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Review

Clinical use of dimethyl fumarate in multiple sclerosis treatment: an update to include China, using a modified Delphi method

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Ralf Gold, Michael Barnett, Andrew Chan, Huiyu Feng, Kazuo Fujihara, Gavin Giovannoni, Xavier Montalbán, Fu-Dong Shi, Mar Tintoré, Qun Xue, Chunsheng Yang and Hongyu Zhou

Abstract

Dimethyl fumarate (DMF) is a widely used oral disease-modifying therapy for multiple sclerosis (MS). Its efficacy and safety profiles are supported by over a decade of experience. Differences exist between Asia and Europe/United States in the prevalence and characteristics of MS; most data for DMF are derived from populations outside Asia. DMF was recently (2021) approved for use in China. The objectives of this review were to evaluate the evidence for DMF's profile, to provide an update to healthcare providers on current knowledge surrounding its use and to assess the relevance of existing data to use in China. This study used a modified Delphi method based on the insights of a scientific Steering Committee (SC), with a structured literature review conducted to assess the data of DMF. The literature review covered all papers in English (from 01 January 2011 to 21 February 2022) that include 'dimethyl fumarate' and 'multiple sclerosis', and their MeSH terms, on PubMed, supplemented by EMBASE and Citeline searches. Papers were categorized by topic and assessed for relevance and quality, before being used to formulate statements summarizing the literature on each subject. SC members voted on/revised statements, requiring ⩾80% agreement and ⩽10% disagreement for inclusion. Statements not reaching this level were discussed further until agreement was reached or until there was agreement to remove the statement. A total of 1030 papers were retrieved and used to formulate the statements and evidence summaries considered by the SC members. A total of 45 statements were agreed by the SC members. The findings support the positive efficacy and safety profile of DMF in treating patients with MS. Limited Chinese patient data are an ongoing consideration; however, based on current evidence, the statements are considered applicable to both the global and Chinese populations. DMF is a valuable addition to address unmet MS treatment needs in China.

Registration: Not applicable

Keywords: China, Delphi method, dimethyl fumarate, multiple sclerosis, review

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Correspondence to:
Ralf Gold
Department of Neurology, Ruhr University Bochum, Bochum 44791, Germany.
ralf.gold@rub.de

Michael Barnett
Brain and Mind Centre, University of Sydney and Royal Prince Alfred Hospital, Sydney, NSW, Australia

Andrew Chan
Department of Neurology, Inselspital (Bern University Hospital), University of Bern, Bern, Switzerland

Huiyu Feng
Department of Neurology, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou, China

Kazuo Fujihara
Department of Multiple Sclerosis Therapeutics, Fukushima Medical University School of Medicine, Fukushima, Japan

Gavin Giovannoni
Department of Neurology, Blizard Institute, Barts and the London School of Medicine and Dentistry, Queen Mary University of London, London, United Kingdom

Xavier Montalbán
Mar Tintoré
Neurology Department, Multiple Sclerosis Center of Catalonia (Cemcat), Vall d'Hebron University Hospital, Barcelona, Spain

Introduction

Differences in the incidence, prevalence, presentation and prognosis of multiple sclerosis (MS) have been observed between East Asian populations and the rest of the world.[1–8] For example, the prevalence of MS is estimated as 2.39/100,000 in China, 8.62/100,000 in Southeast Asia, 142.81/100,000 in Europe and 43.95/100,000 globally.[9]

Dimethyl fumarate (DMF) is a fumaric acid ester used to treat MS.[10–13] DMF (Tecfidera®;

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Fu-Dong Shi
Department of Neurology, Institute of Neuroimmunology, Tianjin Medical University General Hospital, Tianjin, China

Qun Xue
Department of Neurology, First Affiliated Hospital of Soochow University, Suzhou, China

Chunsheng Yang
Department of Neurology, Tianjin Medical University General Hospital, Tianjin, China

Hongyu Zhou
Department of Neurology, West China Hospital, Sichuan University, Chengdu, China

Biogen-Idec, Cambridge, MA, USA) was approved for treatment of MS in the United States in March 2013[14,15] and the European Union (EU) in January 2014 (starting with 120 mg oral capsules, administered twice daily for 7 days, followed by a twice daily 240 mg maintenance dose).[10,15] In Asia, DMF was approved in South Korea in July 2016 and in Japan in December 2016.[16,17] DMF has been approved in other Asian locations including, but not limited to, India (February 2015), Hong Kong (March 2016), Singapore (July 2016) and Thailand (March 2020).[18–21] DMF is a widely used oral disease-modifying therapy (DMT) for MS,[22] having been prescribed to approximately 580,500 persons globally in the clinical trial and post-market settings, corresponding to 1,267,327 person-years of exposure through 30 June 2022 (data on file; published 2021 data),[23] and was approved for use in the People's Republic of China in 2021.[3]

Although there are more than 13 years of DMF data, including long-term follow-up from its pivotal clinical trials (DEFINE, CONFIRM) and the long-term extension study (ENDORSE),[24–28] comparatively little of this data has been derived from East Asia.[25] It is therefore relevant to consider whether DMF performs similarly in treating these populations, as elsewhere in the world.

Early treatment of MS with DMT is part of the strategy to improve patient prognosis. It is important to continually assess what is known about different DMTs in the light of additional clinical trials and post-marketing studies and real-world experience, to evolve clinical practice. For example, MS organizations and working groups have demonstrated the value of updating practice through agreed statements on the use of DMTs during COVID-19.[29] With the recent approval of DMF in China, it is an opportune time to review global and Asian DMF practice. Therefore, the objective of this work was to use a modified Delphi method to assess the current use of DMF in clinical practice and identify considerations relevant for its use going forward, in China and other countries, so that these serve as a valuable resource to sharing up-to-date evaluation of evidence supporting good clinical practice for treatment of MS.

Methods

This study used a modified Delphi method (Figure 1) based on the insights of a scientific Steering Committee (SC). First, a structured literature review was performed to identify relevant evidence addressing the question, 'How is DMF used in the treatment of MS?' The literature review considered results from a PubMed search (from 01 January 2011 to 21 February 2022) including the core search terms 'dimethyl fumarate' AND 'multiple sclerosis' and their MeSH terms (search strings are detailed in Supplemental material; literature search strategy in Figure 2). Additional terms were used to categorize results into relevant topics.

The main search was supplemented by additional searches of EMBASE and Citeline. The topics of interest were categorized as: efficacy, safety, mechanism of action, pharmacokinetics/pharmacodynamics (PK/PD), treatment sequencing, adverse event (AE) management, infection, progressive multifocal leukoencephalopathy (PML) risk, effects on haematological parameters, effects on organ systems, drug-drug interactions, pregnancy/lactation, COVID-19 and paediatric populations.

