Pragmatic and Observational Research

Dovepress
Taylor & Francis Group

Open Access Full Text Article

ORIGINAL RESEARCH

Evaluation of Disease Modifying Therapies and Prognostic Factors Affecting Multiple Sclerosis Progression in a Local Centre of Hong Kong

Bobby Chun Man Lui, Jessica Tsz Ching Li, Wai Ting Lo, Wing Chi Fong

Department of Neurology, Queen Elizabeth Hospital, Kowloon, Hong Kong

Correspondence: Bobby Chun Man Lui, Email dr.luichunman@gmail.com

Introduction: Multiple sclerosis (MS) is a major demyelinating disease causing disability in young adults. Scarce data exists on the clinical benefits and persistence of disease modifying therapies (DMTs) amongst our local population. The primary aim of this study was to investigate the effectiveness, tolerability and discontinuation pattern of various DMTs amongst Hong Kong patients.

Methods: This was a retrospective study of adult MS patients treated in a tertiary hospital in Hong Kong from 1st December 2012 to 30th November 2022. Demographic, clinical and radiological characteristics were retrieved.

Results: A total of 103 patients were analysed. Interferons (annualised relapse rate (ARR) reduction 0.492, $p < 0.001$) and fingolimod (ARR reduction 0.557, $p = 0.038$) had significant ARR reductions in our cohort. Overall treatment persistence were comparable, but teriflunomide had more discontinuation due to side effects and/or intolerance (hazard ratio (HR) 7.50, $p = 0.029$). Baseline Expanded Disability Status Score (EDSS) more than or equal to 4.0 (odds ratio (OR) 4.56, $p = 0.045$), and presence of brainstem lesions on magnetic resonance imaging (OR 3.15, $p = 0.039$) were associated with greater disability progression, while visual onset symptoms at diagnosis (OR 0.14, $p = 0.007$) were associated with lower risk.

Discussion: This study illustrated the complexity of managing MS patients. Patients' clinical characteristics, disease activity, risk appetite and treatment side effects should be taken in consideration to reach an informed decision on the use of DMTs in our local MS patients.

Keywords: multiple sclerosis, DMT, prognostic factors, adverse effects

Introduction

Background

Multiple sclerosis (MS) is a chronic, immune-mediated neurological condition affecting mostly young individuals worldwide with a variety of clinical manifestations and trajectories, which can lead to permanent disability as it evolves.

MS among Asians is relatively less prevalent compared to Caucasians. Recent meta-analyses reported the incidence and prevalence in Asian and Oceanic regions being 2.4/100,000, and 37.9/100,000, respectively,[1] whereas the incidence and prevalence in Europe were 2/100,000 and 59/100,000, respectively.[2] Local data were sparse with the latest study more than 10 years ago estimated the prevalence at 4.8/100,000.[3]

Current evidence suggested that the pathological hallmark of MS featured demyelination,[4] which is caused by T-lymphocytes, and with growing evidence, B-lymphocytes[5] as well, though the exact mechanism was still largely unknown. Several demographic and environmental factors including smoking, vitamin D deficiency, Epstein-Barr virus (EBV) infection were recognised to be associated with MS and its prognosis.

McDonald criteria were used for the diagnosis of MS since 2001.[6] According to the updated 2017 McDonald criteria (Supplementary Table 1),[7] the diagnosis of MS requires at least one typical clinical attack with evidence of demyelination in the central nervous system, and dissemination in time and space, without other plausible alternative diagnosis.

Received: 29 July 2025
Accepted: 19 November 2025
Published: 2 December 2025

An attack typically includes optic neuritis, transverse myelitis, brainstem, and cerebellar syndrome.[7] When it occurred in an isolated manner, it was termed clinically isolated syndrome (CIS). In relapsing-remitting MS, the patients have multiple attacks but remain stable in-between. On the other hand, in progressive MS, there exists progressive worsening of disability, with initial remitting relapsing phase present in SPMS and absent in PPMS.[8]

In the recent 30 years, a growing number of DMTs have become available. While none of them can completely cure MS, these were shown to decrease the clinical relapses, and to postpone the progression of this debilitating illness.[9]

The first DMT was Interferons beta (IFN), approved in the USA and Europe in 1993 and 1995, respectively.[10] The mechanisms of action were immunomodulatory, for instance, decreasing T cell activation and inflammatory cytokines production.[11] Azathioprine was a popular therapeutic option historically in MS before specific therapies became widely available as it inhibits purine synthesis and induces T cells apoptosis as a purine analogue.[12]

Fingolimod (FTY) is the first oral DMT used to treat RRMS. It is a sphingosine 1-phosphate receptor modulator,[13] which was shown to influence the mobilisation of lymphocytes, exhibiting its immunomodulatory effect.[14] More specific therapies emerged with time, including dimethyl fumarate (DMF) and teriflunomide (TFN). DMF exerts its cytoprotective effect in the central nervous system,[15] while TFN inhibits B and T cell proliferation through inhibition of dihydroorotate dehydrogenase,[16] which is an enzyme used in pyrimidine synthesis for lymphocytes production.

The scientific development of various monoclonal antibodies opened the door further for the newer treatment options. One example is alemtuzumab which acts on CD-52 to deplete T and B cells from circulation and has been shown to provide an excellent treatment response.[17]

In Hong Kong, IFNs were the first approved therapies for MS since 2012,[18] while the oral DMF and TFN later became popular choices as first line DMTs. In general, FTY remained the second line DMT. When the previously used DMTs were ineffective, use of high efficacy DMTs, for example, alemtuzumab, natalizumab, and cladribine, was considered. This study would like to focus on the more commonly used DMTs in Hong Kong so as to reflect the local treatment practice for our MS patients.

Aims and Objectives

Aim

To date, there were only few observational cohort studies in Hong Kong comparing the efficacy, tolerability and discontinuation pattern of the rapidly growing number of DMTs, and the prognostic factors for local MS patients. Our study aims to provide real-world data on the use of DMT in one of the tertiary hospitals for managing MS patients in HK.

Primary Objectives

To assess the effectiveness, tolerability and discontinuation pattern of various DMTs.

Secondary Objectives

(1) To explore baseline characteristics of MS patients in Hong Kong.
(2) To determine factors leading to DMTs discontinuation.
(3) To assess prognostic factors for MS in terms of worsening of Kurtzke's Expanded Disability Status Score (EDSS)[19] (Supplementary Table 2) and annualised relapse rate (ARR).

Method and Material

Inclusion and Exclusion Criteria

Patients with a diagnosis of MS given by the attending clinician were identified by the Clinical Data Analysis and Reporting System. Adult patients aged over 18 years, who had follow-up visits in the Queen Elizabeth Hospital neurology specialist outpatient clinics during the period between 1st December 2012 and 30th November 2022 were included in our study. The exclusion criteria included alternative diagnoses to MS made by clinicians, and unconfirmed diagnosis of MS.

Study Design

This was a retrospective observational study using data from clinical records or electronic patient record via the Clinical Management System after approval by the ethics committee. Various demographic and clinical parameters were retrieved for further analysis (Table 1).

Demographic factors, including age, ethnicity, smoking status and medical co-morbidities, were either self-reported by the patient or entered by the clinicians. The types of MS were identified by the attending clinician at diagnosis and in the latest visit.

At initial presentation, date of symptom onset reported by patients, date of diagnosis, initial type of symptoms, lesions in magnetic resonance imaging (MRI), baseline Kurtzke's Expanded Disability Status Score (EDSS) were assessed. The presence of Oligoclonal bands (OCBs), and the data in white blood cells and protein level in cerebrospinal fluid (CSF) were analysed for the patients who underwent lumbar puncture. Moreover, the presence of abnormalities in visual (VEP), somatosensory (SSEP), and brainstem auditory (BAEP) evoked potentials, were noted.

A relapse was defined as, a new symptom which lasted for more than 24 hours, in the absence of concurrent illness. An MRI activity was defined as either new or gadolinium contrast-enhancing lesions in the subsequent MRI scans. The study period was from the date of symptom onset, till the censor date, 30th November 2022 or death, whichever earlier.

The annualised relapse rate (ARR) was calculated by dividing the number of relapses by the study period in years. For comparison, ARR 2 years prior to commencement of DMT was recorded. The presence of disability progression with EDSS worsening was also evaluated. It was defined by increase in EDSS score of at least 0.5 point if the baseline EDSS was greater than 5.5, of 1 point if the baseline EDSS was within 1 to 5.5, or 1.5 point if baseline EDSS was 0.

The number of DMT uses, the duration between diagnosis and commencement of DMTs, was recorded in patients who commenced DMTs. Adverse effects by the patient or the attending physician were reported. The duration of DMT was defined as the first use of DMT till discontinuation. Discontinuation of DMT, as defined by the interruption of treatment for 60 days or more, was also evaluated.

Table 1 Demographic and Clinical Parameters for Analysis

Domain	Parameters
Demographic factors	• Gender • Ethnicity • Smoking history
Medical history	• Presence of other medical co-morbidities • Presence of family history
Types	• Types of multiple sclerosis (including CIS, RRMS, PPMS and SPMS)
At initial presentation	• Age of onset • Baseline EDSS • Types of attacks (visual, pyramidal, cerebellar, brainstem, sensory and other symptoms) • Types of initial MRI lesions (optic nerve, spinal cord, cerebral, cerebellar, brainstem region) • Presence of OCB, white cell counts and protein level in CSF • Presence of abnormalities in evoked potentials, including visual (VEP), somatosensory (SSEP) and brainstem auditory (BAEP) evoked potentials • Duration between symptom onset and diagnosis
Clinical course	• Annualised clinical relapse rate (ARR) • Presence of EDSS worsening, SPMS progression
Use of DMT	• Duration between diagnosis and commencement of DMTs • Number and Duration of each DMT uses • Adverse effects and reasons of discontinuation of each DMT

Statistical Methods

Statistical analyses were conducted using Statistical Package for Social Sciences (SPSS) version 26. Descriptive statistics were used for patients' demographic and clinical factors. Percentage was used for categorical data, while mean and standard deviation (SD) were calculated for continuous data respectively. Kaplan-Meier curve was used for the DMT discontinuation with log rank test used between various DMT subgroups, where Cox regression was followed if statistical significance detected. Fisher's exact test was used to study the relationship between EDSS worsening and various factors. Independent samples *t*-test were used to study the relationship between ARR and various factors, respectively. A p-value of less than 0.05 was considered statistically significant. Formal power calculation was not feasible due to the retrospective nature of the study and discussed this as a limitation.

Ethic Issues and Confidentiality

The study was approved by the Research Ethics Committee in Kowloon Central and East Cluster of Hospital Authority. Individual patient was assigned with a unique code for identification purpose. Individual patient consent was waived as this was a retrospective medical record review using anonymised data. Patient confidentiality was maintained throughout the study, in accordance with the Declaration of Helsinki.

