

Treatment of older patients with multiple sclerosis: Results of an International Delphi Survey

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Abstract

Background: People over age 50–55 have historically been excluded from randomized clinical trials for multiple sclerosis (MS). However, more than half of those living with an MS diagnosis are over 55.

Objective: Explore the unique considerations of treating older people with MS (PwMS) using an iterative and structured Delphi-based assessment to gather expert opinions.

Methods: Eight MS neurologists with an interest in older PwMS developed a 2-round survey. Survey respondents were qualified neurologists with ≥ 3 years' experience, personally responsible for treatment decisions, and treating ≥ 20 patients per month, of whom $\geq 10\%$ were ≥ 50 years old. Consensus was defined as $\geq 75\%$ agreement on questions with categorical responses or as a mean score ≥ 4 on questions with numerical responses.

Results: In Survey 1, 224 neurologists responded; 180 of these completed Survey 2. Limited consensus was reached with varying levels of agreement on several topics including identification and assessment of older patients; factors relating to treatment decisions including immunosenescence and comorbidities; considerations for high-efficacy treatments; de-escalation or discontinuation of treatment; effects of COVID-19; and unmet needs for treating this population.

Conclusion: The results of this Delphi process highlight the need for targeted studies to create guidance for the care of older PwMS.

Keywords: Multiple sclerosis, consensus, standards, Delphi technique, older patients, treatment recommendations

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Introduction

Multiple sclerosis (MS) affects at least 2.8 million people worldwide.¹ While most diagnoses of MS are made in young adults between 20 and 40 years of age,² more than half of people living with an MS diagnosis are over 55.³ An increased prevalence of MS in older people may be primarily attributed to the increased life expectancy of people with MS (PwMS) with advances in MS care and treatment; however, the incidence of late-onset MS has also increased.⁴

Care of older PwMS entails the simultaneous management of the MS disease course as well as challenges associated with normal aging, such as the presence of age-related comorbid conditions including brain and cardiovascular diseases, malignancies,

brain reserve and cognitive decline, and reduced remyelination capacity. Comorbidities in general have also been shown to be associated with a risk of relapse and disease progression.^{5–7} Disease presentation also transitions over time, as focal inflammation events characteristic of relapsing MS decrease and compartmentalized chronic inflammation characteristic of progressive disease phenotypes emerges.⁸

The correlation between advanced age and increased immunosenescence presents additional challenges to the care of older PwMS. Immunosenescence has been linked to increased risk of infection,⁹ as well as to diminished vaccine responses in older versus younger individuals.^{10,11} In PwMS, immunosenescence associated with aging may act synergistically

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with anti-inflammatory DMTs to further dampen immune system activity, resulting in an increased risk of infections, tumors, and other immune-mediated disorders compared with healthy individuals.^{12,13} On the other hand, immunosenescence has also been proposed as a mechanistic explanation for the lack of efficacy of anti-inflammatory DMTs in PwMS with progressive forms of MS.¹²

With few exceptions, PwMS older than 50 or 55 have been, and continue to be, excluded from randomized clinical trials for DMTs to treat relapsing and progressive forms of MS.^{14,15} Observational studies with subgroups of “older patients” help fill the information gap left by the exclusion of older patients from randomized trials. However, the definition of “older” varies across these real-world studies.^{16–18} The resulting lack of detailed information on the effects of comorbidities, immunosenescence, disease progression, and disease phenotype on the efficacy and safety of DMTs for MS in this population complicates treatment decisions.¹⁹

In the absence of clinical data, Delphi-based assessments can provide important information by gathering and assessing expert opinion using iterative and structured processes.²⁰ Successive survey rounds build on the findings from previous rounds to gain a deeper understanding of the topic and/or to reach consensus agreement. Delphi processes add structure to the methodology, help remove bias, and can improve the reliability of the study results. The findings of Delphi-based studies can serve as the basis for further research, inform best practices, and aid the development of treatment guidelines.

The purpose of this international Delphi analysis was to identify unique considerations for the care and treatment of older PwMS, find consensus of how MS practitioners are managing this patient population, and thereby providing real-world clinical perspectives in MS care. Topics included the impact of age and age-related comorbidities on MS treatment, usage and avoidance of DMTs, the impact of coronavirus disease 2019 (COVID-19) on treatment decisions, and unmet needs for treating older PwMS.

