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·Review·

Challenges in randomized controlled trials and emerging multiple sclerosis therapeutics

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The remarkable global development of disease-modifying therapies (DMTs) specific for multiple sclerosis (MS) has significantly reduced the frequency of relapse, slowed the progression of disability, and improved the quality of life in patients with MS. With increasing numbers of approved DMTs, neurologists in North America and Europe are able to present multiple treatment options to their patients to achieve a better therapeutic outcome, and in many cases, no evidence of disease activity. MS patients have improved accessibility to various DMTs at no or minimal out-of-pocket cost. The ethical guidelines defined by the Edinburgh revision of the Declaration of Helsinki strongly discourage the use of placebo control groups in modern MS clinical trials. The use of an active comparator control group increases the number of participants in each group that is essential to achieve statistical significance, thus further increasing the difficulty of completing randomized controlled trials (RCTs) for the development of new MS therapies. There is evidence of a high prevalence of MS and a large number of patients in Asia. The belief of the existence of Asian types of MS that are distinct from Western types, and regulatory policies are among the reasons why DMTs are limited in most Asian countries. Lack of access to approved DMTs provides a good opportunity for clinical trials that are designed for the development of new MS therapies. Recently, data from RCTs have demonstrated excellent recruitment of participants and the completion of multi-nation and single-nation MS trials within this region. Recent studies using the McDonald MS diagnostic criteria carefully excluded patients with neuromyelitis optica (NMO) and NMO spectrum disorder, and demonstrated that patients with MS in Asia have clinical characteristics and treatment responses similar to those in Western countries.

Keywords: multiple sclerosis; clinical trials; research ethics; Asia; immunomodulatory treatment; immunosuppression

Introduction

Evidence-based medicine scrutinizes treatment initiatives, establishes a scientific basis for the use of medications, and assesses the appropriateness of tests. Evidence-based practice (EBP) with standardized protocols and guidelines is increasingly used by healthcare professionals in the diagnosis and treatment of various disorders including multiple sclerosis (MS)[1,2]. EBP enhances the quality of medical practice by improving outcomes, optimizing resources, and minimizing risks. In contrast to practicing medicine according to personal beliefs that are not tested by evidence of benefits outweighing risks, EBP uses the best evidence to make clinical decisions for individual patients. Several steps are involved in EBP. Immediately following the first step of identifying question(s) for individual patients, healthcare professionals retrieve the information necessary to answer the questions. Data from blind randomized controlled trials (RCTs) are considered the strongest evidence for reliable information. When designed and carried out appropriately, RCTs are accepted as class I evidence. Well-designed and executed RCTs

include technical elements such as randomization, placebo control, blinding, allocation concealment to adequately control bias caused by selection or unknown confounders, placebo effects, and co-interventions[3]. Data from RCTs are required for pharmaceutical companies to gain approvals from regulatory authorities in various countries and regions.

The currently available disease-specific therapies for MS are known to modify the disease activity by reducing relapses and slowing the progression of disability, and to be partially effective in treating the relapsing form of MS. New therapies are being tested *via* RCTs and seem to have potent clinical and radiographic efficacy compared to the current approved therapies. In addition to a better therapeutic outcome, these new therapies have improved side-effect profiles and/or offer the convenience of oral administration[4-6].

Approved Disease-Modifying Therapies (DMTs) and Emerging Therapies

The global development of therapies for MS has been very successful for the last 2 decades. The therapeutic armamentarium (Table 1) consists of Avonex®, Betaseron®, Copaxone®, Extavia®, Rebif®, Plegridy®, Gilenya®, Aubagio®, Tecfidera®, Tysabri®, Lemtrada®, Novantrone®, and Ampyra®. Patients with MS can now be treated with DMTs in the form of oral pills, self-administered injections, and office-based intravenous infusions[7]. The early initiation and maintenance of DMTs is critical to control disease activity and slow the progression of disability. Individuals with clinically-isolated syndrome (CIS), a first episode of neurologic symptoms that lasts at least 24 h, with brain and spinal cord MRI lesions similar to those seen in patients with MS, have a high likelihood of conversion to relapsing MS in subsequent years. Avonex®, Betaseron®, Extavia®, and Copaxone® are approved by the US Food and Drug Administration (FDA) for the treatment of CIS.