Results

Of 125 identified patients via Clinical Data Analysis and Reporting System, an electronic health database operated by the Hospital Authority of Hong Kong, 22 were excluded where 18 (17.4%) of them had alternative diagnoses including Neuromyelitis optica spectrum disorder (NMOSD), acute disseminated encephalomyelitis, unconfirmed diagnosis, and 4 (3.2%) due to irretrievable or missing clinical information, leaving 103 patients were included in the study with the mean follow-up period 191.1 (range 14–794, SD 136) months.

Patient Characteristics

Demographic Factors

In the study cohort of 103 patients, 74 (71.8%) and 29 (28.2%) patients were female and male respectively, giving the female:male ratio 2.55:1. The vast majority were of Chinese ethnicity (99, 95.2%). Eighty-three (80.6%) patients were non-smoker while 14 (13.6%) of them were ever-smokers at diagnosis. The mean ages of symptom onset and diagnosis were 29.7 (SD 10.1) and 33.2 (SD 10.4), respectively (Figure 1).

Clinical Factors

Fifty-four (52.4%) patients were associated with other medical co-morbidities, which included hypertension, diabetes mellitus, hyperlipidaemia, eczema, fatty liver, thyroid disease. None of the patients had family history of MS.

The clinical characteristics of the patients is listed in Table 2. The most common type of MS at initial diagnosis was RRMS, with 69 (67.0%) patients, followed by CIS (16, 15.5%), PPMS (6, 5.83%) and SPMS (9, 8.74%) respectively. The types of 3 (2.91%) patients at diagnosis were untraceable. In 83 (80.6%) of the patients, the baseline EDSS were either recorded or extrapolated with most commonly lies below 3.5 (74, 71.9%).

The commonest types of signs and symptoms at initial presentation were presented as paresthesia (38, 36.9%), followed by visual symptoms (30, 29.1%) and limb weakness (29, 28.2%), with the rest in Table 2. Among the 88 (85.4%) patients with clear period of symptom onset and diagnosis, the mean duration between symptom onset and diagnosis was 36.8 (range 0–262, SD 54.3) months.

All except 1 (0.97%) patient had MRI lesions at the initial clinical presentation. For that particular patient, she had normal MRI scan at first at her initial diagnosis of optic neuritis, and had MRI lesions on subsequent scans. The types of initial MRI lesions in 97 (94.2%) patients were presented in Table 2, including most frequently supratentorial (85, 82.5%), followed by infratentorial (28, 27.2%) and spinal cord (27, 26.2%) lesions, while the data were not available in the remaining 5 (4.85%) patients.

In 41 (39.8%) patients with evoked potential studies performed and with available results, at least one abnormal evoke potential study was found in 23 (22.3%) of them as shown in Table 2 including abnormal VEP (16, 15.5%), BAEP

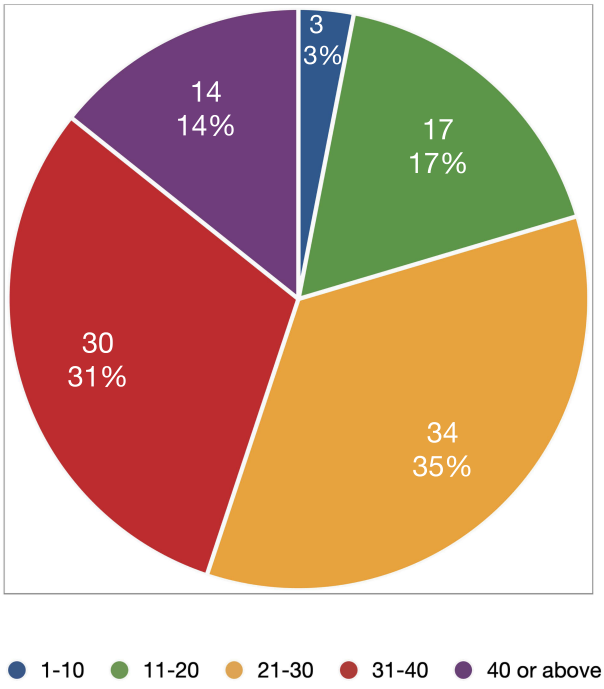

Figure 1 A pie chart of distribution of disease onset across five age groups: 1–10 years (n=3, 3%), 11–20 years (n=17, 17%), 21–30 years (n=34, 35%), 31–40 years (n=30, 31%), and greater than 40 years (n=14, 14%).

(6, 5.83%), and SSEP (10, 9.71%). Sixty-three (61.2%) and twenty-two (21.4%) patients were tested for serum antibodies against aquaporin-4 and myelin oligodendrocyte proteins, with all yielded negative result.

CSF was analysed with data available in 56 (54.3%) patients. Thirty-four (60.7%) of them were tested positive for OCBs. The mean CSF protein level was 0.37 g/L (SD 0.22) and CSF white blood cells count was 4.06 per μL (SD 6.49) with distribution shown in Figures 2 and 3 respectively.

Table 2 Clinical Characteristics of MS Patients

Categories	Types	Number of Patients	Percentage (%)
Type of MS	CIS	16	15.5
	RRMS	69	67.0
	PPMS	6	5.83
	SPMS	9	8.74
	Uncertain / Unavailable	3	2.91
EDSS at initial diagnosis	0.0–1.5	49	47.6
	2.0–3.5	25	24.3
	4.0–5.5	6	5.83
	≥ 6.0	3	2.91
	Unavailable	20	19.4

(*Continued*)

https://doi.org/10.2147/POR.S556886

Table 2 (Continued).

Categories	Types	Number of Patients	Percentage (%)
Type of signs and symptoms at the initial presentation[#]	Visual[#]	30	29.1
	Pyramidal[#]	29	28.2
	Cerebellar and ataxia[#]	14	13.6
	Brainstem[#]	17	16.5
	Sensory[#]	38	36.9
	Other[#]	6	5.83
	Unavailable	5	4.85
Type of initial MRI lesion	Supratentorial	85	82.5
	Infratentorial	28	27.2
	Spinal cord	27	26.2
	Optic nerve	21	20.4
	Normal	1	0.00971
	Unavailable	5	4.85
Evoked potentials	Normal EP	16	15.5
	Abnormal VEP	16	15.5
	Abnormal BAEP	6	5.83
	Abnormal SSEP	10	9.71
	Not performed / Unavailable	62	60.2

Notes: [#] Examples of signs and symptoms in initial presentation - Visual: Blurry vision, colour vision disturbance, visual field defect in visual type; Pyramidal: Limb weakness; Cerebellar and ataxia: Vertigo, ataxia; Brainstem: Diplopia, facial weakness, dysarthria; Sensory: Paresthesia; Others: Cognitive impairment, bladder and bowel incontinence, facial twitching, uveitis.

Relapses, Progression and Death

In the 66 RRMS patients with clearly defined study period, 221 relapses were recorded over a mean study period of 16.5 (SD 10.5) years. The mean ARR was 0.25 (SD 0.287). Thirty-eight (36.9%) of the 83 patients with available EDSS data in EDSS had EDSS worsening. Six RRMS patients progressed from RRMS to SPMS.

Eight (7.77%) deaths were recorded during the study period, with a mean age of death of 56 (SD 10.3) years. Four of them died of pneumonia, whereas others died of septicaemia due to Klebsiella and Candida infections, toxic megacolon, and intracerebral haemorrhage, respectively. The cause of death of the remaining patient was uncertain and the case was referred to coroner. The result of the coroner report was not retrievable from the electronic patient record.

DMTs Use

One hundred thirty-seven DMT cycles were commenced in 76 (73.8%) patients. The most common DMT used was interferon - either interferon-beta 1a (Avonex®, Rebif®), or 1b (Betaferon®) (48, 35.0%), followed by dimethyl fumarate (DMF) (41, 30.0%), fingolimod (FTY) (14, 10.2%) and teriflunomide (TFN) (8, 5.84%). Other DMT agents (26 cycles, 19.0%) included traditional steroid-sparing agents like azathioprine, mycophenolate mofetil, methotrexate, and newer agents including cladribine, ocrelizumab, alemtuzumab, and rituximab.

In 76 (73.8%) patients with history of DMT use, a median of 2 DMTs were used. The mean duration between between diagnosis and first DMT treatment was 21.7 (SD 37.7) months. DMTs were not started in 27 (26.2%) patients,

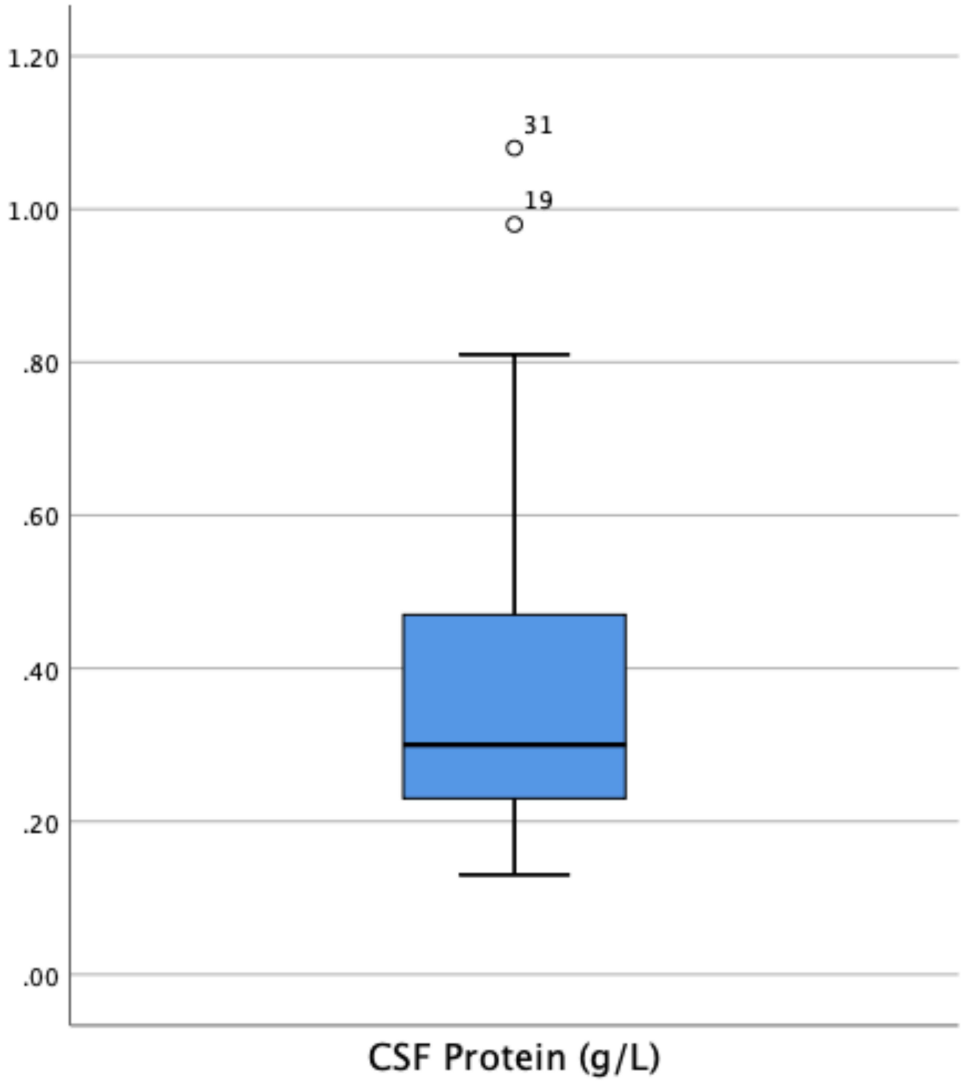

Figure 2 A Box-and-whisker plot of CSF Protein level. The box represented the interquartile range (IQR), where the horizontal line within the box indicates the median. o: outlier greater than 1.5 IQR from the upper quartile boundary.

