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Original Article

Real-world evidence on the safety and effectiveness of fingolimod in patients with multiple sclerosis from Taiwan

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Background/Purpose: Multiple sclerosis is classified as a rare disease in Taiwan. This study evaluated the safety and effectiveness of fingolimod in patients with relapsing-remitting multiple sclerosis (RRMS) from routine clinical practice in Taiwan.
Methods: In this retrospective, multicentre, observational study, we collected clinical data of patients treated with fingolimod 0.5 mg/day in routine clinical practice between September 2012 and December 2015. Primary outcome was the overall safety of fingolimod; secondary outcome was the annualized relapse rate (ARR).

Abbreviations: AE, adverse event; ALT, alanine aminotransferase; ARR, annualised relapse rate; AST, aspartate aminotransferase; AVB, atrioventricular block; CNS, central nervous system; DMT, disease-modifying therapy; ECG, Electrocardiogram; EDSS, expanded disability status scale; IFN, interferon; MRI, magnetic resonance imaging; MS, multiple sclerosis; NMO, neuromyelitis optica; RRMS, relapsing-remitting multiple sclerosis; SAE, serious adverse event.

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Results: Overall, 62/69 (86.1%) patients were on fingolimod by the end of data collection period. Mean age (±standard deviation [SD]) at inclusion was 37.7 ± 10.10 years; mean duration of MS was 5.4 ± 4.52 years and mean duration of fingolimod exposure was 135.8 patient-years. The most common adverse events (AEs) were bradycardia (21.7%; first-dose related), upper respiratory tract infection, dizziness, and hypoaesthesia (numbness) (11.6% each), followed by urinary tract infection and back pain (7.2% each). Seven patients had liver enzyme-related AEs. Eight patients had absolute lymphocyte counts $<0.2 \times 10^3$/uL over the study period. One patient developed second degree AV block after first-dosing. Serious AEs were observed in 11 patients (15.9%; mild-to-moderate). No newly developed macular oedema was detected. The ARR was 0.3 ± 0.74 in fingolimod-treated patients and 66.7% of patients were relapse-free. The mean (SD) change from baseline in expanded disability status scale score was −0.30 ± 1.353.

Conclusion: Fingolimod 0.5 mg/day treatment with an average of 2 years of exposure was associated with a manageable safety profile, and maintained/improved effectiveness in RRMS patients from Taiwan.

Introduction

Multiple Sclerosis (MS), a chronic, immune-mediated disease of the central nervous system (CNS) affects approximately 2.5 million individuals worldwide,[1] predominantly in Northern Europe and North America with a prevalence of over 100 per 100,000.[2] In contrast to the global incidence, MS is relatively less frequent in the Asia-Pacific region (prevalence range: 0—20 per 100,000), with very low prevalence in China, Korea, Taiwan, South East Asia, and Pacific region (range: 0—5 per 100,000).[2] Due to paucity of available epidemiological data, true burden of MS in the Asia-Pacific region remains unknown. Furthermore, another relapsing-remitting CNS demyelinating disease, neuromyelitis optica (NMO) which is known to have high prevalence amongst Asians, shows clinical symptoms that closely mimic those of MS, and thus it often becomes ambiguous to precisely differentiate between the two diseases by neuroimaging studies or differential diagnosis methods.[3,4] In Taiwan, MS is classified as rare disease with an estimated prevalence of 5 per 100,000 for MS and 1 per 100,000 for NMO in 2017.[3]

Although MS treatment modalities have evolved dramatically over the past decades, treatment strategies vary in different countries depending upon the epidemiology, disease burden, heterogeneity or clinical manifestations, and available treatment options. Conventionally, the standard first-line treatments for relapsing MS are injectable disease-modifying therapies (DMTs) such as interferon (IFN) beta-1a, IFN beta-1b, and glatiramer acetate, and oral DMTs including dimethyl fumarate and teriflunomide.[5—7] In Taiwan, the first-line MS therapies include IFNs (beta-1a and 1b), glatiramer acetate, dimethyl fumarate and teriflunomide,[8] followed by second-line options (natalizumab and fingolimod); however, its use is constrained by the reimbursement criteria.[9] Despite established safety profile of injectable DMTs,[10] suboptimal treatment response or poor adherence often related to their mode of administration, limits their effectiveness in clinical practice.[11—13] Available alternatives to regular injections include high-efficacy oral therapies and intravenous therapies that require less frequent administration.[6,10,13]