DMTs can be classified into 2 groups: first-line basic therapies and second-line escalation therapies. The increased number of approved DMTs enables health-care providers to use data generated by RCTs in individualized management to achieve better outcomes and fewer side-effects. In commonly-seen cases of MS, treatment is initiated with one of the first-line basic DMTs. The patient is monitored clinically and with brain and/or spinal cord MRIs.

Table 1. Currently approved disease-modifying therapies for MS

Drug trade name	Bio-chemical	Mechanism of action	Administration	Pharma company	Indications
Betaseron/Betaferon	IFNβ 1b	Immune modulation	250 μg s.c. QOD	Bayer	RR-MS, CIS
Extavia	IFNβ 1b	Immune modulation	250 μg s.c. QOD	Novartis	RR-MS, CIS
Avonex	IFNβ 1a	Immune modulation	30 μg i.m. weekly	Biogen Idec	RR-MS, CIS
Plegridy	PegIFN 1a	Immune modulation	125 μg s.c. bi-weekly	Biogen Idec	RR-MS
Rebif	IFNβ 1a	Immune modulation	22 or 44 μg s.c. 3/week	Merck EMD Serono	RR-MS
Copaxone	Glatiramer acetate	Immune modulation	20 mg s.c. daily	Teva	RR-MS, CIS
Copaxone	Glatiramer acetate	Immune modulation	40 mg s.c. 3/week	Teva	RR-MS, CIS
Gilenya	Fingolimod	S1PR modulation	0.5 mg p.o. daily	Novartis	RR-MS
Tysabri	Natalizumab	Anti-α4-integrin antibody	300 mg i.v. monthly	Biogen Idec	Highly active MS
Aubagio	Teriflunomide	Inhibition of lymphocyte proliferation and activation	7 or 14 mg p.o. daily	Sanofi	RR-MS
Tecfidera	DMF	Cytoprotection and immune modulation	240 mg p.o. BID	Biogen Idec	RR-MS
Lemtrada	Anti-CD52	Depletion of $CD52^+$ cells	12 mg i.v. daily ×5 for 1st year 12 mg i.v. daily ×3 for 2nd year	Sanofi	Highly active MS

For individuals whose MS activity is controlled and who can tolerate the side-effects, the first-line therapy is continued. However, for patients who manifest ongoing clinical and/or radiological MS activity, or are unable to tolerate the side-effects, second-line DMTs or escalation therapies should be considered.

First-Line Basic Therapeutics

Interferon preparations (Avonex®, Betaseron®/Betaferon®, Extavia®, Rebif®, and Plegridy®) and glatiramer acetate (Copaxone®) are immunomodulators and the current first-line basic DMTs. The majority of pivotal RCTs for the first-line basic DMTs were completed more than 20 years ago. The participants in these trials were predominantly Caucasian patients with MS. First-line basic DMTs reduce the annualized relapse rate (ARR) by ~30%. With 2 decades of post-marketing experience, the safety profiles of these DMTs are well established.

The relatively newer oral agents can be used as first-line basic DMTs or second-line escalation therapeutics. Fingolimod[8,9] (Gilenya®), a sphingosine-1-phosphate analogue, is approved for relapsing forms of MS as a first-line basic therapy in Switzerland. The FDA has not specified the position of Gilenya in the armamentarium for the treatment of MS. Neurologists are frequently deterred by its potential side-effects, which include cardiopulmonary and hepatic injury and macular edema. Of note, a Phase III trial of Fingolimod in primary progressive MS (PPMS) showed no significant difference from the placebo group on a combination of disability measures. These findings provide further evidence that PPMS is a distinct disease entity different from relapsing MS (http://www.novartis.com/newsroom/media-releases/en/2014/1875463.shtml).

Teriflunomide[10-13] (Aubagio®) reduces the activity of dihydroorotate dehydrogenase, a mitochondrial enzyme involved in *de novo* pyrimidine synthesis, thus inhibiting the proliferation of T-lymphocytes. The reductions of ARR by Teriflunomide in pivotal trials were similar to those for first-line injectable DMTs, though data from direct comparison trials are not available. The FDA-approved prescribing information for Teriflunomide has a warning of hepatotoxicity and a risk of teratogenicity. Dimethyl fumarate[4, 14] (Tecfidera®) is another oral DMT for relapsing forms of MS. Dimethyl fumarate and its metabolite monomethyl fumarate have been shown to activate the nuclear factor (erythroid-derived 2)-like 2 (Nrf2) pathway, which is involved in the cellular response to oxidative stress. In RCTs, dimethyl fumarate demonstrated a reduction of ARR at a magnitude similar to those reported in the Fingolimod pivotal trials, though no data from trials with direct comparison between Gilenya® and Tecfidera® are available. Dimethyl fumarate can be used as a first-line basic or a second-line escalation DMT.

