MALAYSIAN HEALTH TECHNOLOGY ASSESSMENT SECTION

TechScan Horizon Scanning	Report No.: 000/Year

ETROLIZUMAB FOR INFLAMMATORY BOWEL DISEASE

Keywords: Ulcerative colitis, Crohn's disease, monoclonal antibody, gastrointestinal disease.

SUMMARY OF TECHNOLOGY

Etrolizumab (previously known as rhuMAb Beta7) is an investigational biologic medication developed by Genentech/Roche to treat two major forms of inflammatory bowel disease (IBD); ulcerative colitis (UC) and Crohn's disease (CD).[1] This gut-targeted anti-β7 integrin is a humanised monoclonal antibody which selectively binds the β7 subunit of the heterodimeric α4β7 and αEβ7 integrins with high affinity, blocking binding to their ligands, mucosal addressin cell adhesion molecule-1 (MAdCAM-1) and E-cadherin, respectively.

Physiologically, the α4β7 integrin is a glycoprotein on the surface of circulating T-lymphocytes which is involved in their recruitment to the gastrointestinal (GI) tract. The α4β7 integrin is activated on the lymphocyte surface and it binds with its counter receptor, a glycosaminoglycan ligand on the endothelial surface membrane, the MAdCAM-1. It is selectively expressed on the endothelium of intestinal vasculature. MAdCAM-1 binds the lymphocytes from the endothelial lumen as part of the rolling process. These bound lymphocytes then migrate to the lamina propria and tissue. Abnormal retention in these cells forms a critical part of the inflammatory process in UC which reflects the outcome of a genetic alteration in the innate immune system as well as the amplified responses of adaptive immunity. The αEβ7 integrin is a heterodimeric integrin found on intraepithelial T-cells and facilitates their adhesion to the epithelial cells. This αEβ7 integrin is also found on dendritic cells (DC) which mediate gut homing and induce regulatory T-cell development.[1]

Etrolizumab provides a dual approach mechanism of action through blocking of α4β7–MAdCAM-1 interactions which inhibits leucocyte trafficking to the gut and through blocking of αEβ7–E-cadherin interactions which inhibits the retention of leucocytes in the intraepithelial lining of the gut. This, subsequently reduces β7-positive lymphocyte migration and retention in the inflamed gut mucosa, as shown in Figure 1.[2]

The studied dosage of etrolizumab is 105 mg given subcutaneously once every 4 weeks in 14-weeks induction phase and 52-weeks maintenance phase.[3]

Other anti-intergrin therapy such as natalizumab, which acts on α4-integrin, was the first of such drug to be approved for Crohn's disease, but its use is limited due to the risk of progressive multifocal leukoencephalopathy.[3] Similarly, vedolizumab is also a gut-trophic α4β7 integrin has been approved for treatment of IBD, but it produces few systemic adverse effects.[3] In contrast to vedolizumab and natalizumab, etrolizumab is a dual-action, anti-β7 monoclonal antibody that selectively targets α4β7 and αEβ7 integrins.[4]

As to date, etrolizumab has not received any approval for the treatment of IBD from any regulatory bodies.

Figure 1: Mechanism of action for Etrolizumab.[1]

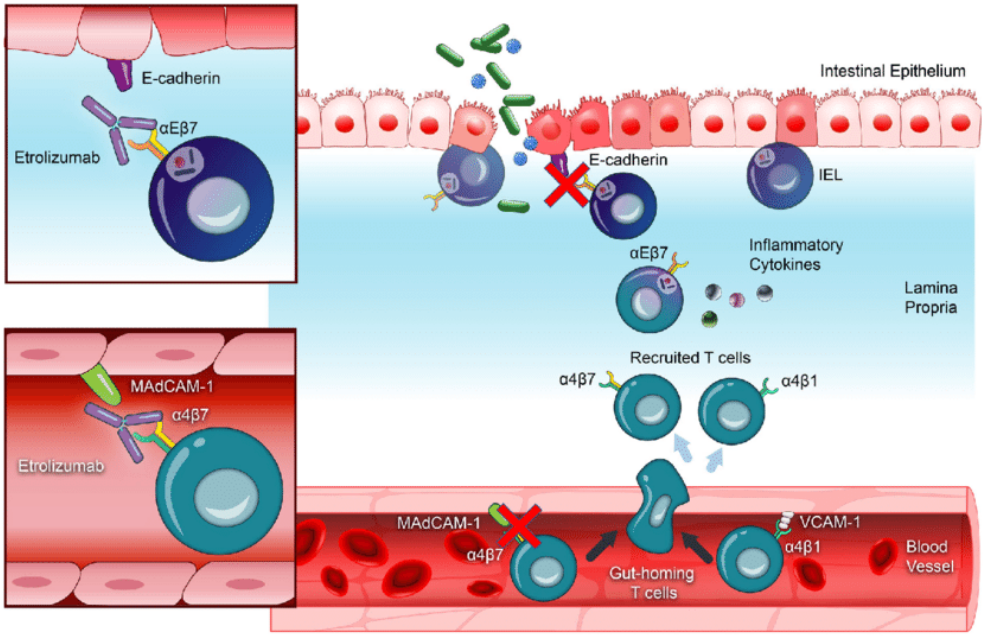

Figure 2 showed the dual action of Etrolizumab by blocking blocking α4β7–MAdCAM-1 and αEβ7–E-cadherin interaction, thereby inhibiting the interactions between leukocytes and intestinal blood vessels[2] *IEL: intraepithelial lymphocyte; MAdCAM-1: mucosal vascular addressin cell adhesion molecule 1; VCAM-1 vascular cell adhesion molecule 1.

