PrescQIPP Community Interest Company

Vedolizumab subcutaneous prescribing

Nationally nearly £400 million is spent annually on the 4 most frequently used biologics in gastroenterology: infliximab, adalimumab, vedolizumab and ustekinumab. Over £80 million is spend on vedolizumab.[1]

Vedolizumab (Entyvio®) is a gut selective humanised monoclonal antibody, that binds to α4β7 integrin. By blocking the receptor, the process that leads to migration of T lymphocytes to the gut is interrupted and local inflammation within the gut is reduced.[2] The intravenous (i.v.) infusion, has been licensed for the treatment of moderate to severe ulcerative colitis and Crohn's disease since 2014. A license extension has recently been granted for the subcutaneous (s.c.) formulation of Entyvio® as maintenance therapy following i.v. induction.[2] This bulletin reviews the place in therapy of s.c. vedolizumab and offers guidance and support materials for NHS organisations considering the prescribing of s.c. vedolizumab as a QIPP project.

The availability of a subcutaneous formulation will give patients the freedom to administer vedolizumab themselves at home, with delivery provided via a homecare provider. This could free up capacity in secondary care by providing an alternative subcutaneous option to s.c. adalimumab and s.c. infliximab.

Recommendations

- Review locally whether homecare capacity allows suitable patients to be switched from i.v. vedolizumab to s.c. vedolizumab.
- Switching suitable patients to the s.c. formulation could help reduce capacity problems at providers. As with all switches, these should be tailored to the individual patient and should take capacity at homecare providers into account as well.
- Ensure that prescribing is in line with its licence and relevant NICE guidance.
- A cost calculator is available here https://www.prescqipp.info/our-resources/bulletins/bulletin-274-subcutaneous-vedolizumab/ for local commissioners and providers to compare costs of biologics used for the treatment of IBD using the tariffs charged locally. Where applicable, costs used in the calculator are split based on patient weight, where this affects dose and therefore costs.
- If more than one biologic is suitable to meet an individual patient's needs, the most cost effective first line options remain biosimilar adalimumab (s.c.) and infliximab (i.v.) based on current contract prices.

National guidance

Vedolizumab is one of several biologics (from different therapeutic classes) licensed for the management of inflammatory bowel disease (IBD). The intravenous formulation is recommended by NICE for IBD treatment.

The recommendations on individual agents in IBD have been summarised in NICE guidelines[3,4] and treatment pathways.[5,6] There are also two technology appraisals (TA342 and TA352) for vedolizumab in IBD which have been incorporated into the guidelines and treatment pathways. These state that vedolizumab is recommended, within its marketing authorisation, as an option for treating moderately to active ulcerative colitis in adults and Crohn's disease only if the company provides vedolizumab with the discount agreed in the patient access scheme.

According to the British Society of Gastroenterology (BSG), first line choice in biologic-naive patients should be determined by clinical factors including co-morbidities, safety data, patient preference, overall cost, likely adherence and local infusion capacity.[7] NICE recommend vedolizumab as 'an option', so the clinician and patient can consider its use alongside other potential treatments. NICE generally recommends in its guidance that if more than one treatment is suitable, the least expensive should be chosen to make the best use of NHS resources. This takes into account administration costs, dosage and price per dose. On this basis, adalimumab and infliximab are currently the main first line choices of biologics for IBD; both are available as biosimilars.

The anti-TNFs infliximab and adalimumab and the interleukin inhibitor ustekinumab are all recommended by NICE as potential first-line biologics in Crohn's disease, with vedolizumab recommended after anti-TNF failure or if anti-TNFs are contra-indicated.[3,6] Unless treatment with anti-TNF therapy is contra-indicated, infliximab or adalimumab are likely to remain the initial choice of biologic for Crohn's disease until more data is available in support of using other biologics preferentially to an anti-TNF, according to the BSG.[7]