Second-Line Escalation Therapeutics

Agents in this category are usually more potent than the first-line basic DMTs. Natalizumab[15,16] (Tysabri®) is a humanized monoclonal antibody that binds to α4-integrin after intravenous infusion. It inhibits the migration of lymphocytes from the circulation to the CNS and largely abolishes the trafficking of lymphocytes to the brain and spinal cord. The association of progressive multifocal leukoencephalopathy (PML), a JC viral infection of the CNS, with natalizumab restricts the use of this potent therapy to certain MS sub-populations with relatively higher risk factors for PML. MS patients with prior immunosuppressive drug use, a serum-positive anti-JC virus antibody test, and natalizumab treatment duration longer than 2 years are at a relatively higher risk of developing PML.

Alemtuzumab[17-19] (Lemtrada®), a humanized anti-CD52 monoclonal antibody, was approved in September 2013 by the European Medicines Agency and in November 2014 by the FDA for the treatment of highly active relapsing-remitting (RR)-MS. Alemtuzumab infusion leads to a long-lasting depletion of circulating CD52-bearing cells (mainly T and B lymphocytes). In the RCTs, Alemtuzumab demonstrated better efficacy than an active comparator, the first-line basic DMT Rebif®. Side-effects associated with infusion and secondary autoimmune disorders such as thyroid diseases, immune thrombocytopenia, and nephritis are among the list of safety issues.

The recently-approved oral MS therapies and peginterferon beta 1a (Plegridy®) improve patients' medical compliance, quality of life, and therapeutic effects. With the existing secondary treatment options in the armamentarium and the emerging highly-effective therapies currently under development (Table 2), the idea of achieving no evidence of disease activity or attaining freedom from detectable disease activity is gaining support, changing the landscape of MS therapeutics. While RCTs are essential in the

Table 2. Emerging disease-modifying therapies for multiple sclerosis

Agent	Target and mechanism of action	Dosage	Reported/potential AEs	References
Ocrelizmab	Anti-CD20 monoclonal antibody	300 mg i.v. on days 1 and 15; 600 mg on weeks 24, 48, and 72	Influenza-like illness, upper respiratory and urinary tract infections, nasopharyngitis, potential opportunistic infections	ClinicalTrials.gov CT01765361
Ofatumumab	IgG kappa monoclonal antibody	100, 300, or 700 mg in 2 treatment courses (2×2 i.v. infusions)	Rash, uticaria, angioedema, interstitial lung disease, diarrhea, pneumonia, pericardial effusion	ClinicalTrials.gov NCT01457924
Daclizumab	Anti-CD25 antibody	2 mg/kg s.c. every 2 or 4 weeks	Skin rash, infections, liver function abnormalities, autoimmune hepatitis, and others	ClinicalTrials.gov NCT00109161
Siponimod (BAF 312)	Selective modulator of S1PR1 and S1PR5	1 or 2 mg daily	Bradyarrhythmic events, liver enzyme elevation, macular edema, lymphopenia	ClinicalTrials.gov NCT01665144
ONO-4641	Selective modulator of S1PR1 and S1PR5	0.05, 0.1, or 0.15 mg daily	Bradyarrhythmic events, liver enzyme elevation, macular edema, lymphopenia	ClinicalTrials.gov NCT01081782
RPC1063	Selective modulator of S1PR1	0.5 or 1 mg daily	Similar to but may be better than other S1P	ClinicalTrials.gov NCT02047734 NCT02294058
Laquinimod	Quinolone-3-carboxamide anti-inflammation and neuroprotection	0.6 mg daily	Liver enzyme elevation, gastrointestinal symptoms, back pain, arthralgia, possible venous thrombosis	NCT01047319 NCT00509145 NCT00605215 NCT01707992