INNOVATIVENESS

Novel, completely new	
Incremental improvement of the existing technology	/
New indication of an existing technology	

DISEASE BURDEN

Inflammatory bowel disease is a chronic condition, characterised by relapsing and remitting inflammation of gastrointestinal (GI) tract. It encompasses Crohn's disease (CD), which can affect any segment of GI tract, and ulcerative colitis (UC), which involves exclusively the rectum and colon. Although UC and CD share a number of similar clinical features, each does have distinct intestinal manifestation.[5]

Inflammatory bowel disease (IBD) was once considered as a Western disease. However, the incidence of IBD is rising in Malaysia, especially in the last one decade.[5] According to one retrospective study conducted in one tertiary centre in Kuala Lumpur showed that mean crude incidence of IBD has increased steadily over the first three decades: 0.36 (1980–1989), 0.48 (1990–1999) and 0.63 per 100,000 person-years (2000–2009).[5] In the 2010 to 2018 period, the mean crude incidence has doubled to 1.46 per 100,000 person-years. This might be associated with the urbanisation and changing diets. The prevalence rate of IBD, UC and CD, respectively were 23.0, 15.67 and 7.36 per 100,000 persons.[5]

Risk factors for UC include genetic susceptibility and factors that influence the gut microbiota, such as antibiotic use and dietary changes, for example, extensive consumption of processed foods.[6]

The risk of colorectal cancer (CRC) is 2-to-5 times higher in patients with UC than the general population, and it is major cause of morbidity and mortality among these individuals.[7] According to one systematic review on 14 surveillance cohort studies of 671 patients with ulcerative colitis with low-grade dysplasia (UC-LGD) showed that 52 patients developed colorectal cancer (CRC) with the pooled annual incidence of CRC was 0.8% (95% CI, 0.4 to 1.3); the pooled annual incidence of advanced neoplasia was 1.8% (95% CI, 0.9 to 2.7).[7]

At present, there is no cure for IBD and therefore the management is aimed at induction and maintenance of the disease remission.[5] Due to its chronicity, IBD can results in significant long-term morbidity, impairment of patient's health-related quality of life and excess health care resource use.[5]

Inflammatory bowel disease affects substantial social and economic burden on governments and health systems. One systematic analysis for the Global Burden of Disease Study 2017 was conducted and it showed that the total years lived with disability (YLDs) attributed to IBD almost doubled over the study period, from 0.56 million (0.39–0.77) in 1990 to 1.02 million (0.71–1.38) in 2017. The age-standardised rate of disability-adjusted life-years (DALYs) decreased from 26.5 (21.0–33.0) per 100 000 population in 1990 to 23.2 (19.1–27.8) per 100 000 population in 2017.[8]

The Mayo Clinic total score (MCS) is one of the most commonly used disease activity indices in placebo-controlled trials in UC. In its complete form, it is composed of four parts: rectal bleeding, stool frequency, physician assessment, and endoscopy appearance. Each part is rated from 0 to 3, giving a total score of 0 to 12. A score of 3 to 5 points indicates mildly active disease, a score of 6 to 10 points indicates moderately active disease, and a score of 11 to 12 points indicates severely active disease. Two abridged versions, the partial Mayo score that excludes the endoscopy subscore and the non-invasive six-point score comprising only the rectal bleeding and stool frequency portions, have been developed and validated. The Mayo score and the partial Mayo score have been demonstrated to correlate with patient assessment of change in UC activity.[9] Clinical response is defined as MCS with ≥3-point decrease[9] and ≥30% reduction from baseline, plus ≥1-point decrease in rectal bleeding subscore or absolute rectal bleeding score of 0 or 1. Clinical remission is defined as MCS ≤2[9], with individual subscores ≤1, and rectal bleeding subscore of 0.[4,10,11] Other terms or key secondary endpoints utilized in the clinical trials include endoscopic improvement (defined as Mayo endoscopic subscore of ≤1), endoscopic remission (defined as Mayo endoscopic subscore of 0) and histological remission (Nancy histological index [NHI] of ≤1 among patients with histological inflammation at baseline).[4,10,11]

CURRENT OPTIONS FOR PATIENTS

According to IBD Treatment Algorithm developed by Malaysian Society of Gastroenterology and Hepatology, the primary objective of treatment of IBD is to induce, and maintain remission; if there is a disease flare this is then promptly addressed in order to induce remission again as soon as possible.[12] Immediately following diagnosis, a baseline assessment is crucial to ascertain the patient's disease status prior initiating treatment. In general, patients are treated using conventional medications first; biologic therapies and/or surgical intervention will be introduced later.[12]

The classes of medications for IBD include anti-inflammatory drugs such as corticosteroids (e.g. budesonide, prednisone) or aminosalicylate (e.g. mesalamine, sulfasalazine); immunomodulators (e.g. azathioprine, 6-mercaptopurine, methotrexate); antibiotics (e.g. rifaximin); and biologics (e.g. infliximab, adalimumab, certolizumab pegol, golimumab, ustekinumab, vedolizumab), all of which may be used alone or in combination.[13] In spite of their long-term effectiveness, many patients do not respond to or cannot sustain treatment with these drugs, due to various side effects.[14,15]

Until recently, in moderate-to-severe active IBD patients, especially if initial treatment with systemic corticosteroids or immunomodulators failed, anti-TNF agents were the only remaining treatment option. Anti-tumor necrosis factor (TNF) agents (e.g. infliximab, adalimumab, certolizumab pegol) were the first biologics used to treat IBD, and the objective of IBD treatment has shifted from controlling symptoms to changing

the progression of disease and preserving the intestinal function. However, anti-TNF agents are not effective in all IBD patients, and a considerable number of patients experience relapse after stopping medication.[3] Moreover, corticosteroid dependence and probability of colectomy remain significant challenges among IBD patients, the latter most commonly due to failed medical therapy.[2] This means that the most appropriate treatment method may vary for each patient, and therefore, constant efforts are being made to develop effective drugs to treat IBD.