13 ie almost half of them were due to patients' reluctance towards treatment after physicians' explanation. DMT was not indicated in 12 patients as there were no recent active attacks at the time of diagnosis, while the EDSS was above 6 in 1 patient that precluded DMT commencement. The record was not available for 1 remaining patient.

DMT Use Pattern

Amongst patients who have been put on DMTs, total number of DMT treatment cycles ranged from 1 to 5, with mean of 1.80 (SD 0.817). The vast majority of IFN (46 out of 48 cycles) was started in treatment-naïve patients without previous DMT used, whereas majority of DMF (27 out of 41 cycles), TFN (5 out of 8 cycles) and all FTY (14 out of 14 cycles) had one or more than one treatment cycles prior (Table 3). For patients having frequent DMT switch up to 5 treatment cycles, it was usually related to highly active disease course.

https://doi.org/10.2147/POR.S556886

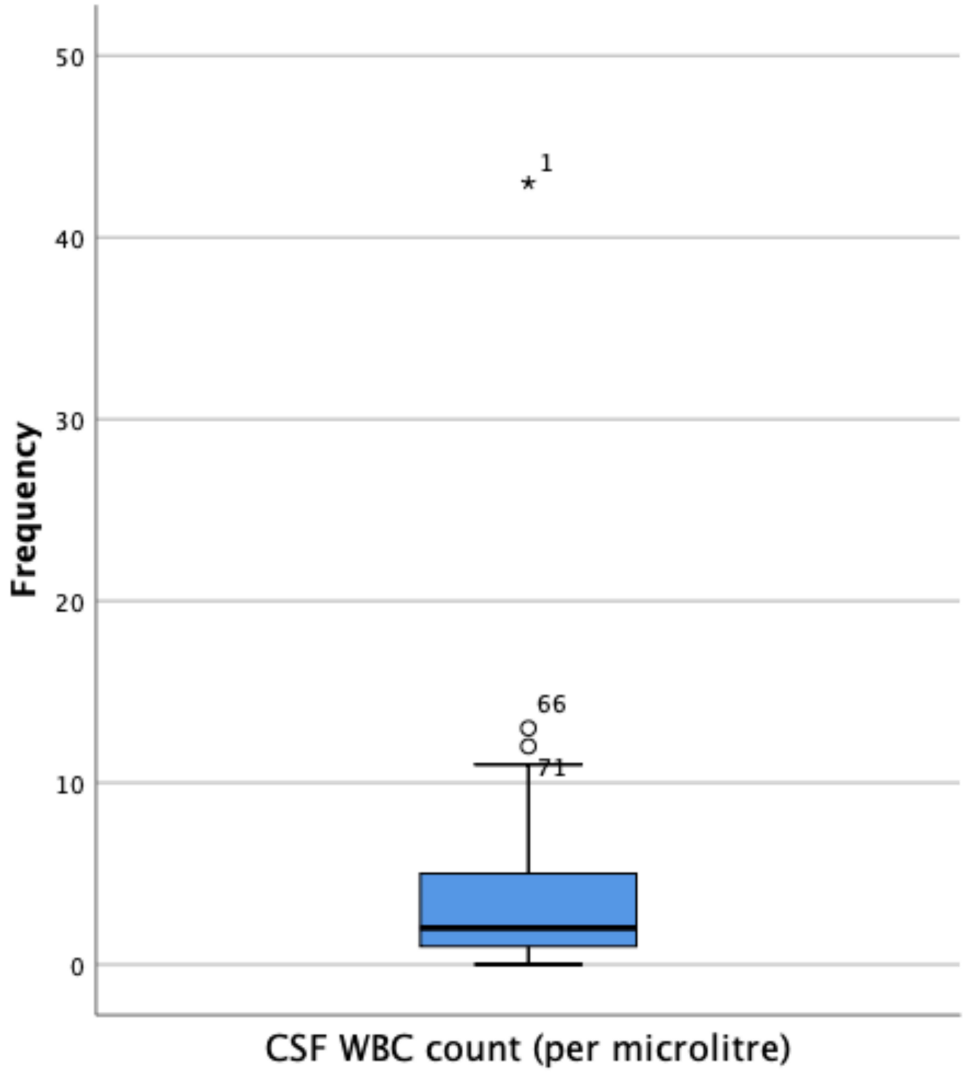

Figure 3 A Box-and-whisker plot of CSF WBC count per microlitre. The box represented the interquartile range (IQR), the horizontal line within the box indicated the median, and the whiskers extended to 1.5 IQR from the quartile boundaries. o: outlier between 1.5–3 IQR from the upper quartile boundary. *: outlier greater than 3 IQR from the upper quartile boundary.

Baseline Characteristics with Respect to DMT Types

Among the 76 patients with history of DMT use, 56 were RRMS subtype. Baseline characteristics in each treatment subgroups (Table 4) included age of symptom onset, gender, smoking status, duration between symptom and diagnosis, types of symptoms and MRI lesions at initial presentation, CSF protein and WBC level, presence of OCB, abnormal evoked potentials, EDSS at diagnosis, and duration of DMT usage.

Table 3 Number of Prior DMTs Used on with Respect to DMT Types

Number of Prior DMT Used	IFN	DMF	TFN	FTY	Other
Total Number of Treatment Cycles, n	*48 (35.0%)*	*41 (30.0%)*	*8 (5.84%)*	*14 (10.2%)*	*26 (19.0%)*
0	46	14	3	0	13
1	2	24	4	8	8
2	0	3	1	5	3
3 or more	0	0	0	1	2

Table 4 Baseline Characteristics of RRMS Patients with Respect to DMT Types

Types of DMT	IFN	DMF	TFN	FTY	Other
Total Number of Patients, n	*38*	*31*	*8*	*13*	*13*
Age of symptom onset, mean (SD)	28.5 (9.99)	27.3 (9.42)	34.9 (7.45)	24.1 (8.36)	30.6 (12.3)
Male, n (%)	10 (26.3%)	7 (22.6%)	1 (12.5%)	1 (7.69%)	6 (46.2%)
Female, n (%)	28 (73.7%)	24 (77.4%)	7 (87.5%)	12 (92.3%)	7 (53.8%)
Current smoker at diagnosis (%)	6 (15.8%)	2 (6.45%)	2 (25.0%)	4 (30.8%)	3 (23.1%)
Duration between symptom and diagnosis, mean (SD), months	35.4 (50.2)	30.7 (40.6)	38.1 (37.8)	29.9 (48.3)	50.7 (62.4)
Types of symptoms at initial presentation (%)					
- Visual	5 (13.2%)	7 (22.6%)	3 (37.5%)	4 (30.8%)	4 (30.8%)
- Pyramidal	9 (23.7%)	7 (22.6%)	4 (50.0%)	3 (23.1%)	3 (23.1%)
- Cerebellar& ataxia	4 (10.5%)	4 (12.9%)	1 (12.5%)	2 (15.4%)	0 (0.00%)
- Brainstem	13 (34.2%)	10 (32.3%)	0 (0.00%)	2 (15.4%)	2 (15.4%)
- Sensory	20 (52.6%)	14 (45.2%)	3 (37.5%)	7 (53.8%)	7 (53.8%)
- Others	4 (10.5%)	2 (6.45%)	1 (12.5%)	2 (15.4%)	1 (7.69%)
Types of MRI lesions at initial presentation (%)					
- Optic nerve	6 (15.8%)	8 (25.8%)	3 (37.5%)	5 (38.5%)	3 (23.1%)
- Supratentorial	32 (84.2%)	24 (77.4%)	7 (87.5%)	11 (84.6%)	8 (61.5%)
- Cerebellar	6 (15.8%)	7 (22.6%)	0 (0.00%)	1 (7.69%)	3 (23.1%)
- Brainstem	9 (23.7%)	10 (32.3%)	0 (0.00%)	1 (7.69%)	3 (23.1%)
- Spinal cord	9 (23.7%)	12 (38.7%)	1 (12.5%)	3 (23.1%)	7 (53.8%)
CSF Protein level, mean (SD), g/L	0.354 (0.254)	0.318 (0.142)	0.285 (0.00707)	0.240 (0.0923)	0.386 (0.295)
CSF WBC level, mean (SD), per μL	2.58 (3.08)	2.39 (2.73)	6.50 (4.95)	2.20 (3.36)	4.22 (4.05)
Presence of OCB in CSF, n (%)	15 (39.5%)	9 (29.0%)	3 (37.5%)	6 (46.2%)	4 (30.8%)
Abnormal evoked potential, n (%)	11 (28.9%)	5 (16.1%)	3 (37.5%)	4 (30.8%)	4 (30.8%)
EDSS, mean (SD)	1.39 (1.35)	1.16 (1.52)	1.83 (1.84)	0.962 (1.30)	1.25 (1.67)
Mean duration of DMT, months (SD)	78.9 (56.5)	22.2 (14.6)	26.1 (20.5)	49.4 (30.4)	69.1 (60.1)

Effectiveness of DMTs

ARR with Respect to Each DMT Use

In 55 RRMS patients with 100 DMT treatment cycles, ARR was calculated for those with a clear definite study period. The ARR 2 years before and that after treatment were shown in Table 5. IFN (−0.492, p-value <0.001) and FTY (−0.557, p-value 0.038) were associated with statistically significant reductions in ARR. The use of DMF had a trend of ARR reduction (-0.095), though not statistically significant. On the other hand, ARR reduction (+0.465) was not shown in TFN

Table 5 ARR Prior to and After Treatment with Respect to DMT Types

Types of DMT	IFN	DMF	TFN	FTY	Other
Total Number of Treatment Cycles, n	*37*	*29*	*7*	*13*	*14*
Mean ARR prior to treatment (SD)	0.649 (0.498)	0.31 (0.618)	0.429 (0.732)	0.769 (0.881)	0.786
Mean ARR after treatment (SD)	0.157 (0.534)	0.215 (0.482)	0.894 (2.25)	0.212 (0.421)	0.363
Mean ARR reduction (augmentation)	0.492	0.095	(0.465)	0.557	0.423
p-value	*<0.001**	*0.346*	*0.466*	*0.038**	*N/A#*

Notes: * p-value less than 0.05 which indicated statistical significance. # p-value was not calculated due to heterogeneity nature of the group.

subgroup. The number of cycles for DMTs other than IFN, DMF, TFN and FTY was too small for individual ARR analysis, or did not have statistically significant findings.

