Technology Guidance

Tofacitinib, ustekinumab and vedolizumab

for treating inflammatory bowel disease

Technology Guidance from the MOH Drug Advisory Committee

Guidance Recommendations

The Ministry of Health's Drug Advisory Committee has recommended:

- ✓ Tofacitinib 5 mg tablet for treating adults with moderately to severely active ulcerative colitis (UC) who have failed conventional therapy and/or anti-TNFα biologics; and
- ✓ Vedolizumab 300 mg/vial powder for concentrate for solution for infusion for treating adults with moderately to severely active Crohn's disease (CD) who have failed both conventional therapy and anti-TNFα biologics.

Subsidy status

Tofacitinib 5 mg tablet and vedolizumab 300 mg/vial powder for concentrate for solution for infusion are recommended for inclusion on the Medication Assistance Fund (MAF) for the abovementioned indications.

Tofacitinib and vedolizumab should be used in line with the clinical criteria for initial and continuing prescriptions for patients with UC and CD in the respective MAF checklists.

Listing on MAF will be implemented from 1 July 2022.

MAF assistance **does not** apply to any formulations or strengths of ustekinumab for treating CD and UC.

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Factors considered to inform the recommendations for subsidy

Technology evaluation

1.1. The MOH Drug Advisory Committee ("the Committee") considered the evidence presented for the technology evaluation of ustekinumab and vedolizumab for treating Crohn's disease (CD) and tofacitinib, ustekinumab and vedolizumab for treating ulcerative colitis (UC). Of these drugs, vedolizumab was previously considered by the Committee for CD and UC in 2018 but was not recommended for subsidy due to unfavourable cost-effectiveness compared with biosimilar infliximab at the price proposed at the time of the evaluation. The Agency for Care Effectiveness (ACE) conducted the evaluation in consultation with clinical experts from the public healthcare institutions. Published clinical and economic evidence for all drugs was considered in line with their registered indications.

1.2. The evidence was used to inform the Committee's deliberations around four core decision-making criteria:

- Clinical need of patients and nature of the condition;
- Clinical effectiveness and safety of the technology;
- Cost-effectiveness (value for money) – the incremental benefit and cost of the technology compared to existing alternatives; and
- Estimated annual technology cost and the number of patients likely to benefit from the technology.

1.3. Additional factors, including social and value judgments, may also inform the Committee's subsidy considerations.

Clinical need

2.1 The Committee noted that conventional therapies (corticosteroids, thiopurines, methotrexate and aminosalicylates) and anti-TNFα biologics (infliximab and adalimumab biosimilars) are already subsidised on the SDL for treating CD and UC. However, up to 80% of patients who have had an inadequate response to these treatments will require non-anti-TNFα biologic therapies such as vedolizumab and ustekinumab to slow disease progression and manage their symptoms. The Committee acknowledged there was a clinical need to subsidise a non-anti-TNFα treatment to improve affordability and ensure appropriate care for patients with CD and UC.

2.2 Local clinical experts confirmed that ustekinumab and vedolizumab are used for treating CD, and tofacitinib, ustekinumab and vedolizumab are used for treating UC in local practice after failure of conventional therapy and/or anti-TNFα biologics, in line with international clinical practice guidelines.

Clinical effectiveness and safety

3.1 Crohn's disease

Ustekinumab

The Committee reviewed the available clinical evidence (induction trials: UNITI-1 and UNITI-2) and noted that ustekinumab was more effective than placebo in achieving clinical response at week 6 in both anti-TNFα biologic treatment-naïve and treatment-failure patients with CD.

3.2 In the maintenance trial (IM-UNITI), the Committee noted that ustekinumab was more effective than placebo in achieving clinical remission at week 44. The Committee also acknowledged a large proportion of patients with CD who received ustekinumab achieved clinically significant improvements in Health-Related Quality of Life (HRQoL) measures from baseline as assessed by the Inflammatory Bowel Disease Questionnaire (IBDQ) and 36-item Short Form Survey (SF-36).

3.3 The Committee noted AE rates reported in the UNITI trials were similar between the ustekinumab and placebo arms.

3.4 **Vedolizumab**

The Committee previously reviewed the clinical evidence for vedolizumab for treating CD in 2018 (GEMINI II) and noted that trial results showed that vedolizumab was not more effective than placebo in achieving clinical response at week 6 (primary endpoint) in a mixed trial population comprising anti-TNFα biologic treatment-naïve and treatment-failure patients. However, the Committee noted that vedolizumab was more effective than placebo in achieving clinical remission at week 6 and maintaining clinical response and clinical remission at week 52.

3.5 In another randomised controlled trial (RCT) comprising 76% patients with CD who had failed anti-TNFα biologic treatment (GEMINI III), the Committee acknowledged that vedolizumab was more effective than placebo in achieving clinical remission at week 10 but not at week 6 (primary endpoint).

3.6 The Committee noted that adverse event (AE) rates were similar between the vedolizumab and placebo arms in both GEMINI II and GEMINI III trials.

3.7 The Committee noted that there were no studies directly comparing vedolizumab or ustekinumab with anti-TNFα biologics, or with each other for treating CD and that indirect comparisons reviewed by overseas reference HTA agencies were limited by heterogeneity issues. The Committee acknowledged that both PBAC (Australia) and CADTH (Canada) concluded that there was insufficient evidence to ascertain a difference in comparative effectiveness and safety of ustekinumab, vedolizumab and anti-TNFα biologics for treating CD.