POTENTIAL IMPACT OF TECHNOLOGY

a. Clinical Impact

Systematic search was conducted from scientific databases such as Medline, EBM Reviews, EMBASE via OVID, PubMed and from the general search engines [Google Scholar and US Food and Drug Administration (US FDA)] on (i) effectiveness of etrolizumab (ii) safety of etrolizumab

There were 7 retrievable published scientific evidence on the effectiveness and safety of etrolizumab for the treatment of UC and 3 on-going clinical trials including treatment for CD as shown in Table 1 and Table 2.

Table 1 shows the summarized list of retrieved clinical trials for etrolizumab for ulcerative colitis and crohn's disease.

Study	Study design	Population	Therapy	On anti-TNF	Outcome
NCT 00694980 (induction)[2]	Phase I RCT	48 adults patients	Etrolizumab vs placebo	no	Clinical response on day 29 in single ascending dose and day 43 and 71 in multiple doses group.
NCT 03478956 (induction)[16]	Phase I RCT	24 paediatric UC and DC	Etrolizumab vs placebo	no	Clinical response at week 16
EUCALYPTUS (induction)[17]	Phase II RCT	124 adult patients	Etrolizumab vs placebo	no	Clinical remission at week 10

HIBISCUS I & II (induction)[11]	Phase III RCT	358 adult patients in each study	Etrolizumab vs adalimumab vs placebo	no	Clinical remission at week 10
HICKORY (induction & maintenance)[18]	Phase III RCT	609 adult participants	Etrolizumab vs placebo	yes	Clinical remission at week 14 and week 66.
LAUREL (maintenance)[10]	Phase III RCT	214 adult participants	Etrolizumab vs placebo	no	Clinical remission at week 62
GARDENIA (treatthrough)[4]	Phase III RCT	397 adult participants	Etrolizumab vs infliximab	no	Clinical response at week 10 and remission at week 54

Table 2 shows the on-going clinical trials on UC and CD.

Study	Study design	Description	Exposure to anti-TNF	Comment
COTTONWOOD[19]	Phase III	Open label extension from 5 RCT on UC. Expected to complete 2025	yes	Long term efficacy and severity of side effect
BERGAMOT[19]	Phase III	Etrolizumab vs placebo in CD patients. On-going.	yes	Clinical remission and response at week 14
JUNIPER[19]	Phase III	Open label extension trials on CD. Expected to complete 2025	yes	Long term efficacy and severity of side effect

Effectiveness

Among seven trials, only one clinical trial was conducted among paediatric population with inflammatory bowel disease. This multicentre, open-labelled, randomised phase 1 study (NCT03478956) was done among patient aged 4 to 17 years old with moderately to severely active UD or CD who had an inadequate response, loss of response, or intolerance to prior treatment with immunosuppressants, corticosteroids, and/or antitumor necrosis factor therapies. The participants were randomly assigned to receive either high-frequency subcutaneous etrolizumab (1.5 mg/kg once every 4 weeks) for a total of 4 doses (given at weeks 0, 4, 8, and 12) or low-frequency subcutaneous etrolizumab (3.0 mg/kg once every 8 weeks) for a total of 2 doses (given at weeks 0 and 8). Efficacy outcomes were exploratory and consisted of clinical response at week 16. In patients with ulcerative colitis, clinical response was assessed with the Pediatric Ulcerative Colitis Activity Index (PUCAI) and was defined as a decrease from baseline (study day 1) of at least 20 points at week 16. In patients with Crohn's disease, clinical response was assessed with the Pediatric Crohn's Disease Activity Index (PCDAI) and was defined as a decrease from baseline (study day 1) of at least 15 points at week 16. The finding showed that at week 16, 6 of 10 patients (60%) with Crohn's disease experienced a clinical response based on the PCDAI; each dose group had 3 responders. Among patients with ulcerative colitis, 9 of 14 patients (64.3%) experienced a clinical response based on the PUCAI at week 16: 5 responders were in the 1.5 mg/kg dose group, and 4 responders were in the 3.0 mg/kg dose group. There were no clinically meaningful changes in serum C-reactive protein levels or faecal calprotectin levels were observed from baseline to the end of the randomised study phase. This study was not adequately powered to demonstrate etrolizumab efficacy, and any exposure-response relationship could not be appropriately evaluated in this phase 1 study because of the small sample size.[16]