The literature was first screened by title and abstract by editorial support staff from MIMS Limited for relevance and quality. Due to the known level of variation in the formulation of compounded products,[30] only papers using commercially produced DMF were included. Quality was based on the totality of several factors: type of publication (guidelines > systematic reviews > meta-analyses > opinion pieces > case reports), study design (randomized controlled trials (RCTs) > observational or cohort studies > case studies; and direct comparisons were considered superior evidence to indirect comparisons) and study size (more than 500 participants > fewer than 500 participants). Funding sources were also noted. The culmination of these factors was reflected in an overall evidence rating (high, medium high, moderate, medium low and low). Statements were developed based on the evidence and reviewed by SC members along with the supporting evidence and evidence rating.

The SC comprised 14 expert members (neurologists) representing clinical expertise from Germany ($n=1$), United Kingdom ($n=1$), Australia ($n=1$), Spain ($n=2$), Japan ($n=1$), Switzerland ($n=1$) and China ($n=7$). SC members were selected based on their clinical experience with MS, publication record and any previous contributions to

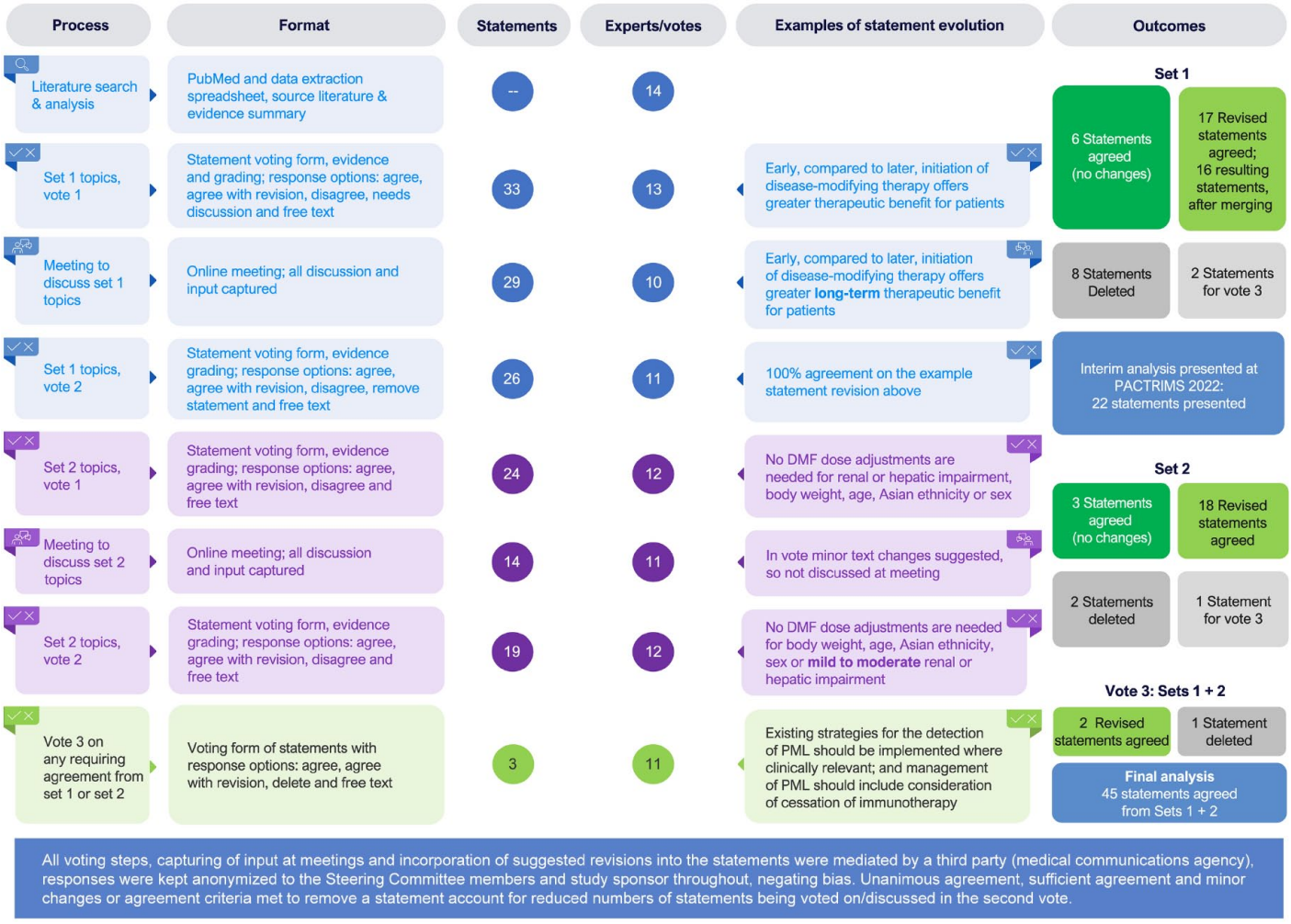

Figure 1. Study flow for this modified Delphi process.
Each topic set underwent voting with thresholds for agreement of ⩾80% and disagreement of ⩽10%. Statements not meeting the criteria were discussed at one of two online SC meetings for revision. For statements with a response exceeding the disagreement threshold, the second round had a voting option for statement deletion.
DMF, dimethyl fumarate; PACTRIMS, Pan-Asian Committee for Treatment and Research in Multiple Sclerosis; PML, progressive multifocal leukoencephalopathy.

MS treatment guidelines. For practicality, topics were split into two sets: Set 1 topics, for Statements 8–24, 29–33 and 40–41, were discussed at the first meeting and Set 2 topics, for Statements 1–7, 25–28, 34–39 and 42–46, were discussed at the second meeting (Figures 1 and 3). Each topic set underwent two or more anonymous voting rounds with thresholds for agreement of ⩾80% and disagreement of ⩽10%. Statements not meeting the criteria were discussed at one of two online SC meetings for revision (Figure 1).

Voting administration, collation of responses, collating meeting minutes and statement revision were conducted by the editorial support team to negate bias. In addition to 'Agree' and 'Disagree', SC members could indicate agreement 'with revision', with suggestions provided as free-text entries, which were collated for discussion with highlighting of the incorporated updates (examples given in Figure 1). Statements discussed during meetings were revised and re-circulated for a second round of voting. For statements with a response exceeding the disagreement threshold, the second round had a voting option for statement deletion. After two voting rounds for each statement set, statements requiring higher levels of agreement were revised and voted on in the same round until agreement was reached on either a revised wording or deletion of the statement.

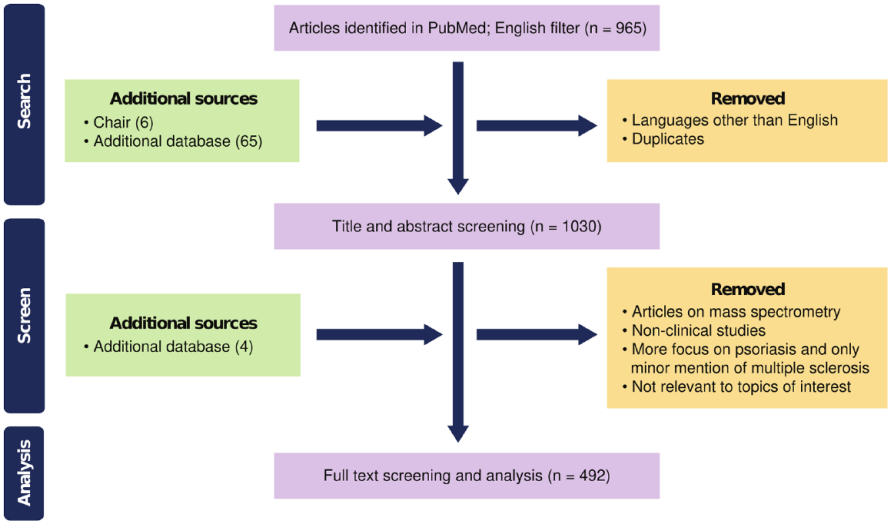

Figure 2. Literature search strategy.