Methods

Delphi steering committee, survey development, and respondents

The Delphi steering committee consisted of eight neurologists with expertise in MS treatment and an interest in older PwMS. Survey 1 was developed by the

steering committee and consisted of 25 questions based on identified key considerations for the treatment of older PwMS (Supplemental File 1). Survey respondents were MS neurologists with ≥ 3 years since qualification, were personally responsible for treatment decisions, and treated ≥ 20 patients per month, of whom $\geq 10\%$ were aged ≥ 50 years. Based on the assessment of Survey 1 results, the steering committee developed a 27-question follow-up Survey 2 (Supplemental File 2). Respondents who completed Survey 1 were asked to complete Survey 2.

The objective of this Delphi survey was to find consensus from MS specialists on their treatment strategies and considerations for effective management of older PwMS. An exploratory objective was to note any detectable regional differences in clinical practice approaches in managing patients with MS.

Ethics statement

This study was conducted in accordance with relevant market research and data protection privacy guidelines.

Statistical analysis

Survey responses were anonymized and summarized using descriptive statistics. Consensus was defined as $\geq 75\%$ agreement on questions with categorical responses. For questions using a 5-point Likert scale, consensus was defined as reaching a mean score of ≥ 4.0 . Results of ranked choice survey questions are reported without consensus defined. Region-specific comparisons were assessed using a 2-tailed Z-test, with significant differences defined as $p < 0.05$.

Results

Respondents

Between October and November 2021, Survey 1 was anonymously completed by 224 qualified MS neurologists from nine countries (Argentina, Chile, Colombia, Czech Republic, Germany, Italy, Spain, UK, and US). During May 2022, Survey 2 was completed by 180 respondents, 178 of whom had completed Survey 1; two neurologists did not complete Survey 1. Characteristics of the respondents are shown in Table 1. Nearly two-thirds were European with about 14 years as a practicing MS neurologist. At the time of the surveys, respondents on average treated 75 PwMS per month. Approximately 40% of respondents indicated that between 31% and 50% of their patients were ≥ 50 years old; over 50% indicated that between 11% and 30% of their patients were ≥ 50 years old.

Age as a determinant of clinical management

In comparing older and younger PwMS, 76% of respondents agree or strongly agree (mean score of 3.9) that “Older individuals have MS management that is different from those of younger individuals (eg, monitoring, treatment, comorbidities)”. However, there was no clear agreement on what age is considered “older” (Supplementary Figure S1A) or on the age at which the patient management approach is typically impacted (Supplementary Figure S1B). There was consensus agreement that the impact of comorbidities was

greater for older than for younger PwMS (87%), and the majority of respondents agreed that older PwMS need more frequent monitoring (52%), have greater disability progression (51%), have lower MS disease activity (56%), and have fewer DMT options (51%) than younger PwMS (Figure 1).

Consensus was reached that patient age was useful in establishing immunosenescence (81%) (Supplementary Figure S2A), although fewer than 30% thought that age alone was sufficient. Respondents also did not agree on the age at which treatment decisions are impacted by immunosenescence, but 68% of respondents consider immunosenescence to usually be an impact by the time a patient is 60 years old (Supplementary Figure S2B).

Table 1. Characteristics of respondents who completed Survey 1 and Survey 2.

Characteristic	Survey 1 (n = 224)	Survey 2 (n = 180)
Years as qualified MS neurologist, mean	14	14
Practice setting, %		
Hospital	46	45
University/ academic center	28	28
Group practice or clinic	20	20
Individual practice or clinic	6	8
Managed care	0	0
Patients treated per month, mean	75	76
Proportion of patients ≥50 years of age, %		
≤10% of patients	0	0
11%–30% of patients	53	54
31%–50% of patients	39	40
>50% of patients	8	6
Percentage of time spent per month, mean		
Patient care	84	85
Academics/research	8	8
Administrative/other	8	8
Geographic region, %		
Europe ^a	60	59
South America ^b	21	21
US	19	20
MS: multiple sclerosis.		
^a Includes Czech Republic, Germany, Italy, Spain, and United Kingdom.		
^b Includes Argentina, Chile, and Colombia.		

Although a specific consensus statement was not reached, a majority of respondents indicated that they assessed cognitive (71%) and visual (69%) function in older PwMS at least annually (Supplementary Figure S3), and neuropsychologists and ophthalmologists were among the most commonly consulted specialists for management of older PwMS (43% and 35% of respondents, respectively).