Persistence and Safety Profile of DMTs

Persistence and Discontinuation of DMTs

Out of the 76 patients with DMT use, a total number of 137 DMTs were used. Seventy-one (51.8%) treatments were continued throughout the study period in Table 6, most commonly DMF (34, 82.9%), followed by FTY (10, 71.4%). The median treatment duration ranges from 20.0 months in DMF to 58.5 months in IFN.

The Kaplan-Meier curve in Figure 4 portrayed the continuation of DMTs with respect to DMT types. No between-group statistical difference existed in the probability of DMT continuation with p-value of 0.367 in Log rank test.

On the other hand, 48.2% of treatment discontinued, ie either stopped or switched to other DMTs, most seen in IFN (41, 29.9%), followed by TFN (4, 0.03%). Among them, 13 discontinued within first year, including 3 in TFN and 4 in IFN. The reasons of discontinuation included most due to side effects, intolerance, or patient preference (32, 23.3%), followed by disease activities (23, 16.8%), and other reasons included pregnancy and change of diagnosis.

Individual breakdown into DMT types listed in Table 6 with most common reason of discontinuation was side effects, intolerance in IFN (23 out of 41) and TFN (3 out of 4), and disease activities in DMF (7 out of 7).

Side Effects and/or Intolerance with Discontinuation of DMTs

Side effects, intolerance or personal preference led to discontinuation in 32 (23.4%) of the 137 treatment cycles. Table 7 summarised the side effects reported, though a large portion of the patients continued with the DMTs even with the side effects.

Fifteen (10.9%) IFN cycles were discontinued due to various side effects, most commonly due to injection reactions in 12 patients, and other reasons included mood disturbance, deranged liver function, and poor appetite. Four (2.92%) TFN cycles were discontinued due to intolerance and impaired liver function. Two (1.46%) FTY cycles were discontinued as potential culprit for impaired liver function and lymphopenia. Two (1.46%) patients discontinued azathioprine due to personal preference and proneness to infections. One patient switched to rituximab therapy, but she developed septicaemia afterwards, and then the patient refused subsequent cycles. No patients discontinued DMF due to side effects or intolerance.

Table 6 Continuation and Discontinuation of DMTs with Respect to DMT Types

Types of DMT	IFN	DMF	TFN	FTY	Other
Total Number of Treatment Cycles, n	*48*	*41*	*8*	*14*	*26*
Median treatment duration, months [IQR]	58.5 [26.5–125.8]	20.0 [13.0–29.0]	25.5 [9.8–35.8]	52.0 [20.3–72.8]	45.0 [16.0–70.0]
Continue throughout study period (n, %)	*7 (14.6%)*	*34 (82.9%)*	*4 (50.0%)*	*10 (71.4%)*	*16 (61.5%)*
Discontinuation throughout study period (n,%)	*41 (85.4%)*	*7 (17.1%)*	*4 (50.0%)*	*4 (28.6%)*	*10 (38.5%)*
Discontinuation within first year (n,%)	*4 (8.33%)*	*1 (2.44%)*	*3 (37.5%)*	*2 (14.3%)*	*3 (11.5%)*
Side effects and/or intolerance	23	0	3	2	4
Disease activities	11	7	1	1	3
Pregnancy	4	0	0	0	0
Change of diagnosis	2	0	0	0	2
Unknown	3	0	0	1	1

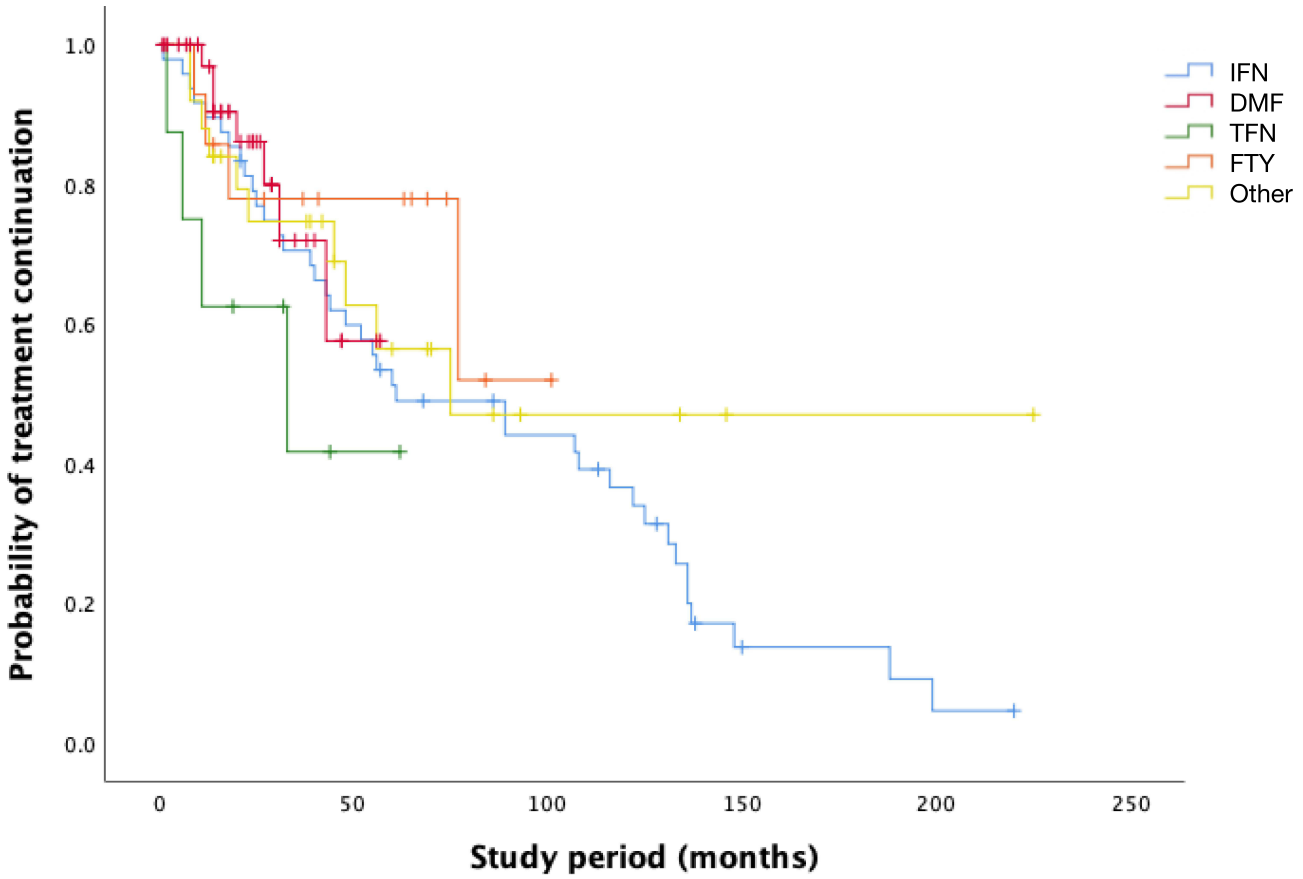

Figure 4 Kaplan-Meier curves showing the probability of DMT continuation over time among patients with different DMT types. The x-axis represented the study period in months, where the y-axis shows the probability of treatment continuation. IFN (blue), DMF (red), TFN (green), FTY (Orange), and other DMTs (yellow) are plotted separately; censored data are denoted by crosses.

The following Kaplan-Meier curve in Figure 5 portrayed the discontinuation of DMTs due to side effects and/or intolerance. There exists statistical significance between various DMTs with p-value of 0.013 by Log rank test. Performing the Cox regression, it was found that TFN was associated with an increased HR of 7.50 (Confidence interval (CI): 1.23–45.7), with statistical significance of p-value 0.029.

Table 7 Side Effects Reported in Various DMTs

Types of DMT	Side Effects Reported
IFN	• Local injection site reaction (pain, induration) • Poor appetite and weight loss • Depression and mood disturbance • Deranged liver function
DMF	• Gastrointestinal upset • Flushing
TFN	• Oral ulcer • Alopecia • Gastrointestinal upset • Deranged liver function

(*Continued*)

https://doi.org/10.2147/POR.S556886

Table 7 (Continued).

Types of DMT	Side Effects Reported
FTY	• Lymphopenia • Deranged liver function
Other	• *Azathioprine*: Immunocompromised state • *Rituximab*: Immunocompromised state • *Alemtuzumab*: Infusion reaction, thyroiditis

Disease Activities Associated with Discontinuation of DMTs

The following Kaplan-Meier curve in Figure 6 portrayed the discontinuation of DMTs due to disease activities with respect to DMT types. Twenty-three (16.8%) of the treatment cycles were terminated due to increased activities, including 11 (8.03%) of interferons, 7 (5.11%) of dimethyl fumarate, 2 (1.46%) of azathioprine, 1 (0.73%) of teriflunomide, fingolimod and cladribine respectively. No statistically significant inter-group difference was demonstrated by log rank test with p-value of 0.348.

In IFN groups, 7 of them were switched to fingolimod, while 4 of them switched to DMF. In DMF groups, all except 2 were switched to FTY whereas the remaining were switched to cladribine and alemtuzumab respectively. For FTY group, one switched to TFN, while another switched to alemtuzumab. Two of azathioprine therapies were switched to mycophenolate mofetil and methotrexate respectively. One patient switched use of cladribine to rituximab.