Where the level of disagreement was below the threshold, the statement was included, as such statements reflect majority opinion, although not necessarily unanimity. In situations where practice or evidence differed significantly between regions, statements about global and Chinese or East Asian populations are presented separately.

Results

A total of 965 papers were retrieved with the search terms and a further 70 distinct references (one duplicate was removed) were used to supplement the search from additional sources. The number of participants voting in each round and the levels of agreement attained are summarized in Figures 1 and 3, respectively.

In the first round of voting on Set 1 statements (expressed as per cent responses on total number of votes received on all statements), there was 81% agreement, 13% agreement with revisions, 3% requesting further discussion at the meeting and 3% disagreement. The level of overall agreement increased to 88% by the second vote, with a further 6% agreeing with revisions (4% disagreement and 2% suggested deletions).

For the Set 2 statements, at round 1 there was 70% overall agreement, 17% agreement with revision and 12% disagreement. After the second vote there was 94% overall agreement on the statements, 5% agreement with revision and 1% disagreement.

The most common reason for disagreement in both sets was a perceived lack of supporting evidence. Agreement with revision was typically for the correction of language-related issues such as simplifying wording. In total, 45 statements were finally included (Figure 3).

Mechanism of action

Two statements were proposed on the mechanism of action of DMF. DMF's effects on the immune system are complex and multi-faceted (Figure 3, Statements 1 and 2); DMF influences both B cell and T cell populations and pro-inflammatory cytokine production to reduce inflammatory activity.[31–37] One of the main pathways of activity of DMF is via nuclear factor erythroid 2-related factor 2 (Nrf2), which has anti-oxidative and anti-inflammatory effects.[13,38–42] The anti-oxidative and anti-inflammatory effects of the Nrf2 pathway may contribute to the cytoprotective abilities of DMF.[38,39] DMF may prevent demyelination and axonal loss through reduction in pro-inflammatory reactive astrocytes.[43] Changes in immune cell populations, including a reduction in pro-inflammatory Th17 cells and increase in Th2 naïve/anti-inflammatory cells, induced by DMF produce a net shift away from a pro-inflammatory immune state.[44] Reductions

Category	Agreed statement	Evidence rating	Vote 1 responses	Vote 2 responses	Vote 3 responses
Mechanism	1) DMF is thought to exert its clinical effects in multiple sclerosis via anti-inflammatory and anti-oxidative pathways. The precise mechanism of action of DMF continues to be investigated	+/Medium high	67 33	100	N/A
	2) DMF has potential multifaceted and beneficial effects on central nervous system cells, including modulation of microglia via the Nrf2 pathway	+/Medium high	42 42 17	92 8	N/A
PK/PD and dose adjustments	3) DMF is rapidly metabolized to monomethyl fumarate (MMF), which is CNS and CSF penetrant, and does not accumulate due to a short half life	=/Moderate	83 8 8	N/A, agreed at meeting	N/A
	4) Taking DMF with a meal changes the PK/PD of DMF by delaying T_{max} and reducing C_{max} without changing AUC; these changes do not affect the clinical effectiveness parameters of DMF	+/Medium high	75 17 8	100	N/A
	5) Taking DMF with a meal may lower the likelihood of a patient experiencing flushing or severe gastrointestinal adverse events, potentially by delaying T_{max} and reducing C_{max}	+=/Moderate high	75 17 8	100	N/A
	6) No DMF dose adjustments are needed for body weight, age, Asian ethnicity, sex or mild to moderate renal or hepatic impairment	+/Medium high	83 8 8	100	N/A
Efficacy	7) DMF is an efficacious therapy for relapsing-remitting MS; it reduces relapses, annualized relapse rates, radiological evidence of disease, serum neurofilament light levels, and disability progression	++/High	100	N/A	N/A
	8) Early, compared with later, initiation of disease-modifying therapy offers greater long-term clinical benefit for patients	++/High	92 8	100	N/A
	9) In treatment-naïve patients, serum neurofilament light chain levels (sNFL) may predict response to disease modifying therapies including DMF; DMF reduces levels of sNFL in such patients after initiation	+=/Moderate high	85 8 8	N/A	N/A
Hematology & infection risk	10) DMF treatment is associated with a decline in absolute lymphocyte counts over the first year of treatment, which then typically stabilises; the degree of lymphopenia is not conclusively linked with efficacy	++/High	100	N/A	N/A
	11) The risk of infections in patients with lymphopenia receiving DMF is low in most cases; nonetheless, ongoing monitoring of absolute lymphocyte count remains important	++/High	85 15	82 18	N/A
	12a) Prolonged severe/grade 3 lymphopenia, with absolute lymphocyte counts <500 mm^3 (0.5 x 10^9/L), is rare but a reason for discontinuation, that healthcare providers should be aware of and check for	++/High	85 8 8	91 9	N/A
	12b) Prolonged severe/grade 3 lymphopenia, with absolute lymphocyte counts <500 mm^3 (0.5 x 10^9/L), is rare but a risk factor for progressive multifocal leukoencephalopathy	++/High	77 15 8	91 9	N/A
	13) Factors influencing the risk of progressive multifocal leukoencephalopathy (PML) with DMF include age (≥50 years) and prolonged severe (≥grade 3) lymphopenia; PML may occur without severe prolonged lymphopenia	++/High	85 8 8	100	N/A
	14) Existing strategies for the detection of PML should be implemented where clinically relevant; and management of PML should include consideration of cessation of immunotherapy	EO	92 8	82 18	91 9
	15) Severe opportunistic fungal, bacterial, and viral infections are very rare with DMF, but patients should still be monitored for such infections	+/Medium high	100	100	N/A
	16) Currently, there is no evidence suggesting that treatment with DMF leads to immunoglobulin deficiency	=/Moderate	62 31 8	100	N/A
	17) Latent tuberculosis infection (LTBI) may be more common in China than in patients included in the clinical trials of DMF. However, the risk of reactivation of LTBI in patients treated with DMF appears to be low	=/Moderate	54 15 8 23	73 27	91 9

Agree Agree with revision Request further discussion Disagree

Figure 3. (Continued)