Fingolimod (FTY720, Gilenya®), a sphingosine-1-phosphate receptor (S1PR) modulator, is the first oral DMT approved for relapsing-remitting MS (RRMS),[14—16] with efficacy and safety demonstrated in pivotal Phase 3 trials versus placebo (FREEDOMS,[17] FREEDOMS II[18]) and IFN beta-1a (TRANSFORMS),[19] as well as in extension studies.[20,21] The effectiveness and safety of fingolimod from real-world settings is reported across different geographical locations.[22—28]

In Taiwan, fingolimod is designated as an orphan drug with conditional license approval in 2014. There is no local fingolimod data available in Taiwanese MS patients nor from fingolimod clinical trial program to guide treatment decisions in routine clinical practice. Therefore, this retrospective, non-interventional study was conducted to collect and review clinical data in Taiwanese patients who had ever been on fingolimod 0.5 mg since its initial availability in Taiwan, and to assess the safety and effectiveness of fingolimod in real-life clinical practice at the request of Taiwan health authorities.

Methods

Study design

This was a retrospective, multicentre, non-interventional cohort study in RRMS patients who had been prescribed fingolimod in clinical practice since its availability in Taiwan in September 2012 under early access/compassionate use programme. Clinical data on fingolimod users were retrospectively collected from 6 participating study centres between September 2012 and December 2015 by reviewing medical records of past/current RRMS patients treated with fingolimod, regardless of treatment duration.

Patients

Eligible patients had RRMS diagnosis confirmed by treating physicians (McDonalds 2010) and were prescribed fingolimod 0.5 mg/day as per local labelling requirements. Patients were required to have initiated fingolimod within the data collection period, irrespective of treatment duration. Exclusion criteria included patients with NMO and those who could not provide written informed consent for medical record review. For patients diagnosed with NMO later in the study but had received fingolimod, data were collected until treatment discontinuation.

Ethics and good clinical practice

This study was conducted according to International Conference on Harmonisation Guidelines[29] for Good Clinical Practice and Declaration of Helsinki.[30] Institutional review board/independent ethics committee approved the protocol and all amendments before the study, and approved retrospective data collection from participating study centres. All patients provided written informed consent for medical record review.

Data collection, study outcomes and assessments

The following data were extracted and reviewed from the electronic/paper medical records of all patients meeting the eligibility criteria: demographics, medical history, MS relapses, prior MS therapies, ophthalmic tests, vital signs/lab results, pregnancy status; adverse events (AE) or serious AEs (SAEs); change in therapy or discontinuations/withdrawals; effectiveness as measured by relapse rate, and expanded disability status scale (EDSS) scores (pre-/post-treatment). Relevant tests/assessment data were collected at baseline and at scheduled follow-up visits/closer to that time point. For data collection up to the last time point (December 2015), first dose of fingolimod must be administered by August 2015, to allow ~4 month observation window.

The primary outcome measure was the overall safety; secondary outcome measure was MS relapse activity (annualised relapse rate [ARR]).

Safety

Safety assessments included collection of AEs, SAEs and assessment of their severity and relationship to the study drug. The proportion of patients with AEs, SAEs, AEs leading to treatment discontinuation, were also recorded. Any clinically significant abnormalities in laboratory parameters, physical examination, vital signs, and clinical chemistry were reported. Ophthalmic examinations captured visual acuity for both eyes and macular oedema status at baseline and at Month 3 or 4 visit after fingolimod treatment.

During first-dose observation, patients underwent complete cardiac evaluation before starting fingolimod to exclude alterations in heart rate (HR) and atrioventricular block (AVB). This included monitoring sitting blood pressure (mm Hg), sitting pulse (beats per minute, bpm), any new event/worsening of bradycardia, and concomitant therapy if necessary. Electrocardiographic monitoring was also performed in all patients 6 h after the first dose.

Effectiveness

ARR and changes from baseline in EDSS scores were recorded during the follow-up visits to assess effectiveness of fingolimod. Relapse was defined as appearance of a new neurological abnormality/worsening of previously stable/improving pre-existing neurological abnormality lasting >24 h, separated by at least 30 days from onset of a preceding clinical demyelinating event.