3.8 Ulcerative colitis

Tofacitinib

The Committee considered the clinical evidence (OCTAVE trials) and noted that tofacitinib was more effective than placebo in inducing and maintaining clinical remission at weeks 8 and 52 in both anti-TNFα biologic treatment-naïve and treatment-failure patients with UC. The Committee also noted that tofacitinib was more effective than placebo in improving HRQoL as measured by IBDQ during both induction and maintenance treatment.

3.9 The Committee noted that AE rates were similar between tofacitinib and placebo.

3.10 **Ustekinumab**

The Committee noted in the UNIFI trial that ustekinumab was more effective than placebo in inducing and maintaining clinical remission at week 8 (induction phase) and 44 (maintenance phase) in patients with UC who were either anti-TNFα biologic treatment-naïve or failed anti-TNFα biologics. The Committee acknowledged that ustekinumab was associated with a clinically significant improvement in HRQoL as measured by IBDQ compared to placebo during induction and maintenance treatment.

3.11 The Committee also noted that AE rates were similar between ustekinumab and placebo.

3.12 **Vedolizumab**

The Committee previously reviewed the clinical evidence for vedolizumab for treating UC in 2018 (GEMINI I) and acknowledged that vedolizumab was more effective than placebo in inducing and maintaining clinical remission and clinical response in a mixed trial population of anti-TNFα biologic treatment-naïve and treatment-failure patients.

3.13 The Committee also noted that an additional RCT (VARSITY) comprising mainly anti-TNFα biologic treatment-naïve patients with UC showed that vedolizumab was more effective than adalimumab in achieving clinical remission at week 52. There was no direct evidence comparing vedolizumab with infliximab.

3.14 The Committee noted AE rates were similar between vedolizumab and placebo or adalimumab in the GEMINI I and VARSITY trials, respectively.

3.15 The Committee noted that there were no studies directly comparing tofacitinib, ustekinumab or vedolizumab with anti-TNFα biologics (except for VARSITY) or with each other for treating UC and acknowledged that indirect comparisons reviewed by overseas reference HTA agencies were limited by heterogeneity issues. The Committee acknowledged that there was insufficient evidence to ascertain a difference in comparative effectiveness and safety of tofacitinib and ustekinumab versus vedolizumab, anti-TNFα biologics or with each other for treating UC.

Cost effectiveness

4.1 The Committee acknowledged there were no local cost-effectiveness evaluations. Based on available evidence, the Committee agreed a cost-minimisation approach was appropriate to assess the cost-effectiveness of all three drugs for their respective indications, in view of their comparable efficacy and safety.

4.2 Crohn's disease
The Committee acknowledged the results from the cost-minimisation analysis (CMA) which showed that the treatment cost of vedolizumab was lower than for ustekinumab and agreed that vedolizumab was likely to be an acceptable use of healthcare resources for CD at the prices proposed by the manufacturers.

4.3 In view of the higher cost of vedolizumab compared with anti-TNFα biologics, the Committee recommended restricting the use of vedolizumab to after failure of conventional therapy and anti-TNFα biologic treatment to ensure appropriate use.

4.4 Ulcerative colitis
The Committee noted that the treatment cost of tofacitinib was lower than for ustekinumab and vedolizumab in the CMA. The Committee considered that it was likely to be an acceptable use of healthcare resource in the local setting after failure of conventional therapy and/or anti-TNFα biologics.

Estimated annual technology cost

5.1 The Committee noted that the annual cost impact in the first year of listing vedolizumab for treating CD and tofacitinib for treating UC on the MAF was estimated to be less than SG$1 million each.

Recommendations

6.1 Crohn's disease
Based on available evidence, the Committee recommended vedolizumab 300 mg/vial powder for concentrate for solution for infusion be listed on MAF for treating CD in view of the clinical need and favourable clinical effectiveness and cost-effectiveness at the price proposed by the manufacturer.

6.2 The Committee recommended not listing ustekinumab on the MAF due to unfavourable cost-effectiveness compared with vedolizumab at the price proposed by the manufacturer.

6.3 Ulcerative colitis

Based on available evidence, the Committee recommended tofacitinib 5 mg tablet be listed on MAF for treating UC in view of the clinical need and favourable clinical effectiveness and cost-effectiveness at the price proposed by the manufacturer.

6.4 The Committee recommended not listing ustekinumab or vedolizumab on the MAF for treating UC due to unfavourable cost-effectiveness compared with tofacitinib at the prices proposed by the manufacturers.

About the Agency

The Agency for Care Effectiveness (ACE) was established by the Ministry of Health (Singapore) to drive better decision-making in healthcare through health technology assessment (HTA), clinical guidance, and education.

As the national HTA agency, ACE conducts evaluations to inform government subsidy decisions for treatments, diagnostic tests and vaccines, and produces guidance for public hospitals and institutions in Singapore.

This guidance is based on the evidence available to the MOH Drug Advisory Committee as at 18 March 2022. It is not, and should not be regarded as, a substitute for professional or medical advice. Please seek the advice of a qualified healthcare professional about any medical condition. The responsibility for making decisions appropriate to the circumstances of the individual patient remains with the healthcare professional.

Find out more about ACE at www.ace-hta.gov.sg/about

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