Category	Agreed statement	Evidence rating	Vote 1 responses	Vote 2 responses	Vote 3 responses
Comorbidities, organ function and cancer risk	18) Cardiovascular disease can be comorbid with MS and lifestyle modification should be undertaken; DMF has not been associated with cardiovascular adverse events	+=/Moderate high	92 8	100	N/A
	19) In patients with liver disease, DMF or another disease modifying therapy (DMT) with low hepatic toxicity may be a preferred treatment option	=/0 Moderate low	62 15 15 8	100	N/A
	20) DMF transiently elevates ALT/AST (grade 1) in some patients, but the elevation is seldom persistent or severe (≥grade 3) or causes discontinuation	++/High	100	N/A	N/A
	21) Universal screening for HBV and HCV is needed before initiation of most DMTs for MS; as-needed/periodic or 6-monthly liver monitoring is sufficient to assess risk of liver toxicity while on DMF	+/Medium high	77 15 8	91 9	N/A
	22) DMF has a very low risk of liver injury based on post-marketing data	+=/Moderate high	62 31 8	82 18	N/A
	23) DMF is not associated with higher risk of malignancies or neoplasms, but clinicians should be vigilant for such risk	+/Medium high	100	N/A	N/A
Treatment initiation & decision-making	24) DMF is suitable as a first-line therapy for patients with relapsing/remitting multiple sclerosis or clinically isolated syndrome, due to its good balance of efficacy and safety	+/Medium high	33 50 17	100	N/A
	25) In patients initiating treatment with DMF, the starting dose is normally maintained for 7 days; however, gradual up-titration to the full dose may be recommended for up to 4 weeks to minimize adverse events	+/Medium high	92 8	92 8	N/A
	26) Shared-decision making is important in multiple sclerosis care, goal setting and treatment strategy should be undertaken collaboratively and calibrated by patient desires; sensitivity to adverse events and family planning are especially important	=/Moderate	83 17	92 8	N/A
	27) Best disease control, as evidenced by a proxy like NEDA-3 (no relapses, no new radiological evidence of disease, no disability progression) or above is the current benchmark treatment goal in multiple sclerosis therapy	+/Medium high	83 8 8	83 17	N/A
Treatment sequencing	28) DMF is an effective and well-tolerated therapy in both treatment naïve patients and those switching from other first-line therapies	+=/Moderate high	77 23	100	N/A
	29) DMF discontinuation is most commonly due to adverse events occurring early after initiation; particular attention should be paid to early tolerability of DMF to ensure patient safety and enable persistence	++/High	92 8	100	N/A
	30) Patients should switch DMTs as early as possible if an adequate trial of their current DMT shows a lack of efficacy or an intolerable adverse event profile; clinical judgement should be used regarding the duration for assessing adequacy of DMT treatment, which will differ based on the DMT	+/Medium high	85 15	82 18	N/A
	31) Treatment inertia may delay switching, and latency to initiation of an effective therapy may result in poorer outcomes	+/Medium high	92 8	N/A	N/A
	32) In patients who develop lymphopenia on DMF, consider avoiding switching to other DMTs that may also deplete lymphocytes	+/Medium high	62 8 23 8	91 9	N/A
Adverse event management	33) Patients benefit from counselling and education on the adverse event profile of DMF, especially in the early phase of treatment; these activities set expectations, improve tolerance of adverse events, and promotes persistence and adherence	++/High	92 8	N/A	N/A
	34) Gastrointestinal adverse events may be prevented or mitigated by taking doses with food, gradually up-titrating to the full dose, symptomatic therapies, or temporary dose reduction	++/High	100	100	N/A
	35) Flushing may be prevented or mitigated by taking doses with food or the use of symptomatic therapies such as aspirin or antihistamines	+/Medium high	92 8	N/A	N/A
	36) In patients treated with DMF, hypersensitivity reactions are uncommon, typically present as skin lesions (urticaria), and are responsive to steroids and antihistamines	0/Medium low	75 17 8	92 8	N/A

Agree | Agree with revision | Request further discussion | Disagree

Figure 3. (Continued)

Category	Agreed statement	Evidence rating	Vote 1 responses	Vote 2 responses	Vote 3 responses
DMF and symptomatic treatments	37) DMF has no known drug-drug interactions, and symptomatic non-pharmacological and pharmacological therapies, including corticosteroids, may be used as required in treated patients	+/Medium high	58 33 8	100	N/A
	38) DMF may be safely used alongside aspirin, antihistamines, proton pump inhibitors and similar therapies for symptomatic relief of adverse events and to improve tolerability	+/Medium high	92 8	100	N/A
COVID-19 vaccine strategies	39) The risks of MS relapse and associated disability outweigh the hypothetical risk of more severe COVID-19 due to DMT-related immunosuppression; DMF should not be discontinued due to the risk of contracting COVID-19 alone	+/Medium high	92 8	91 9	N/A
	40) Having MS does not increase the risk of adverse events with vaccines studied to date; DMF does not impair the humoral immune response to COVID-19 vaccination and should be maintained, irrespective of the timing of vaccination	+/Medium high	77 15 8	100	N/A
Pregnancy/ Lactation	41) There is no clear evidence of teratogenicity with DMF from clinical trials or post-marketing data	+=/Moderate high	50 25 25	92 8	N/A
	42) In patients who may become pregnant, DMF use can be considered until a pregnancy is confirmed	=0/Moderate low	33 8 58	83 8 8	N/A
	43) There is insuffi cient data regarding the use of DMF during breastfeeding. The metabolites of DMF are present in small quantities in the breast milk of lactating patients, the benefit of treatment should be weighed against the potential risk to the breast fed infant	00/Low	42 17 42	92 8	N/A
	44) Due to the lack of drug-drug interactions with DMF, hormonal contraception can be used as normal in patients taking DMF	=/Moderate	75 8 17	100	N/A
Pediatrics	45) Limited data from open-label studies in pediatric populations aged ≥13 years suggest that DMF has similar efficacy and safety to adult populations at the same dose	=/Moderate	Statement: source = the meeting	92 8	N/A

Figure 3. Summary of voting responses and guiding statements on clinical use of dimethyl fumarate in treating multiple sclerosis.
Each topic set underwent anonymous voting rounds with thresholds for agreement of ⩾80% and disagreement of ⩽10%. Statements not meeting the criteria were discussed at one of two online SC meetings for revision (Figure 1). For statements with a response exceeding the disagreement threshold, the second round had a voting option for statement deletion.
ALT, alanine transaminase; AST, aspartate aminotransferase; AUC, area under the curve; C_{max}, maximum concentration; CNS, central nervous system; COVID-19, coronavirus disease of 2019; CSF, cerebrospinal fluid; DMF, dimethyl fumarate; DMTs, disease-modifying therapies; EO, expert opinion; HBV, hepatitis B virus; HCV, hepatitis C virus; LTBI, latent tuberculosis infection; MMF, monomethyl fumarate; MS, multiple sclerosis; N/A, not applicable; NEDA-3, no relapses, no new radiological evidence of disease activity, no disability progression; Nrf2, nuclear factor erythroid 2–related factor 2; PK/PD, pharmacokinetic/pharmacodynamic; PML, progressive multifocal leukoencephalopathy; SC, Steering Committee; sNFL, serum neurofilament light chain; T_{max}, time to maximum concentration.

in memory T and B cells similarly reduce overactive immune responses and the resulting neuronal damage in MS.[36,44]