Table 3. Demographics of RCTs for MS

	Trial									
	MSCRG	CHAMPS	AFFIRM	FREEDOMS	TRANSFORMS	DEFINE	CONFIRM	ADVANCE	CARE MS I	CARE MS II
DMT tested	IFN β 1a	IFN β 1a	Natalizumab	Fingolimod	Fingolimod	DMF	DMF	Pegylated IFN β 1a	Anti-CD52	Anti-CD52
Number of participants	301	193	942	1272	1292	1234	1416	1512	581	840
Ethnicity *n* (%)										
Asian	0	0	6 (1)	6 (0.5)	18 (1)	116 (9)	107 (8)	171 (11)	NR	NR
Caucasian	278 (92)	166 (86)	899 (95)	1313 (95)	1216 (94)	969 (79)	1191 (84)	1237 (82)	532 (92)	714 (85)
African American	20 (7)	15 (8)	10 (1)	3(0)	16 (1)	26 (2)	27 (2)	7 (0)	NR	NR
Native American	NR	NR	NR	1(0)	1 (0)			NR	NR	NR
Others	3 (1)	12 (6)	27 (3)	50(4)	39 (3)	123 (10)	92 (6)	97 (6)	49 (8)	126 (15)

development of new treatment options for MS, recent years have witnessed increasing difficulties and obstacles to complete RCTs in a timely and cost-effective manner.

Ethical Issues in Human Research: The Revision of the Declaration of Helsinki

In the Edinburgh (2000) revision of the Declaration of Helsinki[20,21], the World Medical Association (WMA) spells out the ethical guidelines for the use of control groups in human research studies. It clearly defines the WMA position on the use of placebo-controlled trials in situations like DMTs for MS where proven therapeutic agents are widely available in the USA, Canada, the European Union, and others. *Paragraph 29: The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.* In October 2001, the WMA published a note to further clarify its position on the use of placebo-controlled trials. In the note of clarification on *paragraph 29*, the WMA reaffirms its position that extreme care must be taken in making use of a placebo-controlled trial and that such a trial should only be used in the absence of existing proven therapy.

However, after more than a decade since the publication of the Edinburgh (2000) revision of Declaration of Helsinki, it is still rather controversial to completely do away with placebo controls in RCTs that are designed and executed to obtain regulatory approval for the treatment of MS. Placebo orthodoxy insists that there are compelling and scientifically sound methodological reasons to conduct placebo-controlled trials. It is believed that such a disagreement played a role in the initial FDA decision for Lemtrada in December 2013. After more than one year in review, the FDA took the position that Genzyme had not submitted evidence from adequate and well-controlled studies demonstrating that the benefits of Lemtrada outweigh its serious adverse effects. In both the CARE MS 1 and CARE MS 2 phase 3 trials, Lemtrada was studied in comparison with the active comparator Rebif, an FDA-approved DMT for RR-MS (http://www.drugs.com/history/lemtrada.html). Given the striking difference in the positions of active-control orthodoxy and placebo-control orthodoxy, many scholars and organizations have moved their stance towards the "middle ground"[22].

Placebo-controlled trials were the standard design for all pivotal trials of the first-line basic DMTs for MS treatment. In an era of many available DMTs, including first-line basic and second-line escalation therapies, placebo-controlled trials can only be justified ethically in a few scenarios: (1) when the outcomes of placebo therapy do not increase the risk of serious or irreversible harm, as in clinical trials of symptomatic agents; (2) in forms of the disease for which there is no established effective therapy, including PPMS and secondary progressive MS in which relapses are no longer present; and (3) when there is an established effective therapy, placebo-controlled trials of novel agents are ethical in individuals who have not responded to the established therapy[23].

Challenges in RCTs for MS

With the increased number of DMTs and their significantly improved availability to the general population in the USA, Canada, the European Union, and many other countries, we have witnessed increasing challenges in the enrollment of participants into various RCTs for MS therapies. The SURPASS trial was a multicenter, randomized, rater-blind, parallel-group, active-controlled study to evaluate the benefits of switching therapy (glatiramer acetate or interferon-1) to natalizumab in participants with RR-MS. Due to slow enrollment and other issues, the SURPASS trial was terminated prematurely. The elimination of placebo controls, and comparison between the trial agent and an approved therapy, significantly increases (usually by >10×) the number of participants required to achieve statistical difference. Often, the original trial protocols have to be amended and the projected enrollment timelines extended. Due to the difficulties in enrollment, one of the two anti-CD52 antibody treatment groups in the CARE MS II trial was eliminated during the enrollment period[17]. ASSESS is a Novartis trial to compare 2 doses of Fingolimod (0.25 mg and 0.50 mg) to glatiramer acetate (20 mg s.c. daily), and to evaluate the efficacy of 0.25 mg Fingolimod for the treatment of RR-MS. Recently, the enrollment in ASSESS had to be extended due to the sluggish enrollment globally (https://clinicaltrials.gov/ct2/show/NCT01633112?term=fingolimod+0.25mg+RR-MS&rank=1).