NICE-recommended first line choices of biologics in ulcerative colitis are the three anti-TNFs infliximab, adalimumab and golimumab, the JAK inhibitor tofacitinib and vedolizumab. The interleukin inhibitor ustekinumab is recommended by NICE as a second line biologic, if treatment with an anti-TNFs has failed or isn't tolerated.[4,5] In practice, golimumab does not have a significant place in therapy when considering the relative costs associated with the different anti-TNFs and the conflicting data on relative efficacy of golimumab, infliximab and adalimumab.[7] Although more expensive compared with infliximab and adalimumab, vedolizumab (given as an i.v. infusion) has demonstrated increased efficacy (increased clinical remission and endoscopic improvement, but not corticosteroid-free remission) compared with adalimumab in a head-to-head trial (sponsored by the manufacturer of vedolizumab) in patients with moderate to severe ulcerative colitis.[8] There is no data available to assess whether the same applies to the s.c. preparation or whether the increased efficacy of i.v. vedolizumab is matched with a higher cost-effectiveness when factoring in the higher cost of vedolizumab to the NHS compared with adalimumab.

Clinical effectiveness and safety

Marketing authorisation for the s.c. formulation of vedolizumab was granted based on the data from two double-blind randomised phase three trials (VISIBLE 1 and VISIBLE 2), and one open-label extension study (VISIBLE OLE).

In both double-blind trials, patients with moderate to severe active disease received two induction doses of vedolizumab 300mg i.v. at weeks zero and two, after which clinical response was assessed. Only patients who achieved a clinical response at week 6 were then randomised to receive s.c. vedolizumab 108mg every two weeks, placebo or (for VISIBLE 1 only) i.v. vedolizumab 300mg every eight weeks (with both regimens providing comparable drug exposure). The total study period of both trials was 52 weeks.

Outcome data of these studies have been published in journals or as part of abstracts presented at conferences[9-12] and are in Appendix 1 and 2.

Ulcerative Colitis

In VISIBLE 1[9] a total of 383 patients enrolled, of which 215 achieved a clinical response at week six. Clinical response was defined as a reduction in complete Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding sub-score of ≥1 point or absolute rectal bleeding sub-score of ≤1. Clinical remission was defined as a Mayo score of ≤2 and no individual sub-score of >1 at week 52. The trial was set-up as a double-dummy trial to minimise the risk of unblinding due to different routes of administration.

In total 216 patients were randomised at week six to receive placebo, vedolizumab s.c. or vedolizumab i.v., 210 who had achieved clinical response and six in error (five patients who had a clinical response

were not randomised). Patients who did not meet the criteria for clinical response at week 6 were given a third i.v. dose and were then given the option to enrol onto the open-label extension study (only s.c vedolizumab) if they achieved a clinical response at week 14. Patients enrolled onto the i.v. vedolizumab arm with a clinical response at week 52 were also offered s.c. vedolizumab in the open-label extension trial.

The primary efficacy endpoint (clinical remission at week 52) was met, with a rate of 14.3% for placebo compared with 46.2% and 42.6% for s.c. vedolizumab ($p<0.001$) and i.v. vedolizumab (p value not stated) respectively. The secondary endpoints of durable clinical response (clinical response at week six and 52) and endoscopic improvement were also met ($p<0.001$). However, although numerically a greater percentage of patients randomised to s.c. vedolizumab reached the secondary endpoints of durable clinical remission and corticosteroid-free remission compared with placebo, they did not reach statistical significance ($p=0.076$ and $p=0.067$ respectively). The outcome data for s.c. and i.v. vedolizumab were numerically comparable; statistical significance and non-inferiority were not assessed. Overall safety data were similar between s.c. vedolizumab and i.v. vedolizumab except for injection site reactions, which were reported more frequently for s.c. vedolizumab: 10.4% and 1.9% of patients respectively, though no patients discontinued treatment because of this.