PK/PD and dosing

Upon ingestion, DMF is rapidly metabolized to monomethyl fumarate (MMF), which can cross the blood-brain barrier to exert its effects (Figure 3, Statements 3–6).[39,40,45] MMF does not accumulate in the body, owing to a short terminal half-life of ~1 h.[45] A high-calorie and fat-rich meal delays T_{max} by hours and reduces C_{max} by approximately 40%.[45] However, area under the curve is not affected by taking DMF with a meal, which enables DMF to maintain efficacy, while reducing side effects.[10,45] The impacts of having a meal on T_{max} and C_{max} reduce both gastrointestinal (GI) AEs and flushing, thereby alleviating DMF's most common undesired effects.[46,47] Patients with severe renal or hepatic dysfunction were excluded from the pivotal clinical trials of DMF. However, neither condition is expected to influence the level of exposure to MMF.[10,12]

Situation in China/East Asia. The studies in East Asian patients used the same dose regimen and reported a consistent AE profile for DMF, as the pivotal trials, which largely included Caucasian patients.[16,48–50] No change in dosing is required for this population.

Efficacy statements

Three efficacy statements were included (Figure 3, Statements 7–9). The overall level of evidence for the efficacy of DMF was considered high, albeit with varying ratings for individual parameters. For relapse rate/annualized relapse rates (ARRs), radiological evidence of disease activity and disability progression, the data are derived from several large RCTs, meta-analyses and systematic reviews,[25–28,49,51–53] and have been incorporated into guidelines from all major MS organizations, including in Japan.[16,54–56] The pivotal clinical trials most convincingly demonstrated improvements in relapse rate/ARR with DMF treatment.[25–28] Long-term data support that DMF treatment results in reductions in disability progression, with few overall relapses, but members of the SC considered this to have less strong support than the stated effects on ARR.[57] Radiological evidence of disease activity is perhaps the least well-supported parameter of this set, given more variability in magnetic resonance imaging (MRI) assessment across centres and studies and therefore a lower quality of evidence.[51] Despite the varying level of evidence for different aspects of efficacy, the overall position of the SC is that data exist for improvements on each of these parameters.

The importance of initiating a DMT soon after diagnosis is highlighted in several international guidelines[54,55] and is supported by convincing evidence from both individual trials (including DMF specifically) and reviews.[58–60] The SC noted the strong evidence for this statement and encourages early, appropriate initiation of a DMT.

Serum neurofilament light chains (sNFLs) are a marker of neuroinflammation and are thought to represent a proxy measure for axonal damage in MS.[61] sNFL is reduced by DMTs in MS,[62] and lower baseline sNFL levels in a small ($n=80$) observational trial predicted a greater response to DMF treatment, assessed by achieving no evidence of disease activity (NEDA) and reducing effector immune cells.[61] The study concords with a slightly larger trial ($n=127$) which showed that DMF reduced NFL in the blood and cerebrospinal fluid (CSF) of treatment-naïve patients and could normalize the CSF levels in 73% of participants.[63] As a comparatively new outcome measure with limited use in clinical practice, sNFL relevance for prognosis or disease outcomes requires further research. Nonetheless, DMF has shown some effects on this marker, and it may be a potential proxy measure for treatment response or prognosis.

Situation in China/East Asia. Evidence for efficacy of DMF in the East Asian population comes primarily from Japan, which contributed the majority (80%) of the East Asian population ($n=142$) in the APEX study, followed by South Korea (14%).[48,49] A post hoc sub-analysis of Asian data from Fox *et al.*[2] has also been performed, confirming treatment efficacy and positive benefit-risk balance. In general, treatment results are similar between East Asian and Caucasian/rest-of-the-world populations, although there is lower incidence of MS but potentially poorer prognosis in Asian populations, possibly due to increased frequency of spinal lesions in this population and incomplete resolution of first attacks. There is no predicted difference for Asian populations which would lead to preferring later

treatment initiation, and considering a higher potential first-year relapse rate and poorer prognosis,[2,64] it may be high priority to initiate treatment of Asian patients early in the clinical course. Many patients with MS in China do not initiate a DMT at the earliest opportunity[4] for reasons of cost,[3] perception of the condition as 'mild' and the advice of neurologists and other healthcare professionals.[3,4] The treatment pattern in China continues to evolve, with early diagnosis and sustained use of DMTs during periods of remission becoming more common.[3]

Haematologic parameters and infection risk

Seven statements on haematological parameters and infection risk achieved agreement (Figure 3, Statements 10–17). In general, the risk of lymphopenia with DMF was recognized – but also that this did not translate to a substantial increase in risk of infections. Very rare occurrences of PML warrant clinical vigilance.

Lymphopenia. DMF studies consistently show a ~30% decline in mean absolute lymphocyte count in treated patients, which typically stabilizes within 6–12 months of treatment initiation.[48,65–67] Lymphopenia is a risk factor for (serious) opportunistic infections and associated mortality in the general population.[68,69] For this reason, it is important to monitor lymphocyte counts in patients receiving a therapy which may induce lymphopenia, such as DMF.[70,71] However, the degree of lymphopenia induced by DMF has not been associated with increased incidence of serious infections,[44,65,72] despite some case reports and database review findings of opportunistic infections.[69,73–80] Degree of lymphopenia has also been proposed by some to predict better responses to DMF, as a proxy measure for a less overactive immune response and pro-tolerogenic profile,[44,70,71,81,82] but most of the data have come from relatively small studies. The data are equivocal, as some studies (e.g. Longbrake *et al.*[31]) including larger controlled trials have found no relationship between lymphopenia and therapeutic efficacy of DMF.[31,44,65] It has also been determined that $CD4^+$ and $CD8^+$ T cell counts correlate with absolute lymphocyte counts, suggesting that separate monitoring is not required.[67] After treatment discontinuation, most patients with lymphopenia experience recovery of lymphocyte count; the extent and duration of lymphopenia influence the time required to attain this.[83] In the opinion of the SC, the data are insufficient to conclusively link lymphopenia with therapeutic efficacy, and lymphopenia is not recommended for use as a prognostic factor.

Vaccination response. Potential suppression of the immune system by DMTs is a risk factor not only for infections but also for a blunted response to vaccination, resulting from a reduced humoral and/or cellular response.[29,84,85] The PROCLAIM study assessed immunoglobulin levels in patients initiating DMF and found no impact of DMF on immunoglobulin levels.[44] Similarly, immune response to vaccination was found to be similar between DMF and interferons.[86,87] The SC therefore supports the conclusion that DMF does not interfere with vaccination.

Tuberculosis. Active tuberculosis infections need to be excluded before starting DMF treatment. In the EU/European Economic Area (EEA), tuberculosis has been estimated to occur at approximately 9.6 cases per 100,000 population (2019).[88] In comparison, the rates in China are estimated to be as high as 58 per 100,000 population, with substantially higher rates of latent infection (2019).[89] In general, screening for latent tuberculosis may be considered before initiating DMF;[90–92] however, DMF is not one of the DMTs for which screening is mandatory.[90–93] The risk for reactivation of latent tuberculosis infection appears to be low,[91,93,94] and the decisions regarding testing ultimately lie with the treating physician.