Statistical methods

Owing to the retrospective nature of this study to include all eligible patients treated with fingolimod in clinical practice, formal sample size calculation was not performed. Approximately 90 patients were estimated to be included considering the current prescription base, and inclusion of new patients before study initiation at the medical centres. However, a total of 72 patients had been screened at the time of the study.

Statistical analysis was performed using descriptive methods. Continuous variables were reported as means, standard deviations, median, and range, whereas discrete data were reported in contingency tables as absolute and relative frequencies. For MS relapse, mean ARR was calculated and presented as overall ARR. The EDSS scores were also estimated descriptively. Time-to-first relapse were analysed by the Kaplan-Meier estimator of the survival functions for the treatment.

All analyses were performed on the enrolled set, which included all patients who had received fingolimod 0.5 mg/day and provided written informed consent for the study participation. The baseline value for the assessments used a maximum 6-month old results before initiation of fingolimod. The patients were marked 'completers' if they were still using fingolimod on the last day of data collection, while the term 'discontinuation' implied that fingolimod was stopped before the data collection period ended.

Results

Patient disposition

Of 72 patients screened, 69 (95.8%) patients were enrolled across 6 participating centres in Taiwan. Three patients failed the screening criteria. Of the 69 patients, 62 (86.1%) continued with fingolimod until the data collection period; remaining 7 (9.7%) discontinued the study primarily due to administrative problems (n = 3, 4.2%), AEs (n = 2, 2.8%), unsatisfactory therapeutic effect, and withdrawal of consent (each n = 1, 1.4%). Post data collection period, 4 patients were later diagnosed with NMO instead of MS diagnosis at the study start.

Baseline demographics and patient characteristics

Patient demographics and baseline characteristics are summarized in Table 1. The mean (±standard deviation, SD) age at inclusion was 37.7 ± 10.10 years and most of the patients (n = 47, 68.1%) were between 31 and 55 years of age. Of all patients, 71% were women and the population was predominantly Asian with Chinese ethnicity (97.1%). At baseline, the mean duration of MS since diagnosis was 5.4 ± 4.52 years. A higher proportion (n = 67, 97.1%) of the population had no ongoing relapse before fingolimod initiation.

Fingolimod exposure

The mean duration of fingolimod exposure was 719.0 ± 328.95 days (135.8 patient-years). Of the 69 patients who received fingolimod, 12 patients (17.4%) had a maximum exposure of 3 years; 40 (58%) and 55 (79.7%) had completed 2 years and 1 year on treatment, respectively; and 64 (92.8%) had continued at least 6 months on treatment.

Safety

Overall, 64 (92.8%) patients experienced at least one AE. The most common AEs (≥10%) were bradycardia (15 patients, 21.7%; first-dose related), upper respiratory tract infection, dizziness, and hypoaesthesia (11.6% each, Table 2). No AE-related drug discontinuations occurred. Bradycardia events were observed on the day of first dose. No subjective discomfort was noted. In patients who experienced bradycardia (<60 bpm), 11 were asymptomatic and no description was mentioned in other 4 cases. One patient required extended monitoring to alleviate bradycardia symptoms but no additional treatment was required. During 6 h first-dose observation, mean HR was within 67.9−77.2 bpm of the entire population. The lowest HR of 46 bpm was recorded in one patient 4 h after the first dose, and HR rose back to 50 bpm after 1 h. No extended monitoring was required for this patient. Mild transient alterations in the systolic/diastolic blood pressure and HR were evident in most of the fingolimod-treated patients during the first-dose monitoring. One patient (1.4%) experienced an event of second-degree AVB while receiving the first dose fingolimod as an in-patient. The exact time of this event observed was not recorded; however, the patient had normal HR in the first 6 h and the nadir (44 bpm) was not reached until 12 h post first dose. It is suspected that AVB occurred around the same time. The patient had no apparent clinical symptoms throughout this time, therefore no intervention was given. After close monitoring, the patient was discharged and fingolimod treatment continued.

Pre-dose monitoring of fingolimod did not reveal clinically relevant abnormalities in the ECG except for one patient who experienced new/worsening ECG abnormalities (T abnormal in anterior leads) twice i.e. at 6 h and 8 h after the first dose. No further action was required for this AE (patient had no past medical history of cardiovascular ailments).