Strategies for Effectively Completing RCTs of MS

A few recently-completed RCTs changed the traditional approach in their enrollment strategies. In contrast to limiting participants exclusively to Western countries (Table 3), these RCTs included MS patients from other regions such as Asia. A total of 9%, 10%, and 11% of participants were recruited from Asian populations in the DEFINE, CONFIRM, and ADVANCE trials[4, 14, 24].

Dimethyl fumarate (Tecfidera®) was approved by the US FDA in 2013. Two global pivotal phase 3 trials (CONFIRM and DEFINE) were completed and included sites in India. The DEFINE study (Determination of the Efficacy and Safety of Oral Fumarate in Relapsing-Remitting Multiple Sclerosis) was a 2-year, randomized, double-blind, placebo-controlled study evaluating the efficacy and safety of oral Tecfidera® in 1,234 patients with RR-MS. The patients were randomized into 3 groups: 240 mg Tecfidera® twice a day (*n* = 410), 240 mg Tecfidera® three times a day (*n* = 416), and placebo (*n* = 408). CONFIRM was another phase 3 study of dimethyl fumarate. It was a 2-year, multicenter, randomized, double-blind, placebo-controlled study that included an open-label reference comparator arm, the glatiramer acetate treatment group. Patients with RR-MS were randomized to receive 240 mg Tecfidera® twice daily (*n* = 359), 240 mg Tecfidera® three times daily (*n* = 345), glatiramer acetate (*n* = 350), or placebo (*n* = 363). Both the DEFINE and CONFIRM trials included Asian patients with RR-MS (Table 4). Of note, the total numbers of Asian patients in all treatment groups and placebo groups were higher than those of African American patients, but lower than those of Caucasian patients.

Distinct Features of Multiple Sclerosis in Asian Countries

Despite the discovery of anti-aquaporin-4 antibody in patients with neuromyelitis optica (NMO) and the establishment of NMO as a separate disease entity[25,26], the belief that Asian MS has unique features compared with the conventional MS in western countries continues to be common in MS research and neurology practice. The relatively high prevalence of opticospinal MS (OSMS)[27] (Fig. 1A, B) in Eastern Asian countries such as China and Japan exemplifies the clinical and radiographic differences between conventional MS and Asian MS. The prevalence of MS varies in different parts of Asia. In Eastern Asian countries such as China (including Hong Kong), Singapore, Thailand, Korea, Malaysia, and Japan, epidemiologic studies are limited[28]. Moreover, most of the studies used the 1983 Poser diagnostic criteria for MS and/or were based on hospitalized patients. Historically, it was believed that the prevalence of MS in Eastern Asia was 1–2 cases per 100 000 population. With multiple revisions of the diagnostic criteria, the improved availability of neurologists, and the increased use of MRI in the diagnosis of CNS

Table 4. Demographic data from DEFINE and CONFIRM trials

	Ethnicity *n* (%)						
	Caucasian	Asian	Unknown	Others	African American	Native American	Native Hawaiian
DEFINE							
Placebo	318 (78)	42 (10)	22 (5)	18 (4)	8 (2)	0	0
DMF 240 mg BID	321 (78)	38 (9)	21 (5)	22 (5)	8 (2)	0	0
DMF 240 mg TID	330 (79)	36 (9)	20 (5)	20 (5)	10 (2)	0	0
CONFIRM							
Placebo	305 (84)	28 (8)	11 (3)	10 (3)	9 (2)	0	0
DMF 240 mg BID	304 (85)	28 (8)	11 (3)	14 (4)	2 (<1)	0	0
DMF 240 mg TID	292 (85)	26 (8)	10 (3)	12 (3)	5 (1)	0	0
GA 20 mg daily	290 (83)	25 (7)	11 (3)	13 (4)	11 (3)	0	0
Total	2,160	223	106	109	53	0	0

disorders, Eastern Asia has witnessed a sharp increase of MS cases in the last 2 decades. A 2003 publication documented a higher prevalence of 8.57 cases per 100 000 population in northern Japan[29,30]. The prevalence of MS in Western Asia and the Middle East (including Kuwait, Israel, Turkey, Jordan, and Iraq) is believed to be higher than that in other parts of Asia, while Southern Asian countries such as India, Pakistan, Bangladesh, Sri Lanka, Nepal have a low rate of MS prevalence[31]. Of note, the DEFINE, CONFIRM, and ADVANCE trials were able to recruit a fairly good number of patients in India.

