MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

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Etrasimod for Ulcerative Colitis

EXECUTIVE SUMMARY

Ulcerative colitis is a chronic inflammatory condition that primarily affects the colon resulting in high morbidity and impaired quality of life. The current treatment options for ulcerative colitis include anti-inflammatory medications, immunosuppressants, and biological therapies. Etrasimod is a novel, small-molecule, oral sphingosine-1-phosphate (S1P) modulator that works by selectively targeting sphingosine-1-phosphate receptors (S1PR) on immune cells, leading to reduced inflammation and improved symptoms in patients with ulcerative colitis. Phase 3 clinical trials (ELEVATE UC12 and ELEVATE UC52) assessing etrasimod in adults with moderate to severe ulcerative colitis demonstrated that patients treated with etrasimod achieved statistically significant improvements in the primary endpoint of clinical remission at week 12 and week 52 compared to those on placebo. Significant improvement was also observed in all key secondary endpoints, including endoscopic improvement, symptomatic remission, and corticosteroid-free clinical remission. These efficacy outcomes were consistent with findings from previous phase 2 studies (OASIS), where the majority of patients who responded positively at week 12 maintained or even improved their responses through week 46. Etrasimod was generally well tolerated, with the majority of side effects being mild to moderate such as anaemia, headache, worsening of ulcerative colitis, infections, hypertension, and bradycardia. As a conclusion, the results from phase 3 trials demonstrated that etrasimod was effective and safe as both an induction and maintenance therapy in patients with moderate to severe ulcerative colitis. Etrasimod could be a potential breakthrough option for patients who are not responding to their current treatment.

Keywords: Etrasimod, sphingosine-1-phosphate, immunomodulatory therapy, inflammatory bowel disease, ulcerative colitis

INTRODUCTION

Ulcerative colitis is a chronic inflammatory bowel disease that leads to irritation, inflammation, and ulcers in the lining of the large intestine (colon), resulting in high morbidity and an impaired quality of life.[1,2] Worldwide, the estimated number of ulcerative colitis cases stands at five million, with Europe and the United States accounting for the highest numbers (2.5 million and one million cases, respectively).[3]

The prevalence of ulcerative colitis in Europe ranges from 2.4 to 294 cases per 100,000 population, while in the United States, it ranges from 35 to 100 cases per 100,000 population.[4,5]

In Malaysia, the prevalence of ulcerative colitis stands at 15.6 cases per 100,000 population, with the highest prevalence observed among Indians, followed by Malay and Chinese populations. Over the years, there has been a notable rise in the incidence of ulcerative colitis, increasing from 0.4 cases per 100,000 population (2000 to 2009) to 0.9 cases per 100,000 population (2010 to 2019). This trend may be linked to urbanisation and dietary changes.[6]

The accelerating increase in the incidence of ulcerative colitis was also observed in other newly industrialised countries of Asia, South America, and Africa, where societies have become more westernised.[3] This increasing global burden of inflammatory bowel disease will bring important challenges to healthcare systems around the world to manage this complex and costly disease.[7]

Over the past few decades, the therapeutic options for patients with ulcerative colitis have expanded significantly.[8] Despite these advances, current treatment approaches continue to face challenges and limitations, such as inadequate treatment response, medication side effects, and the risk of drug resistance.[9,10] Moreover, many existing treatments necessitate parenteral administration, posing additional hurdles.[11] The introduction of oral targeted therapy, which aims to specifically address the underlying mechanisms of ulcerative colitis and alleviate inflammation without inducing significant systemic side effects, could provide a potential solution to overcome these challenges.[12]

The sphingosine-1-phosphate (S1P) modulators, which are small-molecule therapies, represent one of the novel targeted therapies for ulcerative colitis. They act by reducing the migration of lymphocytes to the sites of inflammation.[2] Ozanimod is the first oral S1P modulator that is approved for the treatment of multiple sclerosis and moderate to severe ulcerative colitis.[13] Branded as Zeposia®, it acts by selectively inhibiting the S1PR1 and S1PR5 receptors.[8] Phase III trials have demonstrated the effectiveness of ozanimod in achieving clinical remission and improving the symptoms of ulcerative colitis compared to placebo. However, the incidence of bradycardia was reported more frequently during the induction phase of ozanimod therapy.[14] To minimise the risk of bradycardia in patients taking this medication, ozanimod requires dose titration over seven days upon treatment initiation which could potentially delay the onset of symptom relief in patients with ulcerative colitis. Patients with cardiac disorders such as myocardial infarction, unstable angina, and stroke are contraindicated from taking ozanimod.[2]

Etrasimod is the new FDA-approved S1P modulator that provides a new oral option for patients with moderate to severe ulcerative colitis.[8] This review aims to

summarise the available evidence for the efficacy, safety, and cost of etrasimod as a treatment for patients with moderate to severe ulcerative colitis.