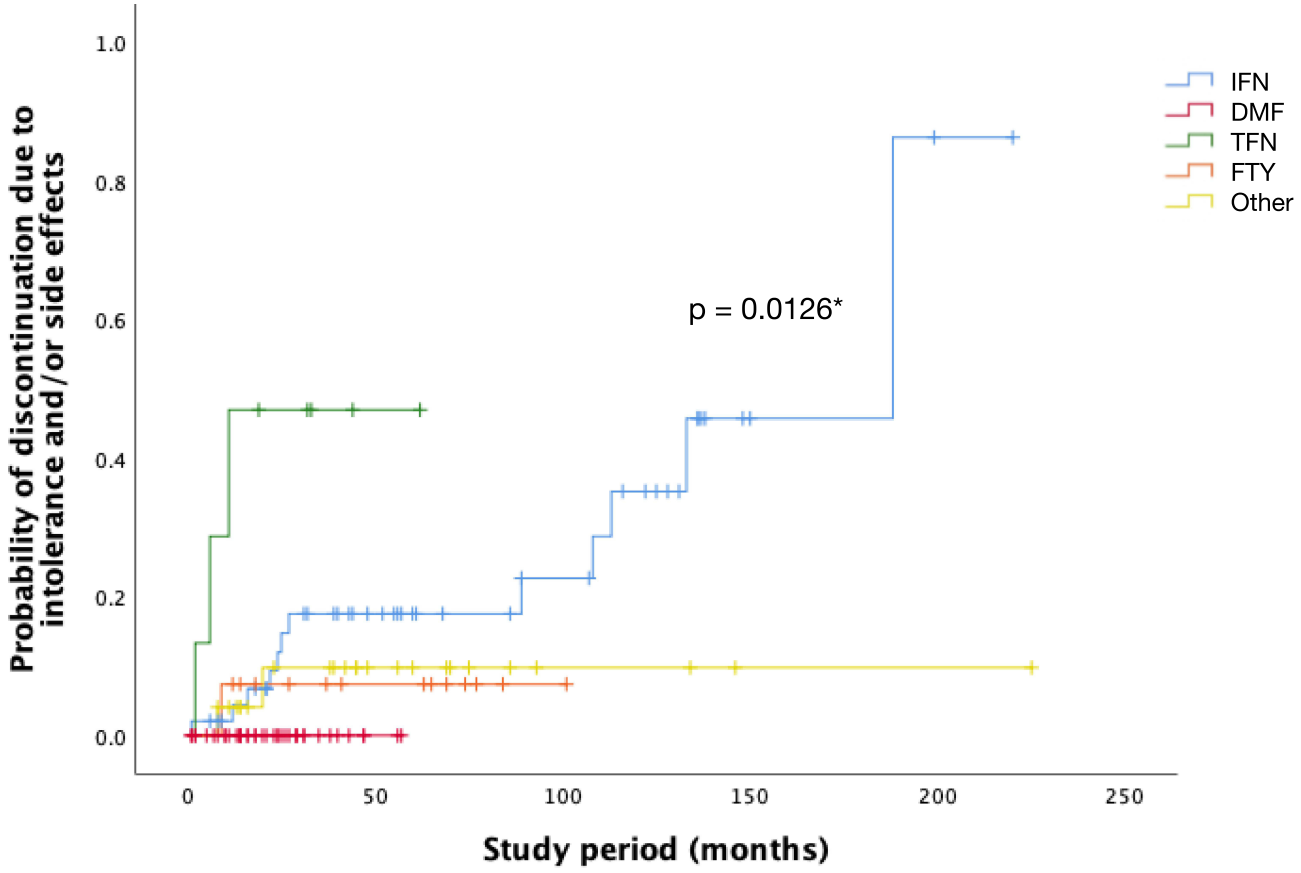

Figure 5 Kaplan-Meier curves showing the probability of DMT discontinuation over time among patients with different DMT types. The x-axis represented the study period in months, and the y-axis showed the probability of discontinuation for each therapy. Lines indicated specific therapies: IFN (blue), DMF (red), TFN (green), FTY (orange), and other DMTs (yellow). Censored data points are indicated with crosses. Discontinuation due to intolerance or side effects was lowest for DMF, with statistical significance is indicated (p = 0.013). * p-value less than 0.05 indicated statistical significance.

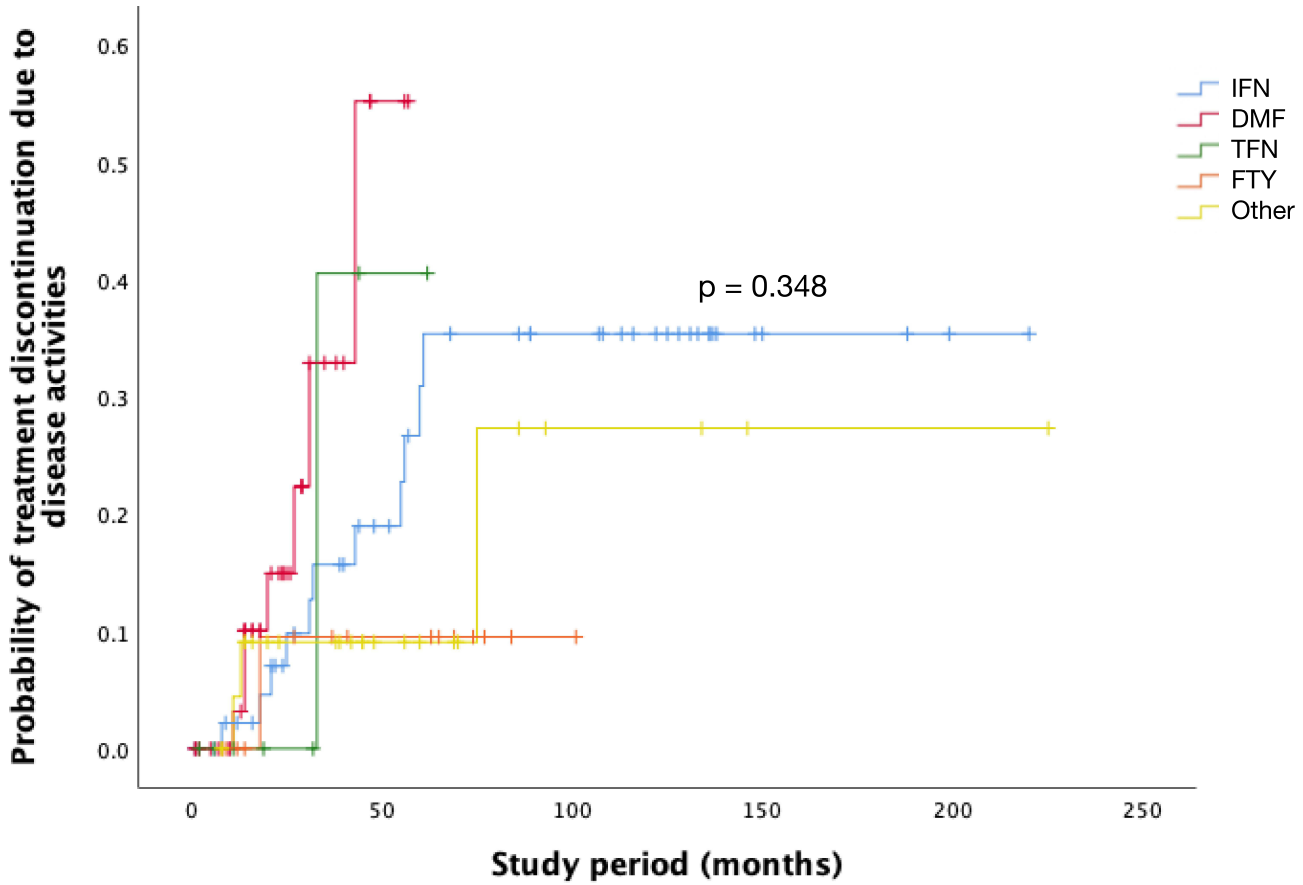

Figure 6 Kaplan-Meier curves showing the probability of disease-modifying therapy (DMT) discontinuation due to disease activity over time, stratified by therapy type. The x-axis shows study period in months, and the y-axis displays probability of discontinuation. IFN (blue), DMF (red), TFN (green), FTY (Orange), and other DMTs (yellow) are plotted separately; censored data are denoted by crosses. The difference in rates of discontinuation across DMTs indicated no significant differences between therapies (p = 0.348).

Other Reasons Associated with Discontinuation of DMTs

Two patients with the use of interferon therapies switched to azathioprine after progression from RRMS to SPMS. Four patients have once discontinued use due to pregnancy.

Azathioprine was commenced in 2 of the patients with initial diagnosis of NMOSD. It was subsequently switched to IFN and TFN, respectively, when the diagnosis of RRMS was established.

Prognostic Factors

Prognostic Factors in Disability and Disease Progression

Various demographic and clinical variables were compared (Table 8), in an attempt to identify their association with EDSS worsening in 83 patients.

It was found that EDSS more than or equal to 4.0 at diagnosis (OR: 4.56, p-value 0.0447), brainstem lesions on initial MRI scan (OR: 3.15, p-value: 0.039) were positively associated with worsening in EDSS. The presence of visual symptoms (OR: 0.144, p-value 0.007) were associated negatively associated with worsening in EDSS. These were associated with statistical significance. Upon binary logistic regression analysis, none demonstrated statistical significance.

Age of onset (OR 2.26, p-value 0.230), ever-smoker status (OR 2.57, p-value 0.145), progressive MS (OR 2.73, p-value 0.132), pyramidal (OR: 1.73, p-value 0.322) and sensory (OR: 2.17, p-value 0.114) symptoms, cerebellar (OR 2.09, p-value 0.193), and spinal cord (OR: 2.03, p-value 0.157) lesions at initial presentation, all had trend of higher odds ratio, though these were statistically insignificant.

https://doi.org/10.2147/POR.S556886

Table 8 Prognostic Factors with Respect to EDSS Worsening

Prognostic Factors	Presence of EDSS Worsening	Absence of EDSS Worsening	Odds Ratio (Confidence Interval)	*pvalue*
Male [Female]	10 [28]	11 [35]	0.88 (0.33–2.37)	*0.806*
Ever smoker [Never smoker] at diagnosis (total n = 82)	9 [28]	5 [40]	2.57 (0.78–8.50)	*0.145*
Age of onset - More than [less than or equal to] 40 year old	8 [29]	5 [41]	– 2.26 (0.67–7.62)	– *0.230*
Types of MS - RRMS - Progressive MS	 27 [11] 8 [30]	 29 [16] 4 [41]	 1.35 (0.54–3.43) 2.73 (0.75–9.92)	 *0.639* *0.132*
Duration between symptom onset and diagnosis - Within [more than] 12 months (total n = 80)	13 [21]	25 [18]	2.24 (0.90–5.63)	*0.109*
Duration between symptom onset and first relapse - Within 12 [more than 12] months (total n = 80)	13 [16]	12 [14]	1.06 (0.36–3.05)	*1.00*
EDSS, n (total n = 81) - More than or equal to [less than] 4.0	6 [30]	3 [42]	4.56 (1.10–18.8)	– *0.045**
Types of signs and symptoms at initial presentation - Visual - Pyramidal - Cerebellar& ataxia - Brainstem - Sensory - Others	 4 [33] 12 [25] 4 [33] 8 [29] 18 [19] 1 [3]	 21 [25] 10 [36] 6 [40] 9 [37] 14 [32] 36 [43]	 0.14 (0.04–0.47) 1.73 (0.65–4.61) 0.81 (0.17–9.38) 1.13 (0.39–3.30) 2.17 (0.88–5.33) 0.40 (0.04–4.00)	 *0.007** *0.322* *1.00* *1.00* *0.114* *0.625*
Types of MRI lesions at initial presentation (total n = 82) - Optic nerve - Supratentorial - Cerebellar - Brainstem - Spinal cord	 7 [29] 29 [7] 11 [25] 13 [23] 14 [22]	 14 [32] 41 [5] 8 [38] 7 [39] 11 [35]	 0.55 (0.20–1.56) 0.51 (0.15–1.75) 2.09 (0.74–5.92) 3.15 (1.10–9.03) 2.03 (0.78–5.25)	 *0.314* *0.351* *0.193* *0.039** *0.157*
CSF Protein level (total n = 54) - More than or equal to [less than] 0.45 g/L	6 [17]	5 [26]	1.83 (0.48–6.97)	– *0.498*
CSF WBC level (total n = 53) - More than or equal to [less than] 10 per μL	1 [22]	5 [25]	0.23 (0.03–2.10)	*0.217*
Presence of OCB in CSF (total n = 51)	13 [8]	18 [12]	1.08 (0.3–3.40)	*1.00*
Abnormal evoked potential (total n = 33)	12 [6]	8 [7]	1.75 (0.43–7.17)	*0.493*

Notes: *p-value less than 0.05 which indicated statistical significance.