Asian-type *versus* Conventional-type Multiple Sclerosis and Responsiveness to DMTs

It is challenging to conduct RCTs in countries where the disease has a high degree of heterogeneity. It is vital to understand the heterogeneity from various aspects, including clinical phenotype, MRI features, and immunological abnormalities. It is well known that African-Americans tend to have a high frequency of clinical MS relapses and a poor long-term prognosis[32]. Patients with cervical spinal cord lesions tend to have Expanded Disability Status Scale progression and develop disability earlier and faster. A significant percentage of MS patients may harbor genetic variations, and possess distinct pretreatment immunologic profiles that render a given DMT ineffective[33].

The perception of more common or a relatively higher prevalence of OSMS in Asia might be attributable to the lack of epidemiologic data on MS and the disproportionate research efforts undertaken in Eastern Asian countries, Japan and China in particular. Reports from India and the Middle East region show OSMS to be rarer than that in Eastern Asia. Of note, African-Americans have relatively more cases of OSMS than Caucasian Americans. In fact, cases of conventional MS are not uncommon in Asian populations (Fig. 1). A contributing factor might be the under-recognition of OSMS in Caucasian Americans due to the traditional use of classic features of Devic's disease, i.e., recurrent severe attacks of optic neuritis and longitudinally extensive spinal cord lesions (LESCLs). In the absence of severe attacks of optic neuritis, LESCLs, or serum anti-aquaporin-4 antibody, the diagnosis of MS is usually given regardless of the presence and/or burden of demyelinating spinal lesions (Fig. 2).

Over the last 2 decades, significant improvements have been made in the diagnosis and differential diagnosis

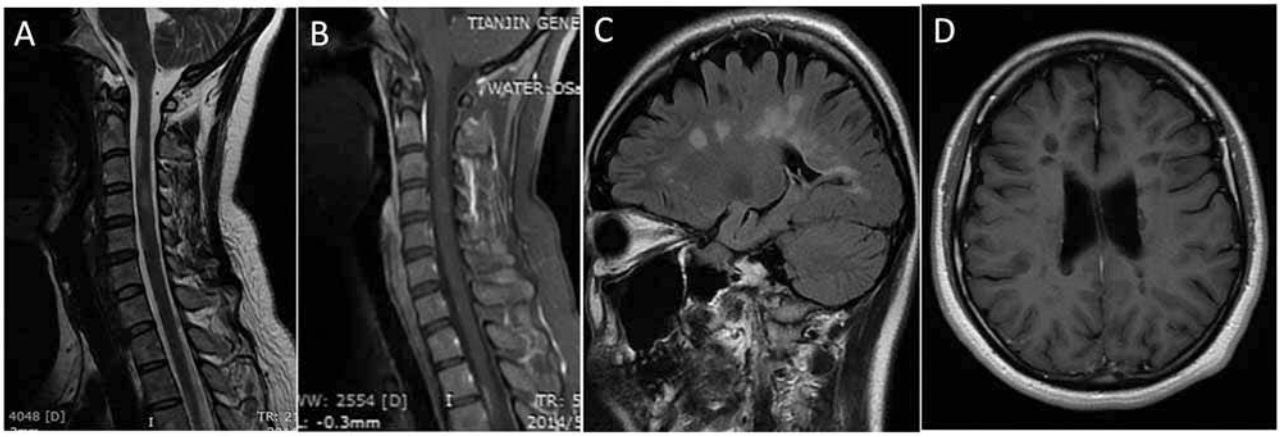

Fig. 1. Opticospinal multiple sclerosis (MS) and conventional MS in an Asian population. A and B. Opticospinal MS in a Chinese female with a history of visual disturbance who presented with weakness in the lower extremities and impaired balance. Serum anti-aquaporin-4 antibody was negative. Visual evoked potentials showed an increased P100 latency on the right side. Brain MRI showed minimal white matter lesions. The cervical spine MRI showed numerous T2 lesions, none of which had the features of longitudinally extensive spinal cord lesions (A), and some of which showed enhancement following administration of gadolinium (B). C and D. Conventional MS in a Chinese female with a remote history of visual decline and pain around her left eye who presented with ataxia and falls. She had conventional Western-type MS with numerous periventricular lesions featuring Dawson's fingers (C) and "block holes" on T1-weighted MRI.