Factors affecting treatment decisions for older PwMS

Based on the mean rankings of factors related to treatment decisions for older PwMS, where 1 was the most important and 15 was the least important, respondents indicated that the most important factor related to treatment decisions was disease activity (mean ranking 3.5 and first choice of 36% of respondents), followed by current patient age (mean ranking 5.2) and comorbidities (mean ranking 5.5) (Figure 2; Supplementary Figure S4). Caregiver support and the route of DMT administration (mean ranking of 12.5 and 10.8, respectively) were considered the least important factors.

Respondents were asked several questions about strategies for the use of high-efficacy DMTs. Which DMTs were considered high efficacy was left to individual respondents because no explicit list or definition was provided. A majority (63%) of survey respondents indicated that they considered high-efficacy DMTs as a first-line option in newly diagnosed older PwMS. The most commonly cited reasons for choosing a high-efficacy DMT over a more traditional DMT as the first-line therapy were high disease activity (66%) and progressive MS (57%) (Figure 3). De-escalation from a high-efficacy to a moderate- or low-efficacy DMT has emerged as a strategy to balance benefits and risks in older PwMS who are being treated with high-efficacy DMTs.^{21,22} Respondents indicated, however, that fewer than half

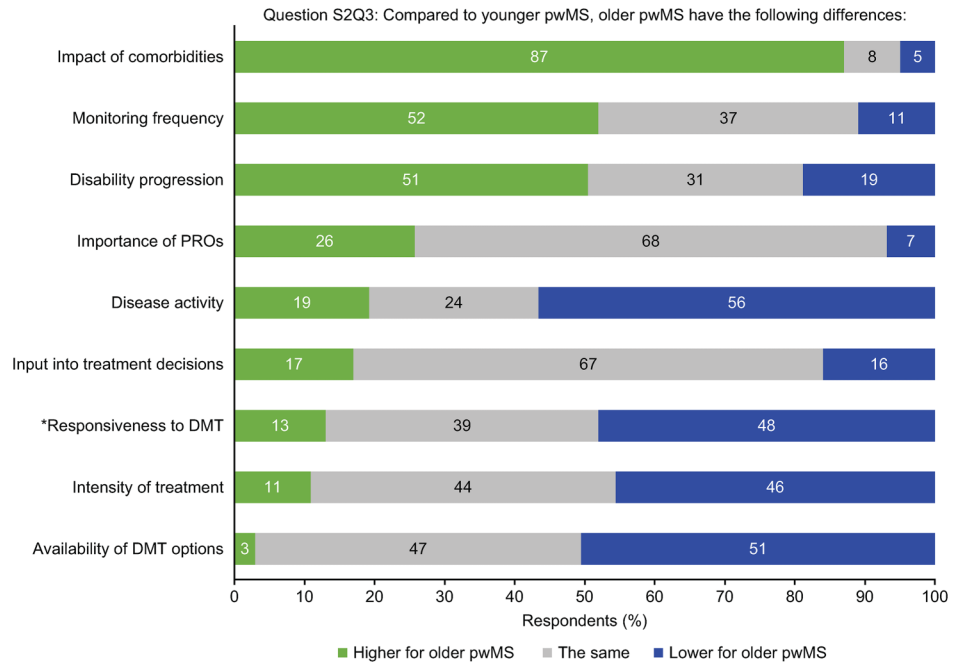


Figure 1. Differences between older and younger PwMS. DMT: disease-modifying therapy; PRO: patient-reported outcome; PwMS: people with multiple sclerosis; S2Q3: Survey 2, question 3. The proportions are based on number of respondents ($n = 180$). *A significant difference in proportion of respondents ($p < 0.05$) between Europe (63%) and South America (16%) or the US (36%).