A double-blind, placebo-controlled, randomised, phase 2 study (EUCALYPTUS) recruited 124 adult patients aged 18 to 75 years old with moderately-to-severely active ulcerative colitis who had not responded to conventional therapy (on stable dosage if they were receiving oral mesalazine (2.4–4.8 g per day), corticosteroids (≤20 mg per day of prednisone), azathioprine, mercaptopurine, or methotrexate. Patients were randomised to three groups either 100 mg subcutaneous etrolizumab given at weeks 0, 4, and 8, with placebo at week 2; or 420 mg loading dose at week 0 followed by 300 mg at weeks 2, 4, and 8; or matching placebo group. Efficacy was assessed in the modified intention-to-treat (mITT) population to look for clinical remission at week 10. The primary endpoint was met showing that 21% [95% CI 7–36; p=0.0040] of patients in the etrolizumab 100 mg group and 10% [0.2–24; p=0.048] of patients in the loading dose group with 300 mg dosing had achieved remission at week 10. There were no patients in the placebo group who had clinical remission at week 10.[17]

HIBISCUS I and HIBISCUS II were identically designed, multicentre, randomised, double-blind, placebo-controlled and active-controlled phase 3 studies comparing etrolizumab, adalimumab (anti-TNF therapy), and placebo in adult aged 18 to 80 years old patients with moderate to severe active ulcerative colitis. HIBISCUS I screened 652 patients and assigned 358 patients (2:2:1) into etrolizumab (n=144), adalimumab (n=142), placebo group (n=72). Whereas HIBISCUS II screened 613 patients and assigned 358 patients (2:2:1) to etrolizumab (n=143), adalimumab (n=143), and placebo group (n=72). Patients receiving stable doses (4 to 6 weeks prior trial) of oral

5-aminosalicylates, oral corticosteroids and immunosuppressants such as azathioprine, 6-mercaptopurine, and methotrexate were included. Etrolizumab group received subcutaneous 105 mg once every 4 weeks. Adalimumab group received subcutaneous injection of 160 mg on day 1, 80 mg at week 2, and 40 mg at weeks 4, 6, and 8. Patients who achieved clinical remission at week 10 underwent a mandatory corticosteroid tapering regimen up to week 14. Baseline doses of immunosuppressant therapy were kept stable throughout the studies. The primary endpoint was induction of remission at week 10 with etrolizumab compared with placebo, analysed using a modified intent-to-treat population. For primary endpoint in HIBISCUS I, 19.4% in the etrolizumab group and 6.9% in the placebo group were in clinical remission at week 10, with significant adjusted treatment difference of 12.3% (95% CI 1.6 to 20.6; p=0.017) in favour of etrolizumab. There were significantly more patients in the etrolizumab group in HIBISCUS I who achieved endoscopic improvement (etrolizumab [40%] versus placebo [22%]; p=0.017) and histological remission (etrolizumab [43%] versus placebo [16%]; p=0.017) at week 10. However, in HIBISCUS II, there were no significant treatment difference between etrolizumab group (18.2%) and placebo group (11.1%) in remission at week 10 with an adjusted treatment difference of 7.2% (95% CI –3.8 to 16.1; p=0.17). In the prespecified pooled analysis of etrolizumab versus adalimumab, no statistically significant differences were observed in the proportion of patients achieving remission (etrolizumab [19%] versus adalimumab [24%]; p=0.13), endoscopic improvement (etrolizumab [40%] versus adalimumab [38%]; p=0.63), clinical response (etrolizumab [55%] versus adalimumab [53%]; p=0.78), histological remission (etrolizumab [37%] versus adalimumab [37%]; p=0.94), or endoscopic remission (etrolizumab [20%] versus adalimumab [24%]; p=0.30) at week 10.[11]

Another double-blind, placebo-controlled, phase 3 study (HICKORY) was conducted which consists of a 14-week induction phase (cohort 1 open-label etrolizumab treatment; cohort 2 blinded, randomised to etrolizumab or placebo), a 52-week maintenance phase (blinded, re-randomised to etrolizumab or placebo), and a 12-week safety follow-up phase. The study recruited 609 adult participants (cohort 1 n=130, cohort 2 n=479) who had established diagnosis of moderate-to-severe active ulcerative colitis with one or two induction regimens that contained anti-TNFs. Patients receiving stable doses of oral 5-aminosalicylates, oral corticosteroids, immunosuppressants such as azathioprine, 6-mercaptopurine, and methotrexate were eligible for the study. Participants in cohort 2 were randomly assigned to the induction phase (etrolizumab n=384, placebo n=95). Clinical responders from both cohorts (n=232) were randomly assigned to etrolizumab or placebo (1:1) in maintenance phase (etrolizumab to etrolizumab n=117, etrolizumab to placebo n=115). In cohort 1, patients received open-label etrolizumab 105 mg every 4 weeks for a 14-week induction period. In cohort 2, patients were randomly assigned (4:1) to receive subcutaneous etrolizumab 105 mg or placebo every 4 weeks for the 14-week induction phase. Those who were eligible for maintenance phase received subcutaneous etrolizumab 105 mg or placebo every 4 weeks through to week 66. Primary efficacy endpoints were remission at week 14, and remission at week 66 among patients with a clinical response at week 14, analysed in modified intent-to-treat (mITT) population. The result showed that in the induction mITT population, significant primary endpoint was achieved with clinical remission at week 14 in 18.5% in the etrolizumab group and 6.3% in the placebo group (adjusted treatment difference 12.2% (95% CI 4.0 to 17.7; p=0.0033). However, in the maintenance mITT population,