THE TECHNOLOGY

Sphingosine-1-phosphate (S1P) is a membrane-derived lysophospholipid widely expressed in all tissues. Sphingosine-1-phosphate (S1P) plays a key role in regulating the trafficking of multiple immune cells, including T and B cells, and is involved in the pathogenesis of multiple immune-mediated inflammatory disorders, including inflammatory bowel disease.[8,15] Sphingosine-1-phosphate (S1P) signals through five subtypes of G-protein coupled receptors (S1PR1 to S1PR5).[15] The expression of these receptors varies by tissue, and the function of each receptor is highly dependent on the cell type on which it is expressed.[2] The S1P modulators such as ozanimod and etrasimod sequester lymphocytes in the lymph nodes, resulting in fewer immune cells in the circulating blood to exacerbate inflammation.[2]

Etrasimod is developed by Pfizer for treating immune-mediated inflammatory disorders including ulcerative colitis.[16] It acts by selectively inhibiting the S1PR1, S1PR4, and S1PR5 receptors (Figure 1). It has an inhibitor effect on pro-inflammatory cytokines and increases the effect of anti-inflammatory cytokines IL-10.[8] Etrasimod is recently approved for the treatment of moderate to severe ulcerative colitis. The recommended dose for etrasimod is 2mg once daily.[16] Etrasimod is dosed without an up-titration regimen and phase 1 studies suggested that etrasimod is metabolised by three different cytochrome P450s with approximately equal contributions, potentially limiting the risk of drug-drug and food interactions.[17]

Etrasimod is orally administered and exhibits rapid absorption, with plasma concentrations typically reaching peak levels within six to eight hours. With a consistent mean elimination half-life of 26.2 to 32.5 hours following a single dose of etrasimod, its pharmacokinetics are dose-proportional and reach a steady-state by day-7.[8]

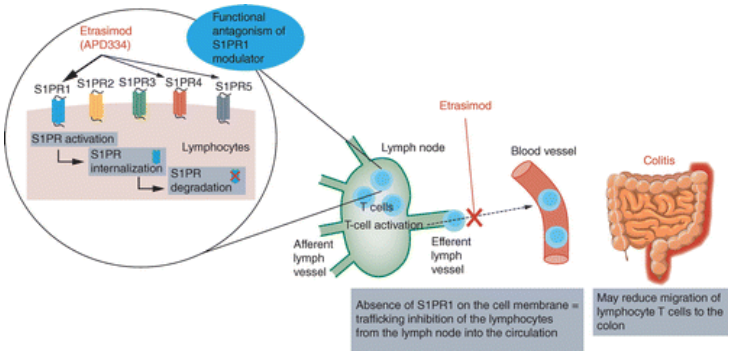

Figure 1. Mechanism of actions for etrasimod

PATIENT GROUP AND INDICATION

Etrasimod is indicated for patients with moderate to severe ulcerative colitis.

CURRENT PRACTICE

Currently, there is no treatment to cure ulcerative colitis. According to the Inflammatory Bowel Disease (IBD) Treatment Algorithm developed by the Malaysian Society of Gastroenterology and Hepatology, the primary objective of the treatment of IBD is to induce and maintain remission. Immediately following diagnosis, a baseline assessment is crucial to ascertain the patient's disease status before initiating treatment.[18]

In general, patients are treated using conventional medications first; biologic therapies and/or surgical interventions such as colectomy will be introduced later if there is a failure in the initial treatment.[18]

The medications currently available for ulcerative colitis include anti-inflammatory, immunomodulators, and biologic therapies. These medications which may be used alone or in combination, are listed below:

Table 1. Medications for treatment of ulcerative colitis[18]

Classes of Medications	Drugs	Function
5-aminosalicylates	Mesalazine, Sulphasalazine,	To reduce inflammation
Corticosteroid	Prednisolone, Budesonide	To reduce inflammation
Thiopurines	Azathioprine	To reduce the immune system activity
Biologic Therapies	Infliximab, Adalimumab, Golimumab, Ustekinumab, Vedolizumab	To reduce inflammation

Etrasimod is a small-molecule therapy that provides a new treatment option for patients with moderate to severe ulcerative colitis.[8]

SAFETY AND EFFICACY

A systematic search was conducted from scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed, and from general search engines such as Google Scholar and the US Food and Drug Administration (US FDA). Based on retrievable evidence up to 10 March 2023, four clinical trials that evaluate etrasimod in ulcerative colitis patients were included in this review.