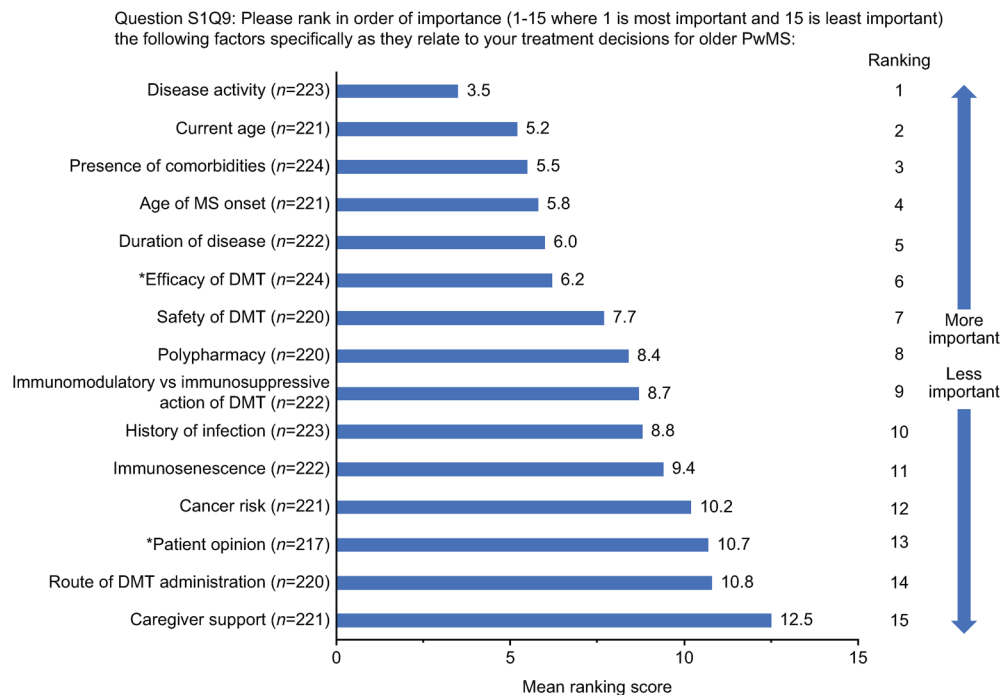


Figure 2. Factors influencing treatment decisions for older PwMS. DMT: disease-modifying therapy; MS: multiple sclerosis; PwMS: people with multiple sclerosis; S1Q9: Survey 1, question 9. *Significant differences in mean ranking score ($p < 0.05$) between respondents in South America and those in Europe or the US (efficacy of DMT: 7.36 vs 6.21 or 4.98, respectively; patient opinion: 12.17 vs 10.67 or 9.07, respectively).

of their older patients de-escalated from high-efficacy therapies (Figure 4A). Overall safety and comorbidity concerns were the most commonly cited circumstances for de-escalation (68%) (Figure 4B); however, there was no consensus on a preferred de-escalation therapy, with similar proportions selecting glatiramer acetate (29%), fumarates (27%), teriflunomide (23%), or interferon betas (21%). When considering DMT switching because of safety concerns not specific to high-efficacy DMTs, respondents also did not demonstrate a clear DMT preference, with 26% overall indicating a preference for glatiramer acetate, followed by fumarates (20%), interferon betas (13%), and teriflunomide (13%).

When asked if they would typically discontinue treatment once a patient is over 55, most respondents (63%) indicated they would not (Supplementary Figure S5). Respondents reached the consensus (83%) that they would continue treating a patient with stable disease with their current high-efficacy or platform DMT, though 38% of respondents also agreed or strongly agreed that they would discontinue treatment based on an absence of clinical or radiological evidence of disease activity in the previous 5 years. Additionally, most respondents (72%) agreed

or strongly agreed that they would discontinue therapy in older PwMS who asked to stop treatment.

Although consensus was not reached, a majority of respondents indicated that they would not prescribe sphingosine-1-phosphate receptor modulators in their older patients with or at risk of cardiovascular events (60%); alemtuzumab in those with or at risk of cancer (54%), lymphopenia (53%), or opportunistic infections (61%); and anti-CD20 therapies or natalizumab in those with or at risk of opportunistic infections (56% and 51%, respectively) (Supplementary Figure S6).

On the issue of the potential impact of vaccinations on DMT treatment efficacy, almost half of the respondents (46%) indicated that consideration of vaccine response did not influence their treatment decisions for older PwMS. Respondents reached consensus that vaccines for COVID-19 (85%) and influenza (78%) be recommended for older PwMS, with a majority (66%) also recommending the pneumococcus vaccine. Roughly two-thirds (69%) of survey participants said that accommodation of COVID-19 vaccination at least sometimes led to delays in therapy initiation for older patients. Most respondents said they would not pause administration of most DMTs