Table 1 Patient demographics and baseline clinical characteristics.

Characteristics	Fingolimod 0.5 mg (N = 69)
Age (years)	37.7 ± 10.10
Women, n (%)	49 (71.0)
Race, n (%)	
Asian	67 (97.1)
Caucasian	2 (2.9)
Ethnicity, n (%)	
Chinese	67 (97.1)
Hispanic/Latino	1 (1.4)
Other	1 (1.4)
MS disease history	
Duration since MS diagnosis[a] (years)	5.4 ± 4.52
Duration since the most recent MS relapse (months)[b]	12.9 ± 17.66
Number of MS relapses in last 12 months[c]	1.0 ± 0.85
Number of MS relapses between last 12 and 24 months[c]	0.6 ± 0.63
Total number of MS relapses	1.5 ± 1.09
MS medication history, n (%)[d]	
Interferon beta-1a	41 (60.3)
Interferon beta-1b	12 (17.7)
Glatiramer acetate	11 (16.2)
Azathioprine	3 (4.4)
Interferon beta	1 (1.5)
Baseline EDSS score	2.37 ± 1.512
Varicella zoster virus seropositivity before fingolimod initiation, n (%)	61 (88.4)

Data presented as mean ± SD, unless otherwise stated; [a]n = 66; [b]n = 42; [c]n = 68; [d]six patients had used >1 prior MS therapy. EDSS, expanded disability status scale; MS, multiple sclerosis; N, total number of patients; n, number of patients; SD, standard deviation.

Infections

A total of 23 (33.3%) patients reported AEs related to infections and infestations: upper respiratory tract infection (11.6%), urinary tract infection (7.2%), conjunctivitis, viral upper respiratory tract infection (5.8% each), and oral herpes (2.9%). Herpes zoster was reported in one (1.4%) patient. Only 1 SAE (anal abscess) was related to infection and was considered related to fingolimod.

Lymphocyte counts

Eight patients (11.6%) had absolute lymphocyte counts $<0.2 \times 10^3$/uL (Grade 4, CTCAE v5.0) during the study. The mean change from baseline in absolute lymphocyte counts (10^3/uL) was −1.1 ± 1.78 (baseline [1.8 ± 0.81]; end of

Table 2 Incidence of AEs and SAEs.

	Total (N = 69)
Safety profile, n (%)	
Any AE	64 (92.8)
AEs leading to drug discontinuation	0 (0.0)
AEs requiring drug interruption	8 (11.6)
Any SAE	11 (15.9)
Most common AEs (≥ 3 patients by preferred term; n [%])	
Bradycardia (first-dose related)	15 (21.7)
Upper respiratory tract infection	8 (11.6)
Dizziness	8 (11.6)
Hypoaesthesia	8 (11.6)
Urinary tract infection	5 (7.2)
Back pain	5 (7.2)
Viral upper respiratory tract infection	4 (5.8)
Conjunctivitis	4 (5.8)
Fatigue	4 (5.8)
Anxiety	4 (5.8)
Insomnia	4 (5.8)
Hepatic enzyme increased	3 (4.3)
Headache	3 (4.3)
Anaemia	3 (4.3)
Dry eye	3 (4.3)
Blurred vision	3 (4.3)
Abdominal pain	3 (4.3)
Muscular weakness	3 (4.3)
Depression	3 (4.3)
SAEs, n (%)	
Liver function test increased	1 (1.4)
Back pain	1 (1.4)
Muscle spasms	1 (1.4)
Neck pain	1 (1.4)
Cerebrovascular accident	1 (1.4)
Hemiplegia	1 (1.4)
Seizure	1 (1.4)
Anal abscess	1 (1.4)
Pelvic inflammatory disease	1 (1.4)
Urosepsis	1 (1.4)
Facial pain	1 (1.4)
Pyrexia	1 (1.4)
Accidental overdose	1 (1.4)
Facial bones fracture	1 (1.4)

AE, adverse event; N, total number of patients; n, number of patients; SAE, serious AE.

study [0.4 ± 0.21]). Additionally, average maximum reduction from baseline in circulating lymphocyte counts was 73.8% ± 18.59.