A post-hoc analysis evaluated the efficacy of s.c. vedolizumab after initial treatment with i.v. vedolizumab by combining the data from VISIBLE 1 and the open-label extension study. The results suggest that the efficacy of treatment with i.v. vedolizumab is maintained regardless of the initial duration i.e. two i.v. infusions, three i.v. infusions or 52 weeks of i.v. infusions, prior to transitioning to s.c. vedolizumab. The clinical remission rates were 46.2% at week 52 for two i.v. vedolizumab doses and 39.2% at week 40 for three i.v. doses. The clinical remission rate for the cohort enrolled after 52 weeks (eight infusions) of i.v. vedolizumab was 76.9% at week 24 (starting from a clinical remission rate of 77.1% at week 0).[10] In comparison, the week 52 clinical remission rate in the GEMINI I trial was 41.8% for patients randomised to maintenance with 300mg i.v. vedolizumab every eight weeks, following a clinical response rate of 47.1% at week six after two i.v. infusions.[13]

Crohn's Disease

In VISIBLE 2, 644 patients with moderate to severely active Crohn's disease despite prior treatment were enrolled to receive induction therapy with two induction doses of vedolizumab 300mg i.v. at week zero and week two. Patients with a clinical response at week six (n=409; 63.5%) were randomised to receive maintenance therapy with either s.c. vedolizumab 108mg every two weeks or s.c. placebo starting from week six for up to 52 weeks. Clinical response was defined as a ≥70 point reduction in Crohn's disease Activity Index (CDAI) score.[11]

Patients not reaching clinical response at week six were offered a third dose but were not randomised onto one of the treatment arms.[12]

The primary endpoint was clinical remission (defined as Crohn's CDAI score ≤150 at week 52). At week 52, 48.0% of patients on vedolizumab versus 34.3% of patients on placebo were in clinical remission ($p=0.008$).[11] As a comparison, 39.0% of patients randomised to vedolizumab 300mg i.v. every eight weeks in GEMINI 2 achieved clinical remission.[14]

52% vs. 44.8% of patients on s.c. vedolizumab and placebo reached the secondary endpoint of enhanced clinical response (defined as a reduction of ≥100 in CDAI score), however, a statistically significant difference was not achieved ($p=0.167$).[11]

No new safety signals were observed apart from local injection site reactions, which were reported in <3% of patients on s.c. vedolizumab.[11]

The SmPC for i.v. vedolizumab includes the option of increasing the frequency of dosing in patients losing efficacy. However, it is unclear from current data whether patients with a decrease in effect whilst on maintenance therapy with s.c. vedolizumab would benefit from an increase in dosing frequency as well.[2]

Overall, 86.2% (330/383) of ulcerative colitis patients and 82.6% (532/644) of Crohn's disease patients achieved a clinical response after two or three vedolizumab intravenous infusions.[12]

COVID-19

Patients on biologics are considered to be at moderate to high risk of COVID-19. During the height of the pandemic those in the moderate risk group were advised to adhere to stringent social distancing as a minimum, while those at high risk were recommended to shield.[15] In response to the pandemic, NICE has also issued several rapid guidelines around managing conditions at risk of COVID-19. This includes patients treated with biologics. The COVID-19 rapid guideline relevant to IBD includes the recommendation to consider alternative routes of (existing) medication that would limit the need for hospital attendances.[16] Switching existing patients from the intravenous to the subcutaneous preparation of vedolizumab would be one of the options to reduce hospital attendances and allow shielding without compromising treatment with a biologic. However, care should be taken not to stop/switch medication (other than route of administration) to avoid flares in patients whose IBD is controlled.[15]

Patient factors

Choice of agent is guided by a combination of clinical factors, patient choice, overall cost, likely adherence and local infusion capacity. NICE generally recommends in their guidance that if more than one treatment is suitable, the least expensive should be chosen (taking into account administration costs, dosage and price per dose) to make the best use of NHS resources.

On this basis, infliximab and adalimumab (both available as biosimilars) are currently the most cost effective first line choices for IBD if more than one biologic is suitable to meet the needs of a patient.

Cost comparison

Due to the sensitivity of pricing information, a direct price comparison based on current contract prices cannot be published in this bulletin. A cost calculator has been developed for local organisations to enable comparisons based on the latest contract or acquisition costs and administration costs and is available here https://www.prescqipp.info/our-resources/bulletins/bulletin-274-subcutaneous-vedolizumab/

Switching options

Switching from vedolizumab infusions to subcutaneous injections in patients responding well to vedolizumab and who are willing and able to self-administer, could increase capacity in day units and give patients the flexibility to inject at home.