there were no significant differences between etrolizumab and placebo group (24.1% versus 20.2%; adjusted treatment difference 3.8%, 95% CI –7.1 to 14.6; p=0.50) in clinical remission at week 66. At week 14, a significantly greater proportion of patients in the etrolizumab group had a clinical response (46% versus 32%; p=0.024). However, there were no significant differences observed between etrolizumab and placebo for endoscopic improvement (33% versus 25%; p=0.16), endoscopic remission (17% versus 9%; p=0.39), or histological remission (30% versus 25%; p=0.59) at week 14. The mean change from baseline to week 6 in rectal bleeding subscore was significantly greater with etrolizumab (–0.7) versus placebo (–0.4; p=0.035). Though maintenance endpoint was not met, it was observed that nominally the etrolizumab had statistically significant greater proportion of patients had endoscopic improvement at week 66 compared with placebo (36% versus 21%; p=0.015). Differences in histological remission were also nominally significantly greater in the etrolizumab group (31% versus 14%; p=0.0073) as were results for endoscopic remission (23% versus 11%; p=0.017) at week 66. Among patients receiving corticosteroids at baseline, a higher proportion of patients treated with etrolizumab versus placebo achieved corticosteroid-free remission at week 66, however this difference was not significant (19% versus 11%; p=0.28). Finally, similar proportions of patients achieved sustained remission between the etrolizumab and placebo groups (37% versus 34%; p=0.95).[18]

A randomised, double-blind, double-dummy, parallel-group, phase 3 study (GARDENIA) was conducted to compare the efficacy of etrolizumab with infliximab (an anti-TNF) among 397 adult participants aged 18 to 80 years old with moderate-to-severe ulcerative colitis who were naive to tumour necrosis factor inhibitors. Participants were randomly (1:1) assigned to etrolizumab group (n=199) received subcutaneous injection of 105 mg once every 4 weeks plus an intravenous dummy infliximab treatment of 250 mL saline placebo at weeks 0, 2, and 6, then every 8 weeks thereafter, until week 54. Whereas the infliximab group (n=198) received intravenous infliximab 5 mg/kg at weeks 0, 2, and 6, then every 8 weeks, plus a subcutaneous dummy etrolizumab treatment of 0.7 mL placebo once every 4 weeks, until week 54. The primary efficacy endpoint was both clinical response at week 10 and clinical remission at week 54. The result showed that etrolizumab was not found to be superior to infliximab, however the proportion of patients who met the primary endpoint with etrolizumab treatment was numerically similar (although not powered to show non-inferiority) to that observed with infliximab treatment which were 18.6% in the etrolizumab group and 19.7% in the infliximab group (adjusted treatment difference –0.9% [95% CI –8.7 to 6.8]; p=0.81). Other than that, etrolizumab also had numerically similar rates of corticosteroid-free clinical remission observed at week 54 as compared to infliximab groups (15% versus 17%; p=0.89). Among patients who had clinical response at week 10, a numerically similar proportion of patients reached clinical remission at week 54 in the etrolizumab and infliximab groups (38% versus 33%; p=0.42). There was no significant difference in the proportion of patients who had sustained clinical remission in the etrolizumab and infliximab groups (11% versus 13%; p=0.46).[4]

Another randomised, placebo-controlled, double-blind, phase 3 study (LAUREL) which focused more on the efficacy and safety of etrolizumab in maintaining remission had recruited 359 adults with moderate-to-severe active ulcerative colitis into the open-labelled induction phase. Following then, 214 (60%) patients who had clinical

response at week 10 were randomly assigned to receive subcutaneous etrolizumab 105 mg (n=108) or matching placebo (n=106) once every 4 weeks during the maintenance phase until week 62. Patients entering the maintenance phase at week 10 underwent a mandatory corticosteroid tapering regimen. Baseline doses of immunosuppressant therapy were kept stable throughout the study. Primary efficacy endpoint was remission at week 62 among patients with a clinical response at week 10. The primary endpoint was not met by which there was no significant differences noted between maintenance etrolizumab and placebo at week 62 (29.6% versus 20.6% with adjusted treatment difference 7.7% [95% CI –4.2 to 19.2]; p=0.19). The secondary endpoint was an exploratory analysis and it was shown that etrolizumab had numerically superior than placebo in endoscopic improvement (38% versus 23%; p=0.024), histological remission (42% versus 22%; p=0.0075) and endoscopic remission (31% versus 17%; p=0.029) at week 62. However, there were no significant differences observed in the endpoints of remission at week 62 (40% in the etrolizumab group versus 27% in the placebo group; p=0.31) or corticosteroid-free remission (18% versus 8%; p=0.14).[10]

b. Cost

There was no retrievable evidence on the cost or cost-effectiveness study of Etrolizumab. One systematic review of the cost-effectiveness of biologics for ulcerative colitis was done in 2017. There were limited data on the cost-effectiveness of UC therapy identified, however majority of the evaluations revealed performed for infliximab (75% of total volume), adalimumab (50%) and golimumab (31%). There were no relevant studies found for etrolizumab and tofacitinib. In majority of studies, the lack of cost-effectiveness was revealed for biologics, which was associated with their high costs. The incremental cost-utility ratios for biologics, compared with standard care, varied significantly between the studies and ranged from US$36,309 to US$456,979. (MYR159,505.44 to MYR2,007,508; 1USD=4.39MYR).[20] Comparatively, the price of intravenous Natalizumab (300 mg/15 mL) which is another anti-intergrin group is around $8,282 (MYR 36192.34; 1USD=4.39MYR) for a supply of 15 milliliters.[21]

c. Societal/ethical

There was no retrievable evidence on societal or ethical issue on Etrolizumab.