Liver enzyme related AEs

Seven patients experienced liver enzyme-related AEs. Hepatic enzyme increases (drug-related) were observed in 3 patients (4.3%). Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels were increased in 1 (1.4%) and 2 patients (2.9%), respectively. Two patients had ALT levels 5 times above upper limit of normal (ULN; 40 U/L). In one of those patients, ALT baseline level was 13 U/L, and 30 U/L one month after the first dose. After 3 months, ALT peaked at 281 U/L while AST also rose to 134 U/L on the same day. No action was taken for this liver enzyme elevation. During next visit, ALT and AST levels dropped back to 32 and 25 U/L, respectively.

Another patient had ALT and AST values of 135 U/L and 72 U/L, which remained stable for a year before increasing to 326 U/L and 122 U/L, respectively, by the study end. Neither instance of liver enzyme elevation led to drug discontinuation.

Eye events and malignancies

Dry eye and vision blurred were noted in 3 patients each (4.3%). There was one case of macular oedema, diagnosed in the left eye of the patient before fingolimod initiation. No newly developed macular oedema was detected. Amongst the cases of neoplasm, two patients (2.9%) had uterine leiomyoma and one patient (1.4%) had lip neoplasm.

Serious adverse events

Overall, 11 (15.9%) patients experienced at least one SAE, the majority were either mild or moderate in severity. The most common SAEs included single events (1.4% each) of elevated liver enzyme tests, back pain, muscle spasms, neck pain, and seizure (Table 2). Severe SAEs were noted in 7 patients during the study.

Effectiveness

A total of 66.7% of fingolimod-treated Taiwanese patients remained relapse free during the data collection period. The ARR was 0.3 ± 0.74 for the total population treated with fingolimod and 0.2 ± 0.48 after excluding 4 NMO patients. Time-to-relapse reduced post-treatment with fingolimod over the study duration (Fig. 1). The proportion of patients free from relapse reached 70% in the initial phase of treatment (i.e. up to 15 months) and thereafter decreased to 60% at the end of the study.

The mean EDSS score showed reductions from a baseline score of 2.20 ± 1.58 (n = 44) to a mean post-treatment score of 1.85 ± 1.81 (n = 27); however, significance of this reduction was not tested in this study. The mean EDSS scores did not show a particular trend from baseline due to differences in patients evaluable at different scheduled visits.

Discussion

The results of this retrospective, non-interventional study provide important post-marketing real-world evidence in RRMS patients treated with fingolimod in routine clinical practice in Taiwan.

The clinical experience of fingolimod in this South-East Asian subpopulation complements its safety and efficacy profile established in predominantly Caucasian populations from the global Phase 3 clinical studies,[17–21] in which Asian MS patients were underrepresented or previously not included. Moreover, the safety and effectiveness results of the current study closely resemble similar studies

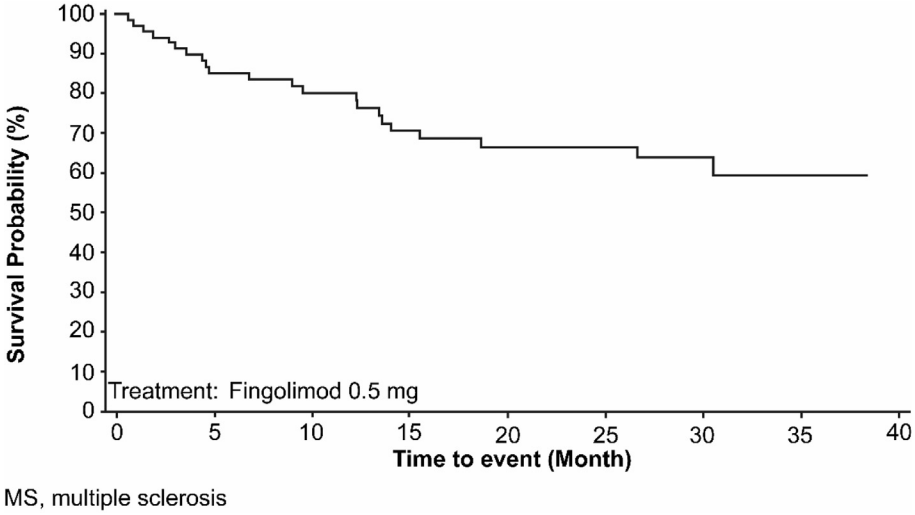

Figure 1 Kaplan-Meier plot of time to the first MS relapse during the study.