Prognostic Factors in ARR

Table 9 listed various demographic and clinical variables, where their respective means of ARR were compared. The result showed that ever-smoker status (0.179, p-value 0.037), more than 10 white blood cells per μL in CSF (0.526, p-value 0.003) and first relapse within 6 months (0.262, p-value 0.006) were associated with higher ARR with statistical significance. OCB in CSF was, however, associated with lower ARR (0.198, p-value 0.043). Multivariate analysis was performed with linear regression, yet none demonstrated statistical significance.

Table 9 Prognostic Factors with Respect to ARR

Prognostic Factors	n (%)	ARR	ARR Difference	*P-value*
Male [Female]	14 (21.2%)	0.249 [0.251]	−0.002	*0.986*
Ever-smoker [Never-smoker] at diagnosis	14 (21.2%)	0.392 [0.213]	0.179	*0.037**
Age of onset - More than [less than or equal] 40 year old	13 (19.7%)	0.186 [0.266]	– −0.080	– 0.368
Duration between symptom onset and diagnosis - Within [more than or equal to] 12 months (total n = 59)	26 (44.0%)	0.190 [0.298]	−0.108	*0.166*
Duration between symptom onset and first relapse - Within [more than or equal to] 6 months (total n = 64)	11 (24.4%)	0.467 [0.205]	– 0.262	*0.006**
Presence of types of symptoms at initial presentation (total n = 64)				
- Visual	17 (26.6%)	0.283 [0.245]	0.038	*0.650*
- Pyramidal	16 (25.0%)	0.316 [0.235]	0.081	*0.333*
- Cerebellar& ataxia	8 (12.5%)	0.274 [0.128]	0.146	*0.186*
- Brainstem	11 (15.4%)	0.212 [0.265]	0.053	*0.593*
- Sensory	27 (42.2%)	0.268 [0.246]	0.022	*0.763*
- Others	5 (7.81%)	0.247 [0.256]	−0.009	*0.946*
Presence of types of MRI lesions at initial presentation (total n = 63)				
- Optic nerve	17 (27%)	0.300 [0.237]	0.063	*0.451*
- Supratentorial	54 (85.7%)	0.228 [0.410]	−0.182	*0.084*
- Cerebellar	12 (19.0%)	0.216 [0.263]	−0.047	*0.619*
- Brainstem	14 (22.2%)	0.233 [0.260]	0.027	*0.761*
- Spinal cord	21 (31.7%)	0.301 [0.232]	0.069	*0.388*
CSF Protein level (total n = 35) - More than or equal to [less than] 0.45 g/L	9 (25.7%)	0.189 [0.320]	−0.131	*0.252*
CSF WBC level (total n = 37) - More than or equal to [less than] 10 per μL	3 (8.33%)	0.772 [0.246]	0.526	*0.003**
Presence of OCB in CSF (total n = 40)	24 (60.0%)	0.196 [0.394]	−0.198	*0.043**
Abnormal evoked potential (total n = 29)	19 (65.5%)	0.231 [0.196]	0.035	*0.71*

Notes: *p-value less than 0.05 which indicated statistical significance.

Discussion

This local cohort study investigated the demographic and clinical characteristics of MS patients in Hong Kong and their DMT selection and preferences.

Patients Characteristics

The baseline characteristics were comparable to those of other Caucasian cohort studies,[20] which contrasted with a previous report that older age of onset, female preponderance was found in the Asian population.[21] It is postulated that the previous cohort might include patients with NMOSD, and a lower availability of aquaporin-4 testing had back then given a limited understanding.

DMT Use

Effectiveness of DMT

The effectiveness of various DMTs was proven in various randomised controlled trials, as compared to placebo,[11,22–30] with some of them also compared to one another.[31–33] Head-to-head comparisons between different DMTs were not widely studied in the literature. In Hong Kong, where majority of MS patients were managed in Hospital Authority. We

started from first line therapies like IFN, DMF and then escalated up to more highly efficacious therapy with disease activities.[34] Comparison was hence difficult due to this usual DMT treatment sequence.

In our study, significant ARR reductions were observed after DMT commencement of IFN, FTY, and other treatments, but not DMF and TFN. The reason could be due to small sample size, and the lateral switch of the DMTs. It was observed that a few of our patients switched from IFN to DMF and TFN after they were made available in our formulary, instead of after having disease activity as they were of good disease control all along. It might partly explain why there was no significant ARR reduction in our study.

Persistence and Discontinuation of DMT

In reality, the effectiveness is often limited by the non-compliance. Adherence to DMT has been shown to decrease risk of relapses.[35] Therefore, study towards the persistence of DMT is important. In our cohort, it was found that the overall discontinuation rate was 48.2%, and the discontinuation rates were similar in various subgroups except TFN, which was mostly in align with findings in a meta-analysis including real-world observational studies in the Western.[36] On the other hand, 9.49% discontinuation rate was observed in the first year, lower than the mean first-year discontinuation rates reported in the same meta-analysis.[36] As limited data in Asia was available, it is uncertain whether these data represent that Asian patients in general have a better tolerance towards DMT.

Side effects were one major factor for the discontinuation.[37,38] For IFNs, the need for self-injection precluded the persistence. Side effects such as injection reactions, flu-like symptoms in our study, were also commonly reported in previous literature. Despite so, most patients tolerated these side effects and continued their uses until the availability of oral alternatives available.

Common side effects of DMF, for instance, gastrointestinal upsets and flushing were reported in our study. However, these appeared well tolerated in our cohort and none discontinued due to side effects. In a multi-centre observational analysis involving mostly Caucasians,[39] DMF was recorded to have the highest discontinuation rate owing to side effects, whereas this is in contrast to an open-label extension study of DMF trial involving Japanese patients,[40] no discontinuation was observed with lower reduction in lymphocyte count and lower incidence of flushing.

In TFN subgroup of our cohort, elevated liver enzymes, gastrointestinal upset, hair loss were reported in 3 out of 8 treatment cycles, with 4 discontinuations observed. In other cohorts, for example, in a retrospective study using healthcare claim data in the United States and a subgroup of Asian patients in a TFN trial,[41,42] the discontinuation rate of TFN was similar compared with overall discontinuation rate. Hence, our observation of higher risk of deterioration with small size in the TFN subgroup required further studies with larger scale to support its significance.

In the studied population, it was observed that a portion of interferons were withheld during pregnancy with previous uncertainty of the safety of their use during pregnancy, either suggested by treating physician or patients themselves. As a result of a meta-analysis[43] showing similar rate in birth defects and emerging of post-market data of interferons, they are nowadays deemed safe to be continued according to the consensus published by the Association of British Neurologists,[44] and the category C warning was removed in the FDA in 2020.[44] In our cohort, none reported adverse pregnancy outcomes, though the size was too small to allow conclusions to be drawn.

Prognostic Factors

A number of environmental, demographic, clinical factors and biomarkers were studied in an attempt to spot out ones with prognostic values. Table 10 depicted factors that were associated with better and worse prognosis in MS found in the literature.

Use of Outcome Measures

ARR and EDSS worsening which we used in our study were common markers to indicate disease activities and progression, respectively.[59–61] For relapse-related outcome measures, ARR is commonly used to reflect inflammatory activities as the data are readily accessible, at the expense of lacking specificity to severity of each attack.[61] For measuring disability progression, EDSS worsening is also commonly used owing to its readiness, though it is limited by its insensitivity to functional system related and cognition-related deficit.[61]

Table 10 Factors with Prognostic Values in MS Reported in Literature

Domain	Factors Associated with Worse (Better) Prognosis
Environmental and demographic factors	• Male[45] • Older age of onset[46,47] • Ever smoking status[48] • Vitamin D Deficiency[48] • Adolescent obesity[48] • Epstein Barr virus infection[48]
Clinical factors	• Higher initial relapse rate[49] • (Longer first inter-attack interval)[49,50] • Higher baseline EDSS score[50] • Multifocal presentation[51] • Pyramidal and cerebellar symptoms[50,52,53] • (Optic neuritis at diagnosis)[52]
Biomarkers	• CSF pleocytosis[54] • Presence of OCB in CSF[50] • High neurofilament chain level[55]
Imaging characteristics	• Baseline infratentorial lesions[56] • Baseline Gadolinium-enhancing lesions[57] • Lesion load, brain atrophy[58]

In our cohort, we observed eight deaths during the study period, its small sample size however precluded further statistical analysis. Two patients had high EDSS score at the time of death with pneumonia as cause of death. It could be postulated to be related to immobilisation, or aspiration due to advanced neurological disease. Another 2 patients on azathioprine, an immunosuppressant, died of pneumonia and septicaemia. It was observed in a Canadian cohort that deaths were commonly caused by infective conditions.[62] Identification of the prognostic factors to all these adverse outcomes could allow better understanding to this disease.

Environmental and Demographic Factors

In our study, we were able to identify ever-smoking status at diagnosis was associated with higher risk of EDSS worsening, consistent with result in a meta-analysis where ever-smoking status was associated with poorer outcome.[63] Male sex and age greater than 40, where some were reported to be associated with worse outcome with conflicting results,[45–48,50,52,64] were not found to have worse outcomes in this study.