d. Safety

According to phase 1 study in adult patient (NCT00694980), The overall incidence of treatment-related AEs was marginally higher in the active treatment group, and occurred in the first 24 hours of treatment. There was no dose-dependent increase in the incidence of AEs. Headache was the most common AE occurring more often in actively treated patients. There were no dose limiting toxicities or clinically significant infusion reactions or injection site reactions were reported. Eight patients had serious AEs. Seven in the SAD stage (6:1; etrolizumab:placebo) and one in the MD stage (1:0; etrolizumab:placebo). Exacerbation of ulcerative colitis was the most common serious

AE. There were two patients with impaired wound healing post-urgent colectomy for exacerbation of UC. Both patients had severe UC with baseline MCS of 9 and 11.[2]

In a phase 1 study among paediatric age group (NCT03478956), the safety outcomes measured were incidence and severity of infection-related adverse events, incidence of immunogenicity responses, and incidence and severity of hypersensitivity reaction events. The result showed that the incidence of any-grade adverse events was comparable between high-frequency etrolizumab (1.5 mg/kg once every 4 weeks) and low-frequency etrolizumab group (3.0 mg/kg once every 8 weeks). In the 1.5 mg/kg group, the adverse events with the highest incidence (≥20%) by preferred term were anaemia, pyrexia, and abdominal pain, in descending order. In the 3.0 mg/kg group, the adverse events with the highest incidence (≥20%) by preferred term were exacerbation of Crohn's disease and headache. Most adverse events were grade 1 or 2. Four of 24 patients (17%) experienced seven serious adverse events (namely diarrhea, gastritis, vomiting, anemia, anxiety disorder, exacerbation of ulcerative colitis, exacerbation of Crohn's disease). One serious adverse event (anxiety disorder) in the 1.5 mg/kg dose group was reported by the investigator as related to treatment. No deaths, serious infections, opportunistic infections, malignancies, hypersensitivity reactions, or adverse events of special interest were reported.[16]

In EUCALYPTUS study, patients in the etrolizumab 100 mg group had higher rates of rash, influenza-like illness, and arthralgias than did those in the placebo or etrolizumab 300 mg plus loading dosage group. However, all of these events were regarded as mild to moderate in severity. Most common adverse effects in descending order were ulcerative colitis (17% in the etrolizumab 100 mg group; 23% in the etrolizumab 300 mg plus LD group; and 19% in the placebo group), nasopharyngitis (10% in the etrolizumab 100 mg group; 15% in the etrolizumab 300 mg plus LD group; and 19% in the placebo group), nervous system disorders (15% in the etrolizumab 100 mg group; 10% in the etrolizumab 300 mg plus LD group; and 14% in the placebo group) and headache (12% in the etrolizumab 100 mg group; 10% in the etrolizumab 300 mg plus LD group; and 12% in the placebo group). Serious adverse events were reported (12% in the etrolizumab 100 mg group; 5% in the etrolizumab 300 mg plus LD group; and 12% in the placebo group); five of these patients were related to ulcerative colitis. No serious opportunistic infections were reported. Mild injection site reactions occurred in four patients in the etrolizumab 300 mg plus LD group and in two patients in the placebo group.[17]

According to HIBISCUS study, safety endpoints included the incidence and severity of adverse events, serious adverse events, injection site reactions, laboratory abnormalities, and hypersensitivity reactions. Similar incidences of adverse events were reported across treatment groups both within each study and across studies, with most adverse events considered to be mild to moderate in severity and unrelated to study drug. A numerically higher percentage of patients in HIBISCUS I who had serious adverse events were in the etrolizumab group (6%) compared with the placebo

group (3%) and the adalimumab group (2%); however, the incidence of serious adverse events in the pooled analysis population was similar for etrolizumab (5%) and placebo (5%) and lower for adalimumab (2%). No specific pattern was noted in types of serious adverse events in the etrolizumab group except for two unrelated deaths. Across all treatment groups, the incidence of infections was slightly higher in HIBISCUS I than in HIBISCUS II; however, the incidence of serious infections across all treatment groups was low in both studies, ranging from 0–3%. The adverse events occurring in at least 5% of any treatment group includes ulcerative colitis [HIBISCUS I: placebo (6%) adalimumab (8%) etrolizumab (5%); HIBISCUS II: placebo (14%), adalimumab (9%), etrolizumab (7%)], headache [HIBISCUS I: placebo (4%) adalimumab (6%) etrolizumab (1%); HIBISCUS II: placebo (0%), adalimumab (6%), etrolizumab (2%)], anemia [HIBISCUS I: placebo (3%) adalimumab (2%) etrolizumab (4%); HIBISCUS II: placebo (7%), adalimumab (1%), etrolizumab (4%)] and upper respiratory infection [HIBISCUS I: placebo (0%) adalimumab (2%) etrolizumab (2%); HIBISCUS II: placebo (6%), adalimumab (2%), etrolizumab (3%)].[11]