conducted in other parts of Asia (Japan, Malaysia)[31,32] and Middle-Eastern regions.[33,34]

The overall safety profile of fingolimod in this study was manageable, without any unexpected events, consistent with that reported previously in the core and extension studies of fingolimod[17–21] and other real-world studies.[22–27] In our relatively small study, observational data did not identify any new, fatal, or late-occurring safety signals in Asian MS patients from Taiwan.

The first dose was tolerated by nearly all patients with alterations seen in blood pressure and HR; 21.7% patients experienced transient non-serious bradycardia on the first day of treatment. Nevertheless, majority of bradycardia events were asymptomatic and did not require overnight monitoring except one (no additional treatment needed). In the FIRST study (n = 2415), nine patients required extended monitoring >7 h on day 1 but none discontinued fingolimod and were discharged on the same day; second degree AVB cases were infrequent (n = 5).[35] This suggests that occurrence of AVB is low; our case of second degree AVB was asymptomatic throughout the course of HR drop and AV block, and did not require active intervention. Notwithstanding, fingolimod is not recommended for patients with a history of heart disease/cardiovascular risks, and first dose monitoring should be followed as per prescribing information. Of note, these first dose observations were also reported in the pivotal fingolimod clinical studies[17–21] as well as global observational[22–27] and local real-world studies from Asia[31,32] Pooled analysis of Phase 3 studies revealed that bradycardia is known to resolve over 6 h with limited clinical impact and specific therapy is generally not required.[36]

Reduction in circulating lymphocyte counts is a known pharmacodynamic class effect of fingolimod. The percentage of patients (11.3%) with reduced absolute lymphocyte counts in our study was comparable to that seen in earlier integrated safety report (12%)[37] and in FREEDOMS II study (18%).[18] Similar to mean lymphocyte count reductions observed in our study (73.8%), the previous safety report[37] also noted an approximate 73% decline in the circulating lymphocyte counts from baseline to 1 month after fingolimod treatment. Although in our study low range of lymphocyte counts were detected in some patients but it did not translate into increased rate of serious or severe infections as observed previously.[37]

Consistent with integrated safety analysis of fingolimod studies,[37] other AEs observed in the current study that are known to be specific to fingolimod included: upper respiratory tract infection, urinary tract infection, liver enzyme elevations, and neoplasms. There were few cases of oral herpes and herpes zoster. One patient had serious infection (anal abscess), however the absolute lymphocyte count taken on the event onset date was 0.312×10^3/uL, which was within the acceptable range ($>0.2 \times 10^3$/uL), not necessitating treatment discontinuation.

Macular edema detected in left eye of one patient was diagnosed a month before the first dose of fingolimod was administered and was therefore not treatment-related. This patient had undergone eye surgery 3 months prior to fingolimod initiation, and also had several concurrent medical conditions of eye disorders, such as punctate keratitis, retinal disorder, and vitreous opacities.

Some questions, however, remain regarding the incidence of liver enzyme elevations as the mechanism responsible for its occurrence with fingolimod is unclear. Three cases observed in this study were considered related to the study drug by the treating physicians; mild variations of laboratory results above ULN and below the lower limit of normal are typically asymptomatic and not deemed clinically relevant unless the abnormal levels persist beyond a few visits.

Response to MS therapies between Caucasian and Asian populations may be influenced by genetic variations, metabolic factors, and lifestyle,[38,31] as well as by differences in MS disease presentation. NMO, a demyelinating disease with overlapping symptoms to MS, has higher prevalence in Asian countries, including Japan and Taiwan, compared with Western countries.[31,39] The differential diagnosis for NMO and MS, particularly in Asian patients, has often been dubious due to the higher NMO prevalence in

this region as well as the similarity in clinical symptoms, which can lead to categorisation challenges.[3] Also, magnetic resonance imaging (MRI) scans may not always be definitive or characteristic and may be subjective to individual physicians' judgment. As per earlier study, approximately one-quarter of NMO patients did not show AQP4 seropositivity (a differential marker for NMO)[40] and therefore, such patients might be misdiagnosed as having MS.[3] Testing methods also affect sensitivity. This echoes well with our study as four patients initially diagnosed with MS at study entry were later categorised as NMO patients. It is therefore possible that not all cases of NMO were excluded initially in our study. Effectiveness was therefore analyzed in two cohorts — total population and after excluding four NMO patients. Taken together, this highlights the need to improve diagnostic accuracy at study screening by reviewing characteristic findings on MRI or by monitoring the immunologic status of NMO and MS patients to prevent exacerbation of the disease.[3]