Now that vedolizumab is available as a subcutaneous injection, vedolizumab will be a more attractive treatment option for patients preferring and able to self-administer. It will come at a higher cost to the NHS if used instead of adalimumab or infliximab. Costs will have to be considered when considering first-line treatment options for individual patients if other factors, including efficacy, safety, adherence and co-morbidities are equal.

Patients responding well to treatment should only be switched to a different biologic if there is a clinical indication to do so. Guidelines for IBD[7] (published before the availability of s.c. infliximab) recommend switching to either a different class of biologic or alternative anti-TNF if there is an indication for discontinuing first-line treatment with adalimumab or infliximab (i.v.). Whether clinically more appropriate to switch to an alternative anti-TNF or a different class of biologic depends on numerous factors, including whether the reason for discontinuation was intolerance, loss of efficacy (and after what time) and what the drug/antibody concentrations in the blood are.

Switch Savings

The availability of s.c. vedolizumab can generate savings by switching current patients from the intravenous to the subcutaneous formulation. It could also help reduce capacity problems where they have been identified and provide patients with the option of administering vedolizumab at home.

However, if more than one biologic is suitable for a patient, biosimilar adalimumab and infliximab (i.v.) remain the most cost-effective first-line choices based on current contract prices and costs of administration.

Overall, infliximab s.c. is more expensive than infliximab i.v. and vedolizumab s.c. is less expensive than vedolizumab i.v, and therefore the difference in costs to the NHS between the two agents has become smaller.

Summary

The introduction of a subcutaneous version of vedolizumab can generate some savings for the cohort currently treated with vedolizumab in hospital. Vedolizumab s.c. will give patients an additional option of a product that can be self-administered, thereby reducing the need to attend hospital and address local capacity issues in hospitals. However, the current costs do not support a move away from adalimumab and infliximab as first line choices if these are suitable to meet the patient's needs.

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Briefing	https://www.prescqipp.info/our-resources/bulletins/bulletin-274-subcutaneous-vedolizumab/
Implementation tools	

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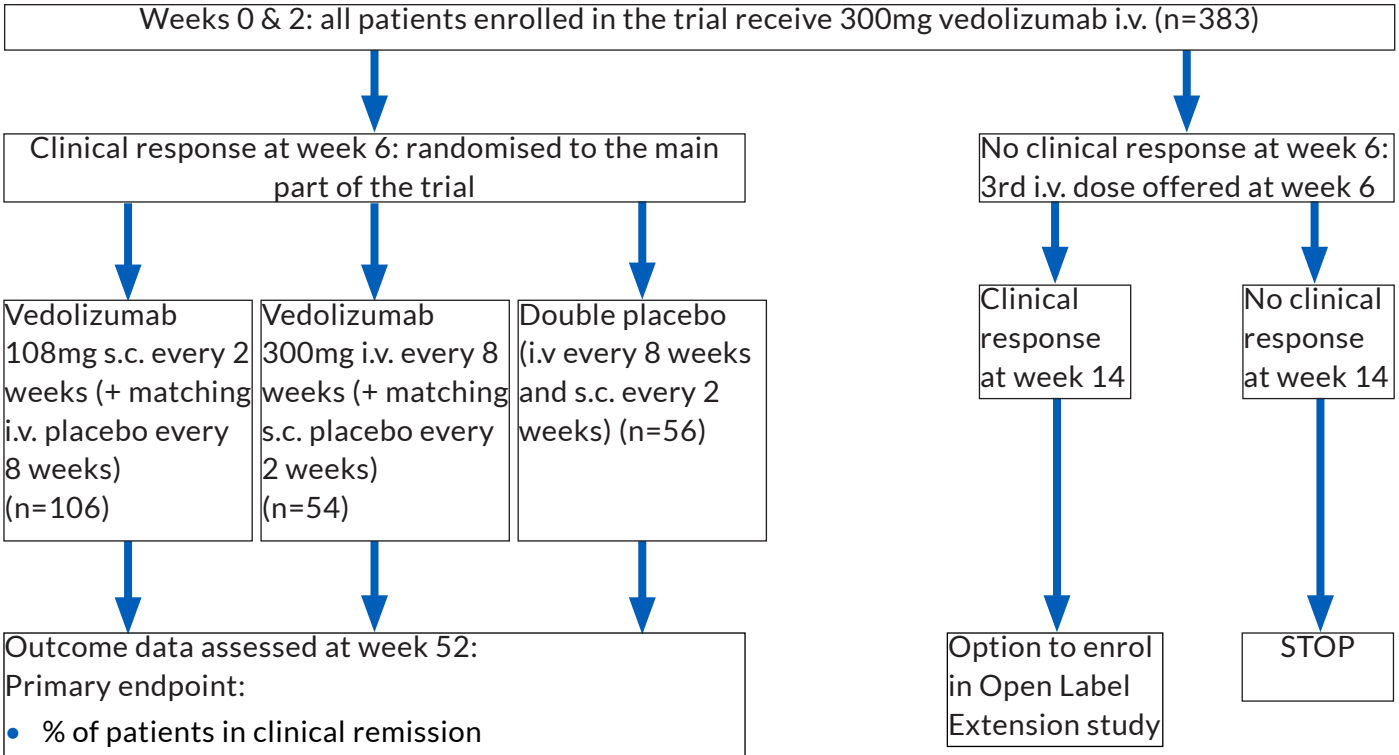
The use and application of this guidance does not override the individual responsibility of health and social care professionals to make decisions appropriate to local need and the circumstances of individual patients (in consultation with the patient and/or guardian or carer). Terms and conditions