of NMO/NMO spectrum disorder (NMOSD)[34] and MS. The use of advanced MRI technology plays an indispensable role in identifying and localizing LESCLs and optic nerve involvement. The pathological hallmark of MS is sharply-demarcated demyelinating plaques with a certain degree of axonal degeneration. In NMO, both axon and myelin are involved with resultant necrotic cavitation. The discovery of anti-aquaporin-4 antibody in patients with NMO suggests a distinct disease entity fundamentally different from MS. However, a large proportion of patients with OSMS do not have anti-aquaporin-4 antibodies. Recent evidence suggests that auto-antibodies other than those of anti-aquaporin-4 may play an important role in the immunopathogenesis and phenotype of NMO/NMOSD (personal communication from Dr. F-D, Shi, Department of Neurology, Tianjin General Hospital).

After careful exclusion of patients with NMOSD, a cohort of 105 Korean patients with MS were not fundamentally different from MS patients in Western countries[35]. The 2005 and 2010 McDonald MS diagnostic criteria were used in this study. In addition, the following patients were excluded: (1) patients with NMO, as

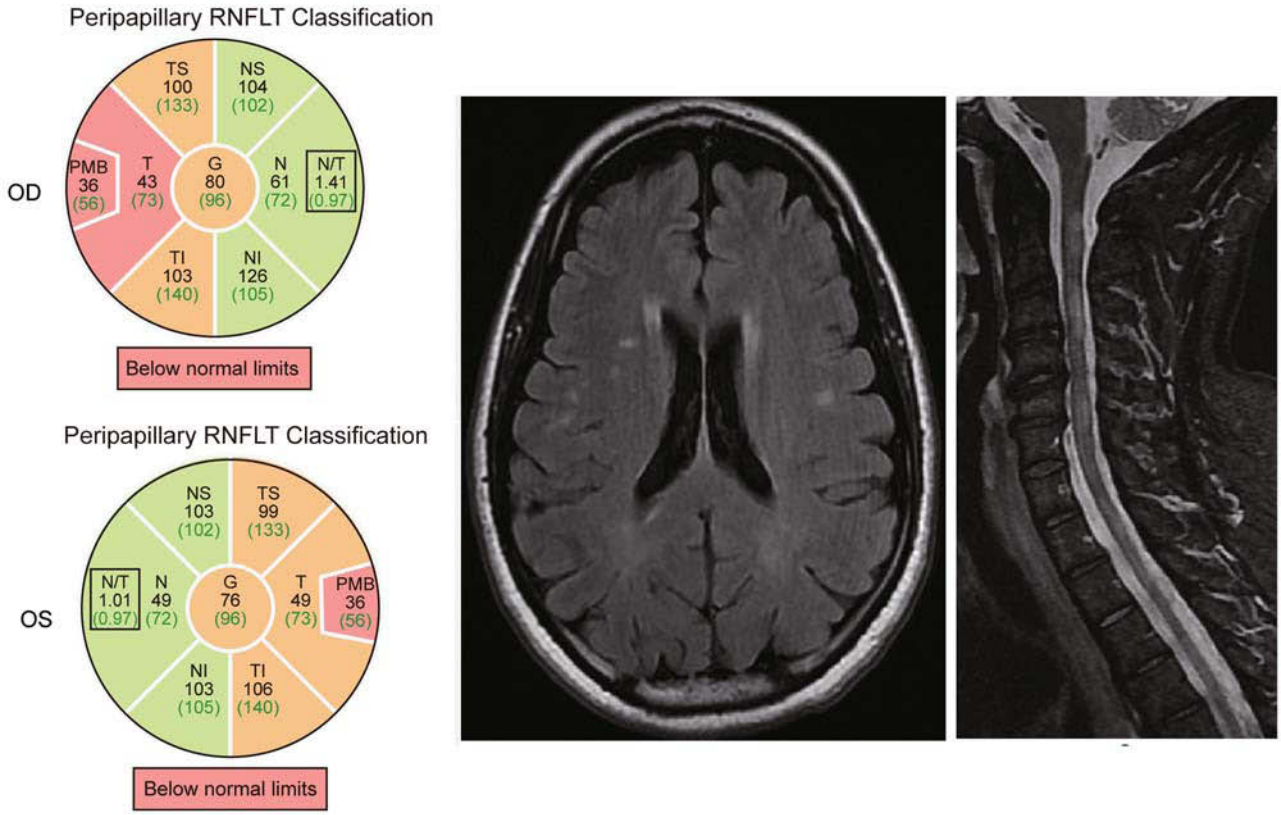

Fig. 2. Predominant opticospinal involvement in a Caucasian woman with multiple sclerosis (MS). A Caucasian female MS patient presented with history of optic neuritis, paresthesia on upper extremities, and weakness in lower extremities. Visual evoked potential showed prolonged P100 latencies (data not shown). Left panel, pie charts depict typical features of thinned retinal nerve fiber layer (RNFL) on the right eye (OD, *Oculus Dexter*) and left eye (OS, *Oculus Sinister*). The global average (G) of the peripapillary circle scan is displayed in the center. The six standard sectors include T (temporal), TS (temporal-superior), TI (temporal-inferior), N (nasal), NS (nasal-superior), NI (nasal-inferior). PMB denotes papillomacular bundle. The black numbers display RNFL thickness for global, each sector and PMB of this woman. The green numbers in parentheses represent the values of normative database from age-matched healthy subjects. The color-coding of the pie chart depicts a specific area of "within normal limits": green; "borderline below normal": orange; and "below normal limits": red. The color-coding bar below each pie chart indicates the overall classification. Middle, brain MRI showed minimal white matter lesions. Right, cervical spine MRI, however, demonstrated a large burden of MS lesions.