Taiwanese MS patients treated with fingolimod 0.5 mg daily demonstrated improved effectiveness outcomes. The proportion of relapse-free patients (66.7%) was in line with 24-month FREEDOMS (70.4%)[17] and FREEDOMS II (71.5%)[18] studies, although slightly lower than the TRANSFORMS (82.5%)[19] study, and real-world evidence from Malaysia (81.1%)[32] and Japan (89.4%).[31]

Lastly, although EDSS assessment had a small number of observations, and varied in different study visits, overall EDSS score of the study cohort showed a 0.30 point reduction from baseline which compares favourably with 0.32 in the Japanese cohort.[32] Interestingly, EDSS score remained rather stable over the period assessed.

Limitations

Due to non-interventional nature of the study with a short study period of 3 years, all data were sourced retrospectively and the evaluation therefore relied on the quality and completeness of the data recorded in the medical records. There could also be selection bias as data were collected only from patients who provided their consent for inclusion, and thus, this may not represent all patients from the hospital dataset who could be enrolled. There was also limitation to obtain information on patients who could have died as our dataset only included patients who provided informed consent, and the study sample was limited to the specified data collection period.

Few patients appeared to have only used fingolimod for a short period of time because there was a constrained timeframe for the data collection which could have led to observation of an incomplete period in the study. Also, no neuroimaging assessments were mandated.

Conclusions

This study provides post-marketing real-world experience with fingolimod 0.5 mg/day over a 3 year period in Taiwanese patients with MS, which adds to the current knowledge of the favourable safety and efficacy of fingolimod in the South-East Asian population as very limited data are available from this region to guide real-life MS-related treatment decisions in the clinical setting.

Declaration of Competing Interest

Drs. Long-Sun Ro, Nai-Wen Tsai, Chou-Ching Lin, Wen-Nan Huang, Thy-Sheng Lin, Jen-Jen Su, Chin-Chang Huang, Rong-Kuo Lyu, Hsin-Hua Chen, Wei-Ju Lee, Po-Lin Chen, do not have any financial or non-financial conflicts of interest to declare. Dr. Chih-Chao Yang received grants from Novartis (Taiwan) Co., Ltd for the study. Dr. Ching-Piao Tsai received personal fees and non-financial support from Novartis Taiwan for study conduct; and personal fees from Novartis Taiwan outside submitted work. Dr. Audrey Yang is employee of Novartis, a company that manufactures fingolimod used in the management of multiple sclerosis.

Author contributions

CCY contributed to the study concept, data acquisition and interpretation and critical revision of the manuscript. **LSR** contributed to the study concept, execution, data acquisition, analysis and interpretation, critical revision of the manuscript, and supervising the research. **NWT** contributed to the data acquisition, analysis and interpretation, and critical revision of the manuscript. **CCL** contributed to the study concept, data acquisition and interpretation and critical revision of the manuscript. **WNH** contributed to the study concept, design, execution, data acquisition, analysis and interpretation and critical revision of the manuscript. **WNH** contributed to the data acquisition and interpretation. **CPT** contributed to the data analysis and interpretation, critical revision of the manuscript. **TSL** contributed to the study execution, acquisition, data analysis and interpretation, critical revision of the manuscript. **JJS** contributed to the interpretation of the data, administrative, technical and material support, and critical revision of the manuscript. **CCH, RKL and HHC** contributed to the acquisition of data, analysis and interpretation, critical revision of the manuscript. **WJL** and **PLC** contributed to the study concept, acquisition of data, analysis and interpretation, critical revision of the manuscript. **AY** contributed to the acquisition of data, analysis and interpretation, and critical revision of the manuscript.

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