Clinical Factors

Optic neuritis at diagnosis was associated with a lower risk of attaining EDSS worsening. It was supported by some cohort studies, including one in Hong Kong.[1,52,65] Pyramidal and cerebellar symptoms were reported to have association with poor prognosis[50,52] though these were not demonstrated in our study.

We found that early relapse within 6 months was associated with a higher risk of ARR. Worse outcomes were found in several studies with a shorter time to reach a higher EDSS score.[52,66] We also noted a higher risk of EDSS worsening in patients with a higher baseline EDSS score, which concurred with a study where patients with EDSS greater than 2.0 were predictive of poor prognosis.[67]

Biomarkers and Imaging Characteristics

We found that ARR was higher in the group with CSF pleocytosis. It was similarly observed in a cohort that a higher number of white blood cells in CSF, with cutoff of 10 cells, was associated with higher ARR in patients with RRMS.[54] Thus, CSF pleocytosis reflects a potential role as a surrogate marker to reflect disease progress in MS.

In our study, OCB was negatively associated with ARR and no effect on EDSS worsening. Despite its potentially useful role as a biomarker in predicting conversion of CIS to RRMS,[68] and a higher probability of worse outcome,[45] an

observational cohort in Austria did not identify any relationship between the two.[64] Therefore, the role in predicting prognosis in RRMS was uncertain where future studies are warranted to confirm this association.

Brainstem, cerebellar and spinal cord lesions were found to have an association with a higher probability of EDSS worsening, though only brainstem lesions were found with statistical significance. It was also similarly found that baseline infratentorial lesions were strong predictors of progression from both CIS to RRMS, and RRMS to SPMS.[56]

Some other biomarkers and MRI characteristics were implicated to have prognostic values.[51] One of them is neurofilament light-chain protein,[55] a neuronal protein that is postulated to be released during axonal damage. Others included a number of MRI lesions, brain volume change and atrophy.[51] Nevertheless, neurofilament testing was not available in Hospital Authority, and the MRI characteristics were not routinely reported by our local radiologists in general. Consequently, these markers were not included in our analysis.

Strength and Weakness

This study provided real-world experience in Hong Kong, regarding the effectiveness, persistence, and discontinuation of DMTs in the epoch with widely available oral options. Baseline characteristics of this local cohort were analysed so that several prognostic factors were found, which potentially aid clinicians in decision-making process.

Yet, there existed quite a few shortcomings, which included retrospective design, missing data, small sample size, and possible selection bias inherent in non-randomised treatment allocation.

A retrospective observational study design without control subgroups was subjected to a number of confounding factors such as disease severity, co-morbidity in the interpretation of efficacy and side effects. For instance, treatment allocation was determined by the attending neurologist's clinical judgment rather than random assignment, confounding by indication cannot be excluded. Also, for those with better clinical course with relatively less relapses or even achieved remission, they were more likely to default follow-up.

Secondly, as a single centre study, its small sample size such that it lacked sufficient power for conducting multivariate analysis. Nevertheless, owing to relatively low prevalence, it encompassed quite a number of MS patients of Hong Kong already. Another important factor is the heterogeneity of our local MS patients, which rendered our review particularly difficult. Still, despite all these, we hoped to gain insights into the usage of DMTs in our local MS patients.

Thirdly, data collection was based on a review of both electronic and handwritten medical records. Variations in documentation completeness and interpretation could have introduced information bias, despite efforts to ensure accuracy through cross-checking.

Finally, missing data were present for certain variables, including EDSS scores and MRI data. Even though these cases were excluded from specific analyses, this might under- or over-estimate the true associations. The definite time of EDSS score change could not be determined with certainty, as it was not included as an outcome measurement in our cohort.

Conclusion

Multiple sclerosis is a chronic neurological illness that commonly affected the young individuals, which could pose significant disability and negative consequences to daily life.

In our study, the use of DMTs pattern appeared similar with other observational cohorts. IFN, FTY and other DMTs were associated with a significant ARR reduction, though the apparent lack of benefit in DMF, TFN could be due to inadequate power with the heterogeneous population. Similar persistence to DMTs with a significantly higher portion of TFN discontinued due to intolerance was demonstrated, though the finding is underpowered.

We identified several poor prognostic factors in our MS patients - ever-smoking status, EDSS more than or equal to 4, short period of relapse, CSF leucocytosis and brainstem MRI lesions. The good prognostic factors were the presence of visual symptoms and OCB in CSF. With the identification of the potential prognostic factors in this cohort, clinicians could make use of these to facilitate communication to allow patients to better understand their disease prognosis. Although no significant association with other factors could be found due to limited sample size, future studies with larger sample size, collaboration with multiple centres, and multivariate analysis were recommended to reduce influence of the other unmeasured factors and to confirm the association.

Overall, this study illustrated the beauty, and complexity in managing MS patients with all the considerations for patients' clinical characteristics, diseases activity, risk appetite and treatment side effects so as to reach an informed decision on the use of DMTs in our local MS patients.

Disclosure

The authors report no conflicts of interest in this work.

References

1. Forouhari A, Taheri G, Salari M, Moosazadeh M, Etemadifar M. Multiple sclerosis epidemiology in Asia and Oceania; A systematic review and meta-analysis. *Mult Scler Relat Disord*. 2021;54:103119. doi:10.1016/j.msard.2021.103119
2. Deuschl G, Beghi E, Fazekas F, et al. The burden of neurological diseases in Europe: an analysis for the Global Burden of Disease Study 2017. *Lancet Public Health*. 2020;5(10):e551–e571. doi:10.1016/S2468-2667(20)30190-0
3. Lau KK, Wong WWY, Sheng B, et al. The clinical course of multiple sclerosis patients in Hong Kong. *J Neurol Sci*. 2008;268(1–2):78–82. doi:10.1016/j.jns.2007.11.006
4. Frohman EM, Racke MK, Raine CS. Multiple sclerosis—the plaque and its pathogenesis. *N Engl J Med*. 2006;354(9):942–955. doi:10.1056/NEJMra052130
5. Krumbholz M, Derfuss T, Hohlfeld R, Meinl E. B cells and antibodies in multiple sclerosis pathogenesis and therapy. *Nat Rev Neurol*. 2012;8(11):613–623. doi:10.1038/nrneurol.2012.203
6. McDonald WI, Compston A, Edan G, et al. Recommended diagnostic criteria for multiple sclerosis: guidelines from the International Panel on the diagnosis of multiple sclerosis. *Ann Neurol*. 2001;50(1):121–127. doi:10.1002/ana.1032
7. Thompson AJ, Banwell BL, Barkhof F, et al. Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol*. 2018;17(2):162–173. doi:10.1016/S1474-4422(17)30470-2
8. Lublin FD, Reingold SC, Cohen JA, et al. Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology*. 2014;83(3):278–286. doi:10.1212/WNL.0000000000000560
9. Chen C, Zhang E, Zhu C, et al. Comparative efficacy and safety of disease-modifying therapies in patients with relapsing multiple sclerosis: a systematic review and network meta-analysis. *J Am Pharm Assoc*. 2023;63(1):8–22.e23. doi:10.1016/j.japh.2022.07.009
10. Filipi M, Jack S. Interferons in the treatment of multiple sclerosis: a clinical efficacy, safety, and tolerability update. *Int J MS Care*. 2020;22(4):165–172. doi:10.7224/1537-2073.2018-063
11. Yong VW, Chabot S, Stuve O, Williams G. Interferon beta in the treatment of multiple sclerosis: mechanisms of action. *Neurology*. 1998;51(3):682–689. doi:10.1212/WNL.51.3.682
12. Elion GB. The pharmacology of azathioprine. *Ann N Y Acad Sci*. 1993;685:400–407. doi:10.1111/j.1749-6632.1993.tb35897.x
13. Kappos L, Radue EW, O'Connor P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):387–401. doi:10.1056/NEJMoa0909494
14. Matloubian M, Lo CG, Cinamon G, et al. Lymphocyte egress from thymus and peripheral lymphoid organs is dependent on S1P receptor 1. *Nature*. 2004;427(6972):355–360. doi:10.1038/nature02284
15. Scannevin RH, Chollate S, Jung MY, et al. Fumarates promote cytoprotection of central nervous system cells against oxidative stress via the nuclear factor (erythroid-derived 2)-like 2 pathway. *J Pharmacol Exp Ther*. 2012;341(1):274–284. doi:10.1124/jpet.111.190132
16. Bar-Or A, Pachner A, Menguy-Vacheron F, Kaplan J, Wiendl H. Teriflunomide and its mechanism of action in multiple sclerosis. *Drugs*. 2014;74(6):659–674. doi:10.1007/s40265-014-0212-x
17. Coles AJ, Cox A, Le Page E, et al. The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy. *J Neurol*. 2006;253(1):98–108. doi:10.1007/s00415-005-0934-5
18. Lee CY, Chan KH. Multiple sclerosis - updates in management. *HK Pract*. 2016;38(3):83–92.
19. Kurtzke JF. Rating neurologic impairment in multiple sclerosis: an expanded disability status scale (EDSS). *Neurology*. 1983;33(11):1444–1452. doi:10.1212/WNL.33.11.1444
20. Weinshenker BG, Bass B, Rice GP, et al. The natural history of multiple sclerosis: a geographically based study. I. Clinical course and disability. *Brain*. 1989;112(1):133–146. doi:10.1093/brain/112.1.133
21. Kim SH, Huh SY, Kim W, et al. Clinical characteristics and outcome of multiple sclerosis in Korea: does multiple sclerosis in Korea really differ from that in the Caucasian populations? *Mult Scler*. 2013;19(11):1493–1498. doi:10.1177/1352458513477712
22. IFNB Multiple Sclerosis Study Group. Interferon beta-1b is effective in relapsing-remitting multiple sclerosis. I. Clinical results of a multicenter, randomized, double-blind, placebo-controlled trial. *Neurology*. 1993;43(4):655–661. doi:10.1212/WNL.43.4.655.
23. PRISMS Study Group. Randomised double-blind placebo-controlled study of interferon beta-1a in relapsing/remitting multiple sclerosis. *Lancet*. 1998;352(9139):1498–1504.
24. Gold R, Kappos L, Arnold DL, et al. Placebo-controlled Phase 3 study of oral BG-12 for relapsing multiple sclerosis. *N Engl J Med*. 2012;367(12):1098–1107. doi:10.1056/NEJMoa1114287
25. Fox RJ, Miller DH, Phillips JT, et al. Placebo-controlled phase 3 study of oral BG-12 or glatiramer in multiple sclerosis. *N Engl J Med*. 2012;367(12):1087–1097. doi:10.1056/NEJMoa1206328
26. O'Connor P, Wolinsky JS, Confavreux C, et al. Randomized trial of oral teriflunomide for relapsing multiple sclerosis. *N Engl J Med*. 2011;365(14):1293–1303. doi:10.1056/NEJMoa1014656
27. Confavreux C, O'Connor P, Comi G, et al. Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet Neurol*. 2014;13(3):247–256. doi:10.1016/S1474-4422(13)70308-9
28. Giovannoni G, Comi G, Cook S, et al. A placebo-controlled trial of oral cladribine for relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):416–426. doi:10.1056/NEJMoa0902533