Progressive multifocal leukoencephalopathy. Several DMTs have been associated with PML, caused by reactivation and viral replication of John Cunningham Virus (JCV) in glial cells, which then causes demyelination.[23,95,96] PML is very rare and, in the cases that exist, occurs more commonly in immunocompromised patients.[95] As of 1 September 2022, there have been 12 cases of PML reported in approximately 580,500 patients treated with DMF, a rate of ~1/50,000 patients (0.9/100,000 patient years of DMF exposure)[23,95] (data shown: on file; previous data referenced).[23]

Prolonged Grade 3 lymphopenia is a risk factor for PML and a reason to discontinue DMF therapy.[29,97] Based on reported trial data, it is estimated that around 5–10% of patients treated with DMF will experience Grade 3 lymphopenia, and 2.2% of patients will have prolonged

(⩾6 months) Grade 3 lymphopenia.[65,98] However, only a few cases have been reported of patients experiencing complications from prolonged severe lymphopenia.[65,97,99,100] Age ⩾50 years is another risk factor for PML; however, neither age ⩾50 years nor severe prolonged lymphopenia are absolute identifiers of those at increased risk of PML, with recorded case reports in patients without these characteristics.[95,101–103]

Closer monitoring of patients with a higher risk of PML is recommended. This includes monitoring for lymphopenia[23,29] and regular (every 6–12 months) MRI scans.[16,103] Discontinuing the suspected causative agent is recommended when patients develop PML.[104]

Situation in China/East Asia. The high incidence of latent tuberculosis infection in China[89,105] and infrastructural challenges in the availability of testing pose a practical obstacle to implementing routine screening before initiating DMF. However, as the risk of reactivation is considered very low,[91,93,94] the recommendation for China is that screening for *latent* infections is *not* mandated.

Through the risk stratification process for PML with natalizumab, clinicians in China may be aware of the use of the JCV antibody index. Based on high JCV antibody positivity detected in MS patients from Hong Kong, JCV seropositivity is expected to be high in China.[106] However, JCV seropositivity does not play a role in risk stratification for DMF. For clinical practice in China, it is important to note that JCV index testing is *not* required with DMF; age and lymphopenia are sufficient criteria for determining PML monitoring.[16,29,95] Clinical vigilance for this condition remains very important, despite its rarity.

Comorbidities, organ function and cancer risk

Four statements on comorbidities and organ function were approved, mostly with a focus on cardiovascular and hepatic safety (Figure 3, Statements 18–22). As MS causes progressive disability, patients are encouraged to maintain a healthy lifestyle, including a balanced diet combined with an exercise programme at a tolerable level.[107] Patients with MS are at higher risk of several forms of cardiovascular disease, including myocardial infarction and heart failure.[108] DMF is not associated with cardiovascular AEs such as arrhythmia or hypertension and is unlikely to contribute to cardiovascular morbidity in patients with MS.[109,110]

Drug-induced liver injury is a recognized risk for patients receiving DMTs for MS.[111] Alanine transaminase (ALT)/aspartate aminotransferase (AST) elevations have been reported in major trials of most DMTs, including DMF.[25,26,48,50,112,113] With DMF, persistent or severe ALT/AST derangement or discontinuation due to liver toxicity occurred in <1–2% of clinical trial participants.[28,112] Post-marketing evidence has identified ALT/AST elevation as relatively common; however, outright liver injury/hepatotoxicity has been recorded in very few DMF-treated patients (n = 4–14).[109,112] In light of the low risk of liver toxicity with DMF, periodic laboratory testing (up to regular 6-monthly testing) is sufficient to monitor for liver toxicity.[29,112] To date, the number of reported cases of hepatotoxicity with DMF is limited to 14, plus one case of acute hepatitis E virus infection.[112,114,115] Of those 14 cases, the earliest elevations of ALT/AST were recorded shortly after treatment initiation; liver injury was mild (six patients) or moderate/severe (eight patients) and there were no cases of liver failure.[115]

In patients with liver disease, DMF may be used with caution, at its normal dosage, as it is metabolized independently of the cytochrome P450 system.[112] Any risk of exacerbation or reactivation of hepatitis B virus (HBV)/hepatitis C virus (HCV) infection is mitigated in part by screening for these infections before initiation of most DMTs.[112]

Situation in China/East Asia. HBV and HCV are more common in China than in the EU,[116] meaning that the requirement to screen for these viruses may yield positive results more frequently. With positive results, antiviral therapy and adjustments to the initiation of DMT should be considered; specialist assistance from hepatology or infectious disease colleagues is required to determine the appropriate course of action.[112]

Cancer risk. A single statement was proposed for cancer risk (Figure 3, Statement 23). An increased risk of malignancy in patients with MS has been investigated repeatedly, including in those with long-term use of DMTs.[117] Overall, the malignancy rate in patients treated with DMF is similar

to age- and sex-matched individuals without MS.[118] Duration of DMF treatment was concluded as a risk protective factor against neoplasms, in a small Spanish study.[119] Recent database analyses have produced conflicting results, with one finding no evidence of an increased cancer risk[120] and the other being the first publication to find an increased risk of neoplasm with DMF.[121] Consequently, it may be prudent to be vigilant in checking for cancer in DMF-treated patients, but this does not yet support a malignancy rate higher than the general population.[118]

Treatment initiation and decision-making

Location and licencing determine the permitted indications for DMF. If permitted by the local label, DMF can be used in both patients with relapsing-remitting multiple sclerosis (RRMS) and patients with clinically isolated syndrome (CIS).[12] The efficacy and tolerability of DMF are well balanced, and it is suitable as an initial therapy.[27,28,122–132] The SC proposed four statements on this topic (Figure 3, Statements 24–27).

Early-in-treatment challenges with tolerability are the largest reason for the discontinuation of DMF.[133,134] To mitigate the risk of AEs, a more gradual up-titration to the target dose may be considered for up to 4 weeks.[10,135–137] It is important to note that the full dose is required for efficacy. Positive relationships between healthcare providers and patients are an important part of goal setting, partly through enhancing adherence. Self-management by patients may be improved by participation in a shared decision-making process.[138] Treatment selection will partly depend on the goals of the patient.[138–141] These aspects of positive patient relationships may help to enhance tolerability when starting a new therapy. As treatments for MS have advanced, the achievable treatment goals/targets have evolved. NEDA-3 (no relapses, no new radiological evidence of disease activity, no disability progression) is the current benchmark proxy for best disease control.[142–145] It may be beneficial to explain this as a target to patients as part of the goal-setting process.

Treatment switching

Five treatment switching statements were approved (Figure 3, Statements 28–32). Evidence for the profile of DMF was initially established in comparison with both placebo and glatiramer acetate in the DEFINE, CONFIRM and ENDORSE trials.[25–28,113] ENDORSE re-randomized patients previously treated with glatiramer acetate to DMF, with similar efficacy and tolerability results to those reported in treatment-naïve patients.[28] Outside pivotal clinical trials, these findings are further supported by observational studies of patients switching from other first-line therapies to DMF.[122,124,132,146–151] Based on these results, horizontal switching, especially from injectable therapies, is a viable use of DMF.