diagnosed according to the 2006 revised NMO criteria; (2) patients seropositive for anti-aquaporin-4 antibody; and (3) patients with isolated recurrent events of longitudinally-extensive transverse myelitis and contiguous spinal cord lesions over three vertebral segments without involvement of other lesions. The clinical characteristics, MRI, cerebrospinal fluid findings, disease evolution, and disability progression were similar to those in Western MS patients. Of note, 85% of these patients were treated with IFN-β and their response was comparable to that in Western MS populations. The efficacy of Fingolimod for Japanese MS patients demonstrated comparable results in a recent RCT[36,37]. A *post-hoc* analysis was performed to explore the efficacy of dimethyl fumarate (Tecfidera®) in minority populations including patients of African, Hispanic, and Asian descent. A trend favoring Tecfidera® was reported in all 3 of these populations. However, the variability of the clinical responses and small sample sizes contributed to the statistically non-significant outcome. Further investigations in these groups are warranted.

MS Trials in Asian Countries and the Emerging Market

Treatment options for patients with MS in most Asian countries are limited. For various reasons, including the difference between Asian-type and conventional MS, many countries in Asia such as China and Japan require pharmaceuticals to complete RCTs locally in order to obtain regulatory approval. Few DMTs that are approved by the US FDA and/or European Medicines Agency have gained a market in Asia. Currently, Betaseron® is the only DMT available in the mainland Chinese market. In addition to IFN formulations, Teva Neuroscience and Novartis have recently obtained approval for marketing Copaxone® and Gilenya® in Japan.

As MS remains underdiagnosed in many parts of Asia, and given the lack of epidemiological data, the size of the Asian market for DMTs for the treatment of MS is unknown. However, given its enormous population, the rapid rise of its economic power, improved living standards, access to health insurance, and the advancement of neurological specialty care in Asia[38], the importance of such an emerging market cannot be overestimated. Some leading contract research organizations (e.g. Quintiles and PPD), which provide clinical trials services to various pharmaceutical companies, have already established local headquarters in Asia. They use central laboratories, and perform clinical monitoring and site management. While placebo-controlled trials for the treatment of MS are increasingly difficult to execute in the USA, Canada, and European countries, they remain feasible and it is relatively easy to recruit participants in Asian countries where limited numbers of DMTs have been approved by the local authorities.

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