Appendix 1. Trial design and outcome data VISIBLE 1 – Ulcerative colitis[9,10]



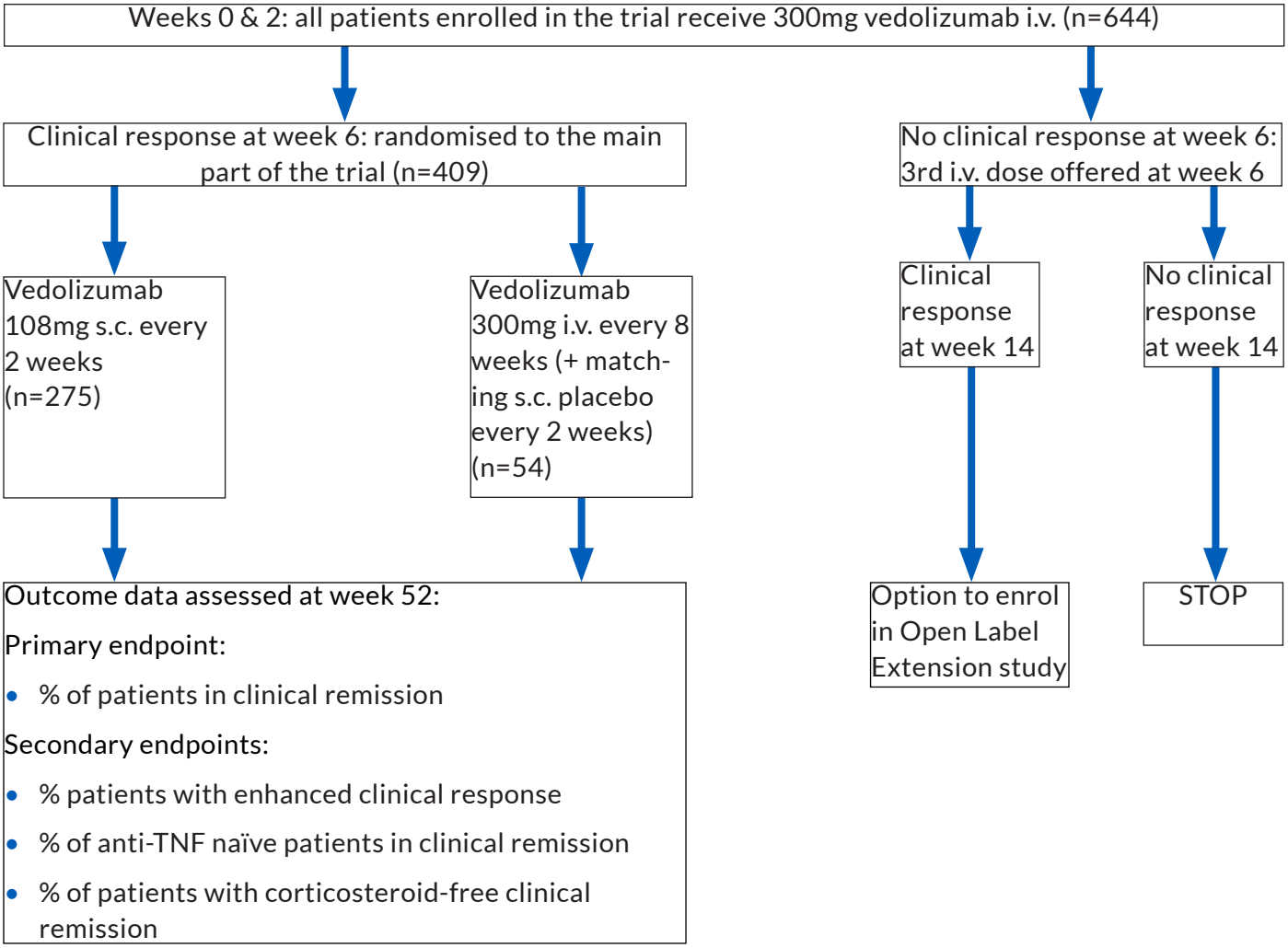
Definitions of outcome measures:

- Clinical response: reduction in Mayo score of ≥3 points and ≥30% from baseline with an accompanying decrease in rectal bleeding sub-score of ≥1 point or absolute rectal bleeding sub-score of ≤1)
- Durable clinical response: clinical response at weeks 6 and 52
- Clinical remission: Mayo score ≤2 and no individual sub-score of >1 at week 52
- Durable clinical remission: clinical remission at weeks 6 and 52
- Endoscopic improvement (referred to as mucosal healing in the study protocol): assessed as a Mayo endoscopic sub-score ≤1 (normal/inactive disease or mild disease)
- Corticosteroid-free remission: discontinuation of oral corticosteroids, followed by clinical remission at week 52, assessed in patients using oral corticosteroids at baseline

Table 1. Outcome data VISIBLE 1

Week 52 outcome data	Vedolizumab s.c. (n=106)	Placebo (n=56)	p-value	Vedolizumab i.v. (n=54, p-values not reported)
% of patients in clinical remission	46.2%	14.3%	<0.001	42.6%
% patients with endoscopic improvement	56.6%	21.4%	<0.001	53.7%
% of patients with a durable clinical response	64.2%	28.6%	<0.001	72.2%
% patients with durable clinical remission	15.1%	5.4%	0.76	16.7%
% of patients with corticosteroid-free remission	28.9%	8.3%	0.67	28.6%

Appendix 2. Trial design and outcome data VISIBLE 2 – Crohn's Disease[11,12]



Definitions of outcome measures:

- Clinical response: a ≥70-point decrease in CD Activity Index [CDAI] from baseline
- Enhanced clinical response: a drop of ≥100 in CDAI score
- Clinical remission: CDAI score ≤150
- Corticosteroid-free clinical remission: discontinuation of oral corticosteroids, followed by clinical remission at week 52, assessed in patients using oral corticosteroids at baseline

Table 2. Outcome data VISIBLE 2

Week 52 outcome data	Vedolizumab s.c. (n=275)	Placebo s.c. (n=134)	p-value
% of patients in clinical remission	48.0%	14.3%	<0.001
% of patients with enhanced clinical response	52.0%	21.4%	<0.001
% of anti-TNF naïve patients in clinical remission	48.5%	28.6%	<0.001
% of patients with corticosteroid-free clinical remission	45.3%	5.4%	0.76