Early (*versus* later) initiation of an effective DMT is linked to better long-term outcomes for patients with MS (see efficacy statements, Figure 3, Statements 7–9), exemplified by achieving NEDA-3 with DMF.[49,54,55,58,151] Treatment inertia may delay switching, and latency to initiation of an effective therapy may result in poorer outcomes, meaning that in addition to initiating DMTs early, switches should be considered if a therapy has proved intolerable or has shown a lack of efficacy in the judgement of the treatment team.[29,142]

When switching to a new therapy it is important to consider its characteristics, to properly prepare the patient for the switch.[56] The most common AEs of DMF treatment are GI symptoms and flushing.[26,46,152] Discontinuation of DMF is more commonly attributable to tolerability issues (68% of discontinuing patients cited this as the main reason for discontinuation) than to a lack of efficacy (15% of patients).[134,153] However, a study of 886 patients in Spain reported similar rates of DMF discontinuation as a consequence of AEs and lack of efficacy (13.2% and 13.5% of patients, respectively).[133,150] Side effects resulting in discontinuation most commonly occur early in treatment,[153,154] suggesting that particular attention can be paid to mitigating AEs and promoting tolerability in the early period of treatment. Rarely, discontinuation may be due to lymphopenia. As a general principle, if a therapy is discontinued for a particular AE, switching to a therapy with a similar AE profile may not be the most appropriate choice. With DMF, limited evidence from a small observational study has suggested that lymphocyte counts may not recover in patients who discontinued therapy and switched to other lymphodepleting agents, because of lymphopenia.[155] Out of caution, such switches should be avoided if possible. A United States study reports that most patients who

discontinued DMF with lymphopenia experienced lymphocyte count reconstitution.[83]

Situation in China/East Asia. In China, as many as 58% of patients do not initiate DMTs upon their diagnosis of MS.[3] The reasons include cost, a historical lack of available DMTs and low patient acceptance of therapy for what they may erroneously perceive as a 'mild' condition.[4] Many patients will therefore be initiating DMF treatment while DMT-naïve. There are no contraindications to initiating therapy with DMF based on prior steroid or other therapies,[10,12] but the timing of initiation may depend on satisfactory condition of the patient, as judged by the neurologist, for example without lymphopenia from corticosteroid or azathioprine use.

Adverse event management and tolerability

As with treatment initiation, important considerations for AE management and tolerability are counselling, shared decision-making and mitigation strategies (Figure 3, Statements 33–36). Forward planning, counselling and expectation setting all assist adherence with DMF by improving tolerability.[46,136,137,156,157] Involving patients in goal setting and integrating their preferences into therapy management is beneficial for initiating DMTs in MS.[136,156]

Mitigation of AEs primarily involves either GI symptoms or flushing.[46] Symptomatic therapies for GI AEs include proton pump inhibitors, antihistamines and assorted other agents for nausea such as metoclopramide, domperidone, diphenhydramine and dimenhydrinate.[46,135] Gradual up-titration (over 4 weeks) or temporary reductions in dose when an AE is encountered help to mitigate the risk of discontinuation.[136,137] The goal is still to achieve the full dose, consistently, as it is required for efficacy.[46] Taking DMF with food continues to be recommended to mitigate GI AEs.[136,157,158]

For flushing, aspirin (75–325 mg) daily, or every second day, can be used typically as pretreatment 30 min before DMF.[11,46,136,159,160] Antihistamines are only rarely required but can also be used.[136,137] Metoprolol, acetaminophen, ibuprofen, cosmetics and counselling have been used for flushing by at least one respondent in a consensus statement.[46]

There have been few reports of hypersensitivity in the literature, despite large numbers of patients treated with DMF.[161–165] Where they have occurred, management has shown a response to steroid and antihistamine treatment.

Concomitant therapies

Two statements summarize DMF use with symptomatic treatment (Figure 3, Statements 37 and 38). Corticosteroids are commonly used in the treatment of acute relapses in patients with MS.[16,54,145] While DMTs aim to avoid relapses, if they occur it is important that the DMT does not prevent acute or symptomatic therapy from being undertaken. DMF has no known drug-drug interactions,[10–12,166] including with single doses of interferon beta-1a (IFN-b1a) and glatiramer acetate, or aspirin. The former characteristic facilitates switching, whereas the latter facilitates symptomatic mitigation of flushing symptoms.[46] GI adverse effects and flushing are the most common side effects with DMF.[46] Symptomatic therapies such as antihistamines (flushing), proton pump inhibitors (GI) and aspirin (flushing), among others, can be used to mitigate these AEs and improve tolerability.[46,137,152] Aspirin mitigates flushing without increasing GI AEs.[159]

In total, the lack of drug-drug interactions means that AEs and relapses may both be managed without concern for the patient's DMF use.

COVID-19 and vaccinations

The use of DMTs during the COVID-19 pandemic has been an important and vibrant topic of clinical consideration. The SC considered two statements on this topic and was aligned with recommendations from numerous societies worldwide (Figure 3, Statements 39 and 40). First, patients treated with DMF have not shown an increased risk of severe COVID-19 infection.[167] It is recommended that DMT selection should continue to be based on the activity and severity of the MS[29] and that the risks from MS outweigh those of COVID-19 in most cases.[85,168,169] Patients with MS may experience a diminished response to vaccines, depending on the DMT which they are receiving and its mechanism of action.[29,87,170,171] The patient response to vaccination, including for COVID-19, has been found to be intact during treatment with DMF, and the

AE profiles of the influenza and COVID-19 vaccines have not been shown to be influenced by DMF.[29,87,172,173] DMF does not interact with vaccines for COVID-19 and patients taking DMF should continue therapy, independent of vaccination timing.[29,167] Data attained with influenza vaccination suggest that vaccine use does not increase the risk of subclinical disease activity in DMF-treated patients.[87]

Pregnancy/lactation

Overall, the lack of accumulation of DMF/MMF makes it suitable for use in *proximity* to pregnancy, although it should still be discontinued during pregnancy (Figure 3, Statements 41–44).

