journal of pediatric gastroenterology and nutrition	Outcome/ intervention - postoperative complications were not an outcome of interest.
Nordenvall C, Rosvall O, Bottai M et al. (2018) Surgical treatment in childhood-onset inflammatory bowel disease-a nationwide register-based study of 4695 incident patients in Sweden 2002-2014, Journal of Crohn's and Colitis, 12, 2, 157-166	Intervention – no results reported for vedolizumab.
Parikh A, Fox I, Leach T et al. (2013) Long-term clinical experience with vedolizumab in patients with inflammatory bowel disease, Inflammatory bowel diseases, 19, 8, 1691-9	Population – adults.
Parikh A, Leach T, Wyant T et al. (2012) Vedolizumab for the treatment of active ulcerative colitis: a randomized controlled phase 2 dose-ranging study, Inflammatory bowel diseases, 18, 8, 1470-9	Population – adults.
Schneider AM, Weghuber D, Hetzer B et al. (2018) Vedolizumab use after failure of TNF-alpha antagonists in children and adolescents with inflammatory bowel disease, BMC gastroenterology, 18, 1, 140	Case series with a small proportion of participants with ulcerative colitis for whom outcomes were not reported separately from those with unclassified inflammatory bowel disease and reporting no additional outcomes of interest.

Schulze H, Esters P, Hartmann F et al. (2018) A prospective cohort study to assess the relevance of vedolizumab drug level monitoring in IBD patients, Scandinavian journal of gastroenterology, 53, 6, 670-676	Population – adults.
Singh N, Rabizadeh S, Jossen J et al. (2016) Multi-Center Experience of Vedolizumab Effectiveness in Pediatric Inflammatory Bowel Disease, Inflammatory bowel diseases, 22, 9, 2121-6	Population – 18% had not previously been treated with TNF-alpha inhibitors. The authors reported a greater response to vedolizumab in TNF-alpha inhibitor-naïve participants compared with those who were not, but the outcomes for each of these groups were not reported separately.
Tse C, Loftus E, Raffals L et al. (2018) Effects of vedolizumab, adalimumab and infliximab on biliary inflammation in individuals with primary sclerosing cholangitis and inflammatory bowel disease, Alimentary Pharmacology and Therapeutics, 48, 2, 190-195	Population - specific to those with primary sclerosing cholangitis.
Zimmerman L, Zalieckas J, Shamberger R et al. (2018) Postoperative complications of pediatric patients with inflammatory bowel disease treated with vedolizumab, Journal of pediatric surgery, 53, 7, 1330-1333	Outcome/ intervention - postoperative complications were not an outcome of interest.
Zoet I, de Boer N, de Meij T et al. (2016) Successful Vedolizumab Therapy in a Sixteen-Year-Old Boy with Refractory Ulcerative Colitis, Journal of Crohn's & colitis, 10, 3, 373-4	Study design – case report.

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

Study	Comment
Ledder O, Assa A, Levine A et al. (2017) Vedolizumab in Paediatric Inflammatory Bowel Disease: A retrospective multi-centre experience from the paediatric IBD Porto Group of ESPGHAN. Journal of Crohn's and Colitis, 11(10), pp.1230-1237.	Included in the evidence review.
Singh N, Rabizadeh S, Jossen J et al. (2016) Multi-centre experience of vedolizumab effectiveness in paediatric inflammatory bowel disease. Inflammatory Bowel Diseases 22(9), pp.2121-6	Excluded from the evidence review. This study was identified in the search but was excluded because 18% of the participants had not previously been treated with TNF-alpha inhibitors. The authors reported a greater response to vedolizumab in TNF-alpha inhibitor-naïve participants compared with those who were not, but the outcomes for each of these groups were not reported separately.
Feagan B, Rutgeers P, Sands B et al. (2013) Vedolizumab as induction and maintenance for Ulcerative Colitis. New England Journal of Medicine, 369(8),pp.699-710	Excluded from the evidence review. This study was not identified in the search because it is in an adult population.

12. Related NICE guidance and NHS England clinical policies

Ulcerative colitis: management NICE guideline CG166

Vedolizumab for treating moderately to severely active ulcerative colitis (for use in adults) NICE technology appraisal guidance TA342

NHS England and NICE have not issued any guidelines or policies on managing ulcerative colitis in children and young people with vedolizumab.

13. Terms used in this evidence summary

Abbreviations

Term	Definition
IQR	Inter-quartile range
PUCAI	Paediatric ulcerative colitis activity index
RCT	Randomised controlled trial
SD	Standard deviation
TNF	Tumour necrosis factor
UCEIS	Ulcerative colitis endoscopic index of severity

Medical definitions

Term	Definition
Colectomy	Surgical removal of all or part of the colon, also known as bowel resection.
Unclassified inflammatory bowel disease	A classification of inflammatory bowel disease where there are features of both ulcerative colitis and Crohn's disease.
PUCAI	The paediatric ulcerative colitis activity index (PUCAI) defines ulcerative colitis disease severity by the following scores: severe (65 or above), moderate (35 to 64), mild (10 to 34) and remission (below 10).
Refractory ulcerative colitis	Ulcerative colitis that has not responded to conventional pharmacological treatment and anti-TNF medicines.
Stool calprotectin	A measurement taken which measures the level of the protein calprotectin in the stool. Increased calprotectin is a sign of inflammation in the intestine.
UCEIS	The ulcerative colitis endoscopic index of severity is a measure of endoscopic response in ulcerative colitis. It is measured on a scale of 0 to 8 and takes vascular pattern, bleeding, erosions, and ulcers into account. Endoscopic remission is defined as a UCEIS score of 0.

14. References

Ledder O, Assa A, Levine A et al. (2017) Vedolizumab in Paediatric Inflammatory Bowel Disease: A Retrospective Multi-Centre Experience From the Paediatric IBD Porto Group of ESPGHAN, Journal of Crohn's & colitis, 11, 10, 1230-1237