In HICKORY study, similar incidences of adverse events were reported between the etrolizumab and placebo groups, with most adverse events considered mild to moderate in severity in both study phases. In the induction phase, 66% of patients in the etrolizumab group and 66% in the placebo group experienced one or more adverse event. In the maintenance phase, 88% patients in the etrolizumab group and 85% patients in the placebo group experienced at least one adverse event. Ulcerative colitis flares were the most common adverse event leading to treatment discontinuation in all groups, with similar incidence in patients receiving etrolizumab for induction and maintenance. The most frequently reported adverse events across both study groups and phases were ulcerative colitis flare, nasopharyngitis, abdominal pain, arthralgia, and headache. During the maintenance phase, a higher proportion of patients in the etrolizumab treatment group reported infections (52% for etrolizumab versus 39% for placebo); nasopharyngitis was the most frequently reported infection in all treatment groups. Most common serious adverse events during induction was ulcerative colitis flare (etrolizumab [3%] versus placebo [2%]). Whereas, the most common serious adverse event in maintenance phase among the etrolizumab to etrolizumab group was appendicitis (2%) and the most common serious adverse events in the etrolizumab to placebo group were ulcerative colitis flare (2%) and anaemia (2%). There were no cases of progressive multifocal leukoencephalopathy reported.[18]

In GARDENIA study, similar incidences of adverse events were reported between the etrolizumab and infliximab groups; 77% in the etrolizumab group and 76% in the infliximab group had one or more adverse events. Most adverse events were mild to moderate in severity. The most common adverse event in both treatment groups was ulcerative colitis (28% patients in the etrolizumab group; 22% in the infliximab group). Ulcerative colitis flares were also the most common adverse event leading to treatment discontinuation in both groups, and this was more common in the etrolizumab group (11%) than in the infliximab group (4%). The incidence of infections was similar

between groups (35% in the etrolizumab group; 31% in the infliximab group); however, gastrointestinal infections were more common in the etrolizumab group (8%) than in the infliximab group (4%).[4]

According to LAUREL study, the safety endpoints included the incidence and severity of adverse events, serious adverse events, laboratory abnormalities, and hypersensitivity reactions. Most of the adverse events were considered mild or moderate in severity. More patients in the placebo group reported one or more adverse events than in the etrolizumab group (80% in placebo group versus 65% in etrolizumab). The adverse events that occurred more frequently with etrolizumab included fatigue, headache, and nasopharyngitis. The most common adverse event in both treatment groups was ulcerative colitis flare, which occurred in 36% in the placebo group and 15% in the etrolizumab group. Ulcerative colitis flares were also the most common adverse event leading to treatment discontinuation in both groups, although this was more common in the placebo group (7%) than in the etrolizumab group (2%). During induction, one patient reported a non-serious adverse event of pruritus, which was considered related to study treatment.[10]

CONCLUSIONS

In conclusion, there were early studies on safety and effectiveness of etrolizumab to be used in induction and/or maintenance phase for adult with moderate-to-severely active ulcerative colitis. Clinical studies on Crohn's disease are yet-to-be-determined. Evidences has shown that etrolizumab has tolerable safety profile. Although clinical remission was barely met in several studies, etrolizumab was found to be superior to placebo in endoscopic improvement, histological remission and endoscopic remission in several studies. When comparing etrolizumab to anti-TNF agents (e.g adalimumab or infliximab), it was shown that etrolizumab had numerically similar results with those agents, cost complications of etrolizumab in both UC and DC need to be further evaluated.

EVIDENCE

1. Rutgeerts PJ, Fedorak RN, Hommes DW, et al. A randomised phase I study of etrolizumab (rhuMAb β7) in moderate to severe ulcerative colitis. Gut. 2013;62(8):1122-1130.
2. Peyrin-Biroulet L, Hart A, Bossuyt P, et al. Etrolizumab as induction and maintenance therapy for ulcerative colitis in patients previously treated with tumour necrosis factor inhibitors (HICKORY): a phase 3, randomised, controlled trial. The lancet Gastroenterology & hepatology. 2022;7(2):128-140.
3. Danese S, Colombel JF, Lukas M, et al. Etrolizumab versus infliximab for the treatment of moderately to severely active ulcerative colitis (GARDENIA): a

randomised, double-blind, double-dummy, phase 3 study. The lancet Gastroenterology & hepatology. 2022;7(2):118-127.
4. Vermeire S, Lakatos PL, Ritter T, et al. Etrolizumab for maintenance therapy in patients with moderately to severely active ulcerative colitis (LAUREL): a randomised, placebo-controlled, double-blind, phase 3 study. The lancet Gastroenterology & hepatology. 2022;7(1):28-37.
5. Rubin DT, Dotan I, DuVall A, et al. Etrolizumab versus adalimumab or placebo as induction therapy for moderately to severely active ulcerative colitis (HIBISCUS): two phase 3 randomised, controlled trials. The lancet Gastroenterology & hepatology. 2022;7(1):17-27.
6. Zhang W, Scalori A, Fuh F, et al. Pharmacokinetics, Pharmacodynamics, and Safety of Etrolizumab in Children With Moderately to Severely Active Ulcerative Colitis or Crohn's Disease: Results from a Phase 1 Randomized Trial. Inflamm Bowel Dis. 2021.
7. Vermeire S, O'Byrne S, Keir M, et al. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. Lancet. 2014;384(9940):309-318.

REFERENCES

1. Creative Biolabs. Etrolizumab Overview. 2022. Available from: https://www.creativebiolabs.net/etrolizumab-overview.htm. Accessed on 3 March 2022.

2. Rutgeerts PJ, Fedorak RN, Hommes DW, et al. A randomised phase I study of etrolizumab (rhuMAb β7) in moderate to severe ulcerative colitis. Gut. 2013;62(8):1122-1130.