DMF has shown some developmental toxicity at clinically relevant doses in animal studies but not in human populations.[174–180] In the United States, DMF is pregnancy category C, meaning it should be discontinued when a patient wants to become pregnant.[10–12,55,175] In humans, there is no evidence of reduced fertility or increased risk of congenital malformation or miscarriage rates with inadvertent exposure to DMF in pregnant patients within the first trimester.[174–180] Clinical evidence is limited, meaning that the characteristics of DMF's formulation contribute to its recommended use. Namely, DMF does not accumulate, so no washout period is required before patients who have been treated with DMF wish to attempt pregnancy.[181]

There are very few published works considering the issue of DMF during breastfeeding. Any potential use of DMF during breastfeeding will need to balance the benefits and potential risks.[10–12,182] The primary active metabolite of DMF (MMF) has been detected in small quantities in breast milk in a small case study of two lactating patients.[183] The authors concluded the risk to the infant was likely to be low, considering the low concentration levels, but there is too little evidence to be confident in this regard.[183]

Aside from pregnancy and breastfeeding, avoiding pregnancy via contraception may be influenced by DMT choice. Norgestimate/ethinyl estradiol oral contraceptives have been studied in a small RCT in combination with DMF, without impact on the efficacy or tolerability of either class of agent.[166] These study findings accord with the DMF prescribing information, which indicates no drug-drug interactions.[10–12] A United Kingdom consensus on MS and pregnancy also advises that DMF does not reduce the effectiveness of hormonal contraception.[179]

Situation in China/East Asia. The DMF prescribing information in China notes that there are no adequate data on developmental risk in pregnant women.[10] The evidence above suggests that therapy should not be continued during pregnancy and that discontinuation of DMF can occur close to pregnancy confirmation and does not need to be stopped (washed out) for a long period in advance of attempts to become pregnant.[181] For breastfeeding, the Chinese label agrees that the risks and benefits of treatment on the mother and the breastfed infant should be considered when making treatment decisions. Family planning and fertility are very important considerations for female MS patients in China, but no differences in practice with DMF are likely based on the generated data.

Paediatrics

DMF has only limited data in paediatric populations, with trial data generated only from the FOCUS and CONNECTED studies of ~20 paediatric patients. In these trials, DMF performed similarly as in adult populations in terms of both efficacy and tolerability (Figure 3, Statement 45).[184,185] In the FOCUS trial, AEs that were common with DMF in paediatric patients included headache ($n=4$, 18%), dysmenorrhea ($n=2$, 9%), GI disorders ($n=12$, 55%) and respiratory, thoracic and mediastinal symptoms such as cough ($n=3$, 14%) and upper respiratory tract infection ($n=2$, 9%).[184] Data from a limited number of case reports, cohort studies and retrospective observational studies support the similarity of DMF performance in paediatric and adult populations (Figure 3, Statement 45).[186–189] The CONNECT study, a phase III open-label randomized clinical trial of DMF ($n=78$) against IFN-b1a ($n=72$), has recently shown that DMF was well tolerated, with favourable MRI and adjusted ARR for DMF-treated paediatric patients;[190] noting it was published after this article's evidence review and it will be considered more completely in future work.

Discussion

More than half a million patients have been treated with DMF since its launch in 2013 (data

on file).[23] The statements agreed in this article were generated by reviewing over a decade of literature on DMF, spanning the original pivotal clinical trials through to the most recent post-marketing data. The data for DMF have remained largely consistent over time.[26] In terms of safety, no new signals have emerged since existing reviews. A small number of PML cases have accumulated, but the condition remains very rare (data on file).[95] The expert opinion of the SC, therefore, supports the positive efficacy and safety profile of DMF as a first-line and switch therapy agent in patients with RRMS and, if permitted by the local label, CIS.

The most recent estimates of MS prevalence in China are 2.39 per 100,000, meaning a potential MS population within the country of more than 34,000.[3] This represents a large new population of patients who could potentially be exposed to and/or benefit from DMF.

Despite over a decade of experience with DMF, data from ethnically Chinese populations comprise a small fraction of the existing data,[3] which presents challenges for understanding how DMF will be used in practice in this country.[48] Post-marketing data from within China will be valuable for further understanding the characteristics of DMF in this population. Important differences within China may include the background prevalence of relevant diseases such as hepatitis and tuberculosis,[89,116] differences in the MS treatment armamentarium available, prevailing practices on patient acceptance of DMTs and healthcare professional attitudes towards MS management and its relative importance as a rare disease.[3] Monitoring infrastructure for serial (follow-up) neuroimaging and/or serology for hepatitis and tuberculosis may also be impacted by regional differences in availability and implementation priority.

The possibility of drug interactions with as-yet-unidentified Chinese medicine products cannot be categorically excluded, and the real-world use patterns of DMF along with the Chinese diet and cultural practices regarding traditional medicine will be a source of new data following its increased use in the country. Nonetheless, with the evidence generated to date, it is anticipated that DMF will behave similarly in the Chinese population as with the rest-of-the-world population. This is consistent with the confidence of the Chinese regulatory agencies in approving DMF for use in MS treatment,[10] based on similar predictions of maintained safety and efficacy in the population.

Obstacles to rational uptake in China will be confusion regarding the monitoring and testing requirements; for example, about whether JCV and latent tuberculosis testing need to be conducted. It should be made clear that neither JCV nor latent tuberculosis testing needs to be performed. Despite this, it is important that clinicians remain vigilant for PML risk alongside any other AEs.

The panel considered additional statements on the role of the gut microbiome in the aetiology of MS and potential influence on DMF efficacy but found insufficient evidence to proceed. This will be a topic of interest in the future as more evidence accumulates.[191–193] Similarly, data from paediatric populations and in patients who are pursuing pregnancy or who are breastfeeding are also sparse; it is hoped that more data will be generated in these groups.

Thus, the limitations of the study include the sparsity of data in Asian patients as well as the level and quality of evidence in some areas, making it difficult to make conclusive recommendations on those topics. As more patients in China are treated with DMF and more experience is gathered, a repeated analysis and update of the information presented here should be conducted.

This project revealed a consistency of data suggesting DMF remains a valuable part of the MS treatment armamentarium. This evidence summary hopes to clarify all relevant aspects for more effective use in China.

Conclusion

A decade of experience with DMF continues to support its positive efficacy and safety profile in treating patients with MS. Although there is a paucity of high-quality evidence from China itself, the limited data that exist from East Asian populations support a similar profile and suggest that DMF will be a valuable addition to the MS therapeutic armamentarium and will help address unmet treatment needs in China. This review of the most recent and extensive previous literature to form conclusive summary statements is aimed to provide a relevant overview to all clinicians treating patients with MS, with the aims of optimizing care and patient outcomes.

Declarations

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Not applicable.

Consent for publication
Not applicable.

Author contributions
Ralf Gold: Conceptualization; Formal analysis; Supervision; Writing – review & editing.

Michael Barnett: Conceptualization; Formal analysis; Writing – review & editing.

Andrew Chan: Conceptualization; Formal analysis; Writing – review & editing.

Huiyu Feng: Conceptualization; Formal analysis; Writing – review & editing.

Kazuo Fujihara: Conceptualization; Formal analysis; Writing – review & editing.

Gavin Giovannoni: Conceptualization; Formal analysis; Writing – review & editing.

Xavier Montalbán: Conceptualization; Formal analysis; Writing – review & editing.

Fu-Dong Shi: Conceptualization; Formal analysis; Writing – review & editing.

Mar Tintoré: Conceptualization; Formal analysis; Writing – review & editing.

Qun Xue: Conceptualization; Formal analysis; Writing – review & editing.

Chunsheng Yang: Conceptualization; Formal analysis; Writing – review & editing.

Hongyu Zhou: Conceptualization; Formal analysis; Writing – review & editing.

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ORCID iD

Gavin Giovannoni https://orcid.org/0000-0001-9995-1700

Supplemental material

Supplemental material for this article is available online.

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