Table 2. Clinical trials on etrasimod

Trials	Population	Intervention	Outcome
ELEVATE UC 52 (Phase III)[19]	N=433	Etrasimod 2mg vs Placebo	• Clinical remission • Endoscopic improvement • Symptomatic remission • Endoscopic improvement-histological remission • Corticosteroid-free clinical remission
ELEVATE UC 12 (Phase III)[20]	N=354		
OASIS (Phase II)[21]	N=156	Etrasimod 2mg, Etrasimod 1mg vs Placebo	• Improvement in modified Mayo Clinic Scores (MCSs) • Endoscopic improvement • Clinical remission • Clinical response
OASIS Open-label Extension[22]	N=118	Etrasimod 2mg	• Endoscopic improvement • Clinical remission • Clinical response

A. Efficacy

Sandborn et al. conducted two randomised, multicentre, double-blind, placebo-controlled phase III trials, ELEVATE UC 52 and ELEVATE UC 12 to evaluate the safety and efficacy of etrasimod in adult patients with moderately to severely active ulcerative colitis. In both trials, patients with an inadequate or loss of response or intolerance to at least one approved ulcerative colitis treatment were randomly assigned (2:1) to once-daily oral etrasimod 2mg or placebo. The primary efficacy endpoints were the proportion of patients with clinical remission at week 12 and 52 in ELEVATE UC 52 and week 12 in ELEVATE UC 12. The secondary endpoints were endoscopic improvement, symptomatic remission, endoscopic improvement-histological remission, and corticosteroid-free clinical remission.[19]

In the ELEVATE UC 52 trial, 433 patients from 315 centres in 40 countries were randomised to etrasimod (n=289) and placebo group (n=144). The trial had a treat-through design that comprised a 12-week induction period followed by a 40-week maintenance period. The trial found that patients in the etrasimod group showed a statistically significant improvement in clinical remission compared to the placebo group at week 12 [74 (27%) of 274 patients versus 10 (7%) of 135 patients, 95% CI 12.9 to 26.6; p<0.001] and week 52 [88 (32%) of 274 patients versus 9 (7%) of 135 patients, 95% CI 18.4 to 32.4; p<0.001].[18] Significant improvements were also observed in the etrasimod group compared to the placebo group for all the secondary endpoints as presented in Table 3 below:

Table 3. The primary and secondary endpoints in ELEVATE UC 52[19]

Endpoints	Week 12	Week 52
	95% CI, p-value	**95% CI, p-value**
Clinical remission	12.9-26.6 (p<0.0001)	18.4-32.4 (p<0.0001)
Endoscopic Improvement	13.0-23.0 (p<0.0001)	19.0-34.4 (p<0.0001)
Symptomatic remission	15.5-33.6 (p<0.0001)	16.2-33.6 (p<0.0001)
Endoscopic improvement-histological remission	10.8-23.0 (p<0.0001)	11.4-25.4 (p<0.0001)
Corticosteroid-free clinical remission	-	18.4-23.4 (p<0.0001)

In the ELEVATE UC 12 trial, 354 patients from 407 centres in 37 countries were randomised to etrasimod (n=238) and placebo group (n=116). The trial comprised a 12-week induction and a four-week follow-up period. The trial also found a statistically significant improvement in clinical remission in the etrasimod group compared to the placebo group at week 12 [55 (25%) of 222 patients versus 17 (15%) of 112 patients, 95% CI 1.1 to 18.2; p=0.026].[18] Significant improvements were also observed in the etrasimod group compared to the placebo group for all the secondary endpoints as presented in Table 4 below:

Table 4. The primary and secondary endpoints in ELEVATE UC 12[19]

Endpoints	Week 12
	95% CI, p-value
Clinical remission	1.1-18.2 (p=0.026)
Endoscopic Improvement	3.0-21.2 (p=0.0092)
Symptomatic remission	6.8-28.2 (p=0.0013)
Endoscopic improvement-histological remission	0.5-14.4 (p=0.036)