29. Coles AJ, Twyman CL, Arnold DL, et al. Alemtuzumab for patients with relapsing multiple sclerosis after disease-modifying therapy: a randomised controlled phase 3 trial. *Lancet*. 2012;380(9856):1829–1839. doi:10.1016/S0140-6736(12)61768-1
30. Montalban X, Hauser SL, Kappos L, et al. Ocrelizumab versus placebo in primary progressive multiple sclerosis. *N Engl J Med*. 2017;376(3):209–220. doi:10.1056/NEJMoa1606468
31. Khatri B, Barkhof F, Comi G, et al. Comparison of fingolimod with interferon beta-1a in relapsing-remitting multiple sclerosis: a randomised extension of the TRANSFORMS study. *Lancet Neurol*. 2011;10(6):520–529. doi:10.1016/S1474-4422(11)70099-0
32. Cohen JA, Barkhof F, Comi G, et al. Oral fingolimod or intramuscular interferon for relapsing multiple sclerosis. *N Engl J Med*. 2010;362(5):402–415. doi:10.1056/NEJMoa0907839
33. Vermersch P, Czlonkowska A, Grimaldi LME, et al. Teriflunomide versus subcutaneous interferon beta-1a in patients with relapsing multiple sclerosis: a randomised, controlled phase 3 trial. *Mult Scler*. 2014;20(6):705–716. doi:10.1177/1352458513507821
34. Hong Kong Multiple Sclerosis Society. *Practice Recommendations for Disease-Modifying Drugs*. 2019.
35. Burks J, Marshall TS, Ye X. Adherence to disease-modifying therapies and its impact on relapse, health resource utilization, and costs among patients with multiple sclerosis. *Clinicoecon Outcomes Res*. 2017;9:251–260. doi:10.2147/CEOR.S130334
36. Mardan J, Hussain MA, Allan M, Grech LB. Objective medication adherence and persistence in people with multiple sclerosis: a systematic review, meta-analysis, and meta-regression. *J Manag Care Spec Pharm*. 2021;27(9):1273–1295. doi:10.18553/jmcp.2021.27.9.1273
37. Río J, Porcel J, Téllez N, et al. Factors related with treatment adherence to interferon beta and glatiramer acetate therapy in multiple sclerosis. *Mult Scler*. 2005;11(3):306–309. doi:10.1191/1352458505ms1173oa
38. Ruggieri RM, Settipani N, Viviano L, et al. Long-term interferon-beta treatment for multiple sclerosis. *Neurol Sci*. 2003;24(5):361–364. doi:10.1007/s10072-003-0190-3
39. Min J, Cohan S, Alvarez E, et al. Real-world characterization of dimethyl fumarate–related gastrointestinal events in multiple sclerosis: management strategies to improve persistence on treatment and patient outcomes. *Neurol Ther*. 2019;8(1):109–119. doi:10.1007/s40120-019-0127-2
40. Ochi H, Niino M, Onizuka Y, et al. 72-week safety and tolerability of dimethyl fumarate in Japanese patients with relapsing-remitting multiple sclerosis: analysis of the randomized, double-blind, placebo-controlled, Phase III APEX study and its open-label extension. *Adv Ther*. 2018;35(10):1598–1611. doi:10.1007/s12325-018-0788-8
41. Araujo L, Geertsen SS, Amedume A, Higuchi K, van Wingerden J. Persistence, adherence, and switching to higher-cost therapy in patients with multiple sclerosis initiating oral disease-modifying therapies: a retrospective real-world study. *Neurol Ther*. 2022;11(4):1735–1748. doi:10.1007/s40120-022-00404-1
42. Miller AE, Xu X, Macdonell R, et al. Efficacy and safety of teriflunomide in Asian patients with relapsing forms of multiple sclerosis: a subgroup analysis of the phase 3 TOWER study. *J Clin Neurosci*. 2019;59:229–231. doi:10.1016/j.jocn.2018.09.012
43. Zhang M, Fu S, Ren D, et al. Maternal and fetal outcomes after interferon exposure during pregnancy: a systematic review with meta-analysis. *Front Reprod Health*. 2021;3:702929. doi:10.3389/frph.2021.702929
44. Dobson R, Dassan P, Roberts M, Giovannoni G, Nelson-Piercy C, Brex PA. UK consensus on pregnancy in multiple sclerosis: 'Association of British Neurologists' guidelines. *Pract Neurol*. 2019;19(2):106–114. doi:10.1136/practneurol-2018-002060
45. Ribbons KA, McElduff P, Boz C, et al. Male sex is independently associated with faster disability accumulation in relapse-onset MS but not in primary progressive MS. *PLoS One*. 2015;10(6):e0122686. doi:10.1371/journal.pone.0122686
46. Trojano M, Liguori M, Bosco Zimatore G, et al. Age-related disability in multiple sclerosis. *Ann Neurol*. 2002;51(4):475–480. doi:10.1002/ana.10147
47. Confavreux C, Vukusic S. Age at disability milestones in multiple sclerosis. *Brain*. 2006;129(Pt 3):595–605. doi:10.1093/brain/awh714
48. Olsson T, Barcellos LF, Alfredsson L. Interactions between genetic, lifestyle, and environmental risk factors for multiple sclerosis. *Nat Rev Neurol*. 2017;13(1):25–36. doi:10.1038/nrneurol.2016.187
49. Scalfari A, Neuhaus A, Degenhardt A, et al. The natural history of multiple sclerosis: a geographically based study 10: relapses and long-term disability. *Brain*. 2010;133(Pt 7):1914–1929. doi:10.1093/brain/awq118
50. Amato MP, Ponziani G. A prospective study on the prognosis of multiple sclerosis. *Neurol Sci*. 2000;21(Suppl 2):S831–S838. doi:10.1007/s100720070021
51. Gajofatto A, Calabrese M, Benedetti MD, Monaco S. Clinical, MRI, and CSF markers of disability progression in multiple sclerosis. *Dis Markers*. 2013;35(6):687–699. doi:10.1155/2013/484959
52. Confavreux C, Vukusic S, Adeleine P. Early clinical predictors and progression of irreversible disability in multiple sclerosis: an amnesic process. *Brain*. 2003;126(Pt 4):770–782. doi:10.1093/brain/awg081
53. Vasconcelos CCF, Aurenção JCK, Thuler LCS, Camargo S, Alvarenga MP, Alvarenga RMP. Prognostic factors associated with long-term disability and secondary progression in patients with multiple sclerosis. *Mult Scler Relat Disord*. 2016;8:27–34. doi:10.1016/j.msard.2016.03.011
54. Lotan I, Benninger F, Mendel R, Hellmann MA, Steiner I. Does CSF pleocytosis have a predictive value for disease course in MS? *Neurol Neuroimmunol Neuroinflamm*. 2019;6(5):e584. doi:10.1212/NXI.0000000000000584
55. Cai L, Huang J. Neurofilament light chain as a biological marker for multiple sclerosis: a meta-analysis study. *Neuropsychiatr Dis Treat*. 2018;14:2241–2254. doi:10.2147/NDT.S173280
56. Chung KK, Altmann D, Barkhof F, et al. A 30-year clinical and magnetic resonance imaging observational study of multiple sclerosis and clinically isolated syndromes. *Ann Neurol*. 2020;87(1):63–74. doi:10.1002/ana.25637
57. Kappos L, Moeri D, Radue EW, et al. Predictive value of gadolinium-enhanced MRI for relapse rate and changes in disability or impairment in multiple sclerosis: a meta-analysis. *Lancet*. 1999;353(9157):964–969. doi:10.1016/S0140-6736(98)03053-0
58. Popescu V, Agosta F, Hulst HE, et al. Brain atrophy and lesion load predict long term disability in multiple sclerosis. *J Neurol Neurosurg Psychiatry*. 2013;84(10):1082–1091. doi:10.1136/jnnp-2012-304094
59. van Munster CEP, Uitdehaag BMJ. Outcome measures in clinical trials for multiple sclerosis. *CNS Drugs*. 2017;31(3):217–236. doi:10.1007/s40263-017-0412-5
60. Sormani MP, Bonzano L, Roccatagliata L, et al. Surrogate endpoints for EDSS worsening in multiple sclerosis: a meta-analytic approach. *Neurology*. 2010;75(4):302–309. doi:10.1212/WNL.0b013e3181ea15aa
61. Tur C, Moccia M, Barkhof F, et al. Assessing treatment outcomes in multiple sclerosis trials and in the clinical setting. *Nat Rev Neurol*. 2018;14(2):75–93. doi:10.1038/nrneurol.2017.171

62. Harding K, Zhu F, Alotaibi M, Duggan T, Tremlett H, Kingwell E. Multiple cause of death analysis in multiple sclerosis: a population-based study. *Neurology*. 2020;94(8):e820–e829. doi:10.1212/WNL.0000000000008907
63. Poorolajal J, Bahrami M, Karami M, Hooshmand E. Effect of smoking on multiple sclerosis: a meta-analysis. *J Public Health (Oxf)*. 2017;39 (2):312–320. doi:10.1093/pubmed/fdw030
64. Bsteh G, Ehling R, Lutterotti A, et al. Long term clinical prognostic factors in relapsing-remitting multiple sclerosis: insights from a 10-year observational study. *PLoS One*. 2016;11(7):e0158978. doi:10.1371/journal.pone.0158978
65. Tintore M, Rovira À, Río J, et al. Defining high, medium and low impact prognostic factors for developing multiple sclerosis. *Brain*. 2015;138(Pt 7):1863–1874. doi:10.1093/brain/awv105
66. Kantarci O, Siva A, Eraksoy M, et al. Survival and predictors of disability in Turkish MS patients. Turkish Multiple Sclerosis Study Group (TUMSSG). *Neurology*. 1998;51(3):765–772. doi:10.1212/WNL.51.3.765
67. Rudick RA, Lee JC, Cutter GR, et al. Disability progression in a clinical trial of relapsing-remitting multiple sclerosis: eight-year follow-up. *Arch Neurol*. 2010;67(11):1329–1335.
68. Dobson R, Ramagopalan S, Davis A and Giovannoni G. (2013). Cerebrospinal fluid oligoclonal bands in multiple sclerosis and clinically isolated syndromes: a meta-analysis of prevalence, prognosis and effect of latitude. Journal of Neurology, Neurosurgery & Psychiatry, 84(8), 909–914. doi:10.1136/jnnp-2012-304695