3. Park SC, Jeen YT. Anti-integrin therapy for inflammatory bowel disease. World journal of gastroenterology. 2018;24(17):1868-1880.

4. Danese S, Colombel JF, Lukas M, et al. Etrolizumab versus infliximab for the treatment of moderately to severely active ulcerative colitis (GARDENIA): a randomised, double-blind, double-dummy, phase 3 study. The lancet Gastroenterology & hepatology. 2022;7(2):118-127.

5. Mokhtar NM, Nawawi KNM, Verasingam J, et al. A four-decade analysis of the incidence trends, sociodemographic and clinical characteristics of inflammatory bowel disease patients at single tertiary centre, Kuala Lumpur, Malaysia. BMC Public Health. 2019;19(4):550.

6. Nature Reviews Disease Primers. Ulcerative colitis. Nature Reviews Disease Primers. 2020;6(1):73.

7. Fumery M, Dulai PS, Gupta S, et al. Incidence, Risk Factors, and Outcomes of Colorectal Cancer in Patients With Ulcerative Colitis With Low-Grade Dysplasia: A Systematic Review and Meta-analysis. Clin Gastroenterol Hepatol. 2017;15(5):665-674.e665.

8. Alatab S, Sepanlou SG, Ikuta K, et al. The global, regional, and national burden of inflammatory bowel disease in 195 countries and territories, 1990&2013;2017: a systematic analysis for the Global Burden of Disease Study 2017. The Lancet Gastroenterology & Hepatology. 2020;5(1):17-30.

9. Canadian Agency for Drugs and Technologies in Health. APPENDIX 5: Validity of Outcome Measures. 2016. Available from: https://www.ncbi.nlm.nih.gov/books/NBK539018/. Accessed on 20 March 2022.

10. Vermeire S, Lakatos PL, Ritter T, et al. Etrolizumab for maintenance therapy in patients with moderately to severely active ulcerative colitis (LAUREL): a randomised, placebo-controlled, double-blind, phase 3 study. The lancet Gastroenterology & hepatology. 2022;7(1):28-37.

11. Rubin DT, Dotan I, DuVall A, et al. Etrolizumab versus adalimumab or placebo as induction therapy for moderately to severely active ulcerative colitis (HIBISCUS): two phase 3 randomised, controlled trials. The lancet Gastroenterology & hepatology. 2022;7(1):17-27.

12. Malaysian Society od Gastroenterology & Hepatology (MSGH). Treatment Algorithm for Inflammatory Bowel Disease. 2021. Available from: https://www.msgh.org.my/files/Malaysian_IBD_Treatment_Algorithms.pdf. Accessed on 5 March 2022.

13. Wheat CL, Ko CW, Clark-Snustad K, et al. Inflammatory Bowel Disease (IBD) pharmacotherapy and the risk of serious infection: a systematic review and network meta-analysis. BMC Gastroenterology. 2017;17(1):52.

14. Na S-Y, Moon W. Perspectives on Current and Novel Treatments for Inflammatory Bowel Disease. Gut Liver. 2019;13(6):604-616.

15. Actis GC, Pellicano R, Rosina F. Inflammatory bowel diseases: Current problems and future tasks. World J Gastrointest Pharmacol Ther. 2014;5(3):169-174.

16. Zhang W, Scalori A, Fuh F, et al. Pharmacokinetics, Pharmacodynamics, and Safety of Etrolizumab in Children With Moderately to Severely Active Ulcerative Colitis or Crohn's Disease: Results from a Phase 1 Randomized Trial. Inflamm Bowel Dis. 2021.

17. Vermeire S, O'Byrne S, Keir M, et al. Etrolizumab as induction therapy for ulcerative colitis: a randomised, controlled, phase 2 trial. Lancet. 2014;384(9940):309-318.

18. Peyrin-Biroulet L, Hart A, Bossuyt P, et al. Etrolizumab as induction and maintenance therapy for ulcerative colitis in patients previously treated with tumour necrosis factor inhibitors (HICKORY): a phase 3, randomised, controlled trial. The lancet Gastroenterology & hepatology. 2022;7(2):128-140.

19. Sandborn WJ, Vermeire S, Tyrrell H, et al. Etrolizumab for the Treatment of Ulcerative Colitis and Crohn's Disease: An Overview of the Phase 3 Clinical Program. Adv Ther. 2020;37(7):3417-3431.

20. Stawowczyk E, Kawalec P. A Systematic Review of the Cost-Effectiveness of Biologics for Ulcerative Colitis. PharmacoEconomics. 2018;36(4):419-434.

21. Drugs.com. Tysabri Prices, Coupons and Patient Assistance Programs. 2022. Available from: https://www.drugs.com/price-guide/tysabri. Accessed on 26 May 2022.

Prepared by:
Dr. Asliza binti Ayub
Medical Officer/Senior Principal Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Reviewed by:
Dr. Syaqirah binti Akmal
Public Health Physician
Senior Principle Assistant Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Dr. Izzuna Mudla binti Mohamed Ghazali
Public Health Physician
Deputy Director
Health Technology Assessment Section (MaHTAS)
Medical Development Division
Ministry of Health Malaysia

Disclosure: The author of this report has no competing interest in this subject and the preparation of this report is totally funded by the Ministry of Health, Malaysia.

Horizon Scanning Unit, MaHTAS,
Medical Development Division,
Ministry of Health, Malaysia

Email: horizonscanningunit.cptk@moh.gov.my
Web: http://www.moh.gov.my