Sandborn et al. also conducted a phase II, randomised, double-blind, placebo-controlled trial (OASIS) to assess the efficacy and safety of etrasimod in patients with moderately and severely ulcerative colitis. Adult outpatients with modified Mayo Clinic Scores (MCSs) (stool frequency, rectal bleeding, and endoscopy findings) of 4 to 9, endoscopic subscores of one or more were randomly assigned to groups given once-daily etrasimod 1mg (n=52), etrasimod 2mg (n=50), or placebo (n=54)

for 12 weeks. The primary endpoint was the mean improvement in MCSs from baseline to week 12, while the secondary endpoints were endoscopy improvement, clinical remission, and clinical repsonse.[20]

The study found patients in etrasimod 2mg group met the primary and secondary endpoints at week 12. A significant improvement in the modified MCSs from baseline was observed in the etrasimod 2mg group compared to the placebo group (difference from placebo, 0.99 points; 90%CI, 0.30 to 1.68; p=0.009). Etrasimod 1mg group also showed improvement from baseline in modified MCSs of 0.43 points more than placebo (90%CI -0.24 to +1.11; p=0.15).[20]

Endoscopic improvement was achieved in etrasimod 2mg group versus placebo (41.8% versus 17.8%; 90%CI 9.8% to 39.0%; p=0.003), and etrasimod 1mg group versus placebo (22.5% versus 17.8%; 90%CI -9.1% to +17.2%; p=0.31). A significant improvement in clinical remission and clinical response was observed in the etrasimod 2mg group compared to the placebo group (33.0% versus 8.1%; 90%CI 13.5% to 38.1%; p<0.001) and (50.6.0% versus 32.5%; 90%CI 2.6% to 35.3%; p=0.03), respectively.[20]

Patients who completed the OASIS trial were enrolled (n=118) in the open-label extension (OLE) study to receive etrasimod 2mg for up to an additional 34 to 40 weeks (46 to 52 weeks in total). A total of 92 (85%) patients completed the study. At the end of treatment, 69% of patients maintained endoscopic improvement, 60% experienced sustained clinical remission, and 85% maintained clinical response. Overall, 22% of patients in this study had steroid-free clinical remission at the end of treatment.[21]

B. Safety

In the ELEVATE UC 52 trial, adverse events were reported in 206 (71%) patients in the etrasimod group and 81 (56%) patients in the placebo group. Twelve (4%) patients in the etrasimod group and seven (5%) patients in the placebo group withdrew from the trial due to treatment-related adverse events. In the ELEVATE UC 12 trial, adverse events were reported in 112 (47%) patients in the etrasimod group and 54 (47%) patients in the placebo group. Thirteen (5%) patients in the etrasimod group and one (1%) patient in the placebo group withdrew from the trial due to treatment-related adverse events. The most reported adverse events in both trials were anaemia, headache, worsening of ulcerative colitis or ulcerative colitis flare, infections, hypertension, and bradycardia. The adverse events were considered either mild to moderate, and no death or malignancies were reported.[19]

The results were consistent with the phase II trial (OASIS) where most adverse events reported were mild to moderate. The most reported adverse events were worsening of ulcerative colitis, upper respiratory infection, nasopharyngitis, and

anaemia. Three patients in etrasimod group had a transient, asymptomatic, low-grade atrioventricular block that resolved spontaneously.[20,21]

Similar to ozanimod, etrasimod is contraindicated in patients with cardiac disorders such as myocardial infarction, unstable angina, and stroke. However, unlike ozanimod, etrasimod does not require dose titration upon treatment initiation.[23]

ESTIMATED COST

The wholesale acquisition price for Velsipity™ (Etrasimod) is $6,164 (RM 29,270) per bottle, providing a 30-day supply at a rate of approximately $976 (RM 4,909) per day.[22] In comparison, the list price for Zeposia (Ozanimod) is $8,890 (RM 42,214) for a 30-day supply.[24]

OTHER ISSUES

A. Organisational

Etrasimod received FDA approval on 13 October 2023 as an oral, once-daily, selective sphingosine-1-phosphate (S1P) receptor modulator for adults with moderately to severely active ulcerative colitis. Etrasimod is branded as Velsipity™, and the approved recommended dose for etrasimod is 2 mg.[16]

B. Societal/ethical

There was no retrievable evidence of societal/ethical issues on etrasimod. One of the advantages of S1P modulators is that they can be taken orally, which is generally more convenient for patients compared to the intravenous or subcutaneous administration required for some biological therapies.[8]

POTENTIAL IMPACT

In conclusion, the results from two phase III trials demonstrated that etrasimod was effective and well tolerated as both an induction and maintenance therapy in patients with moderate to severe ulcerative colitis. Etrasimod could be a potential breakthrough option for patients who are not responding to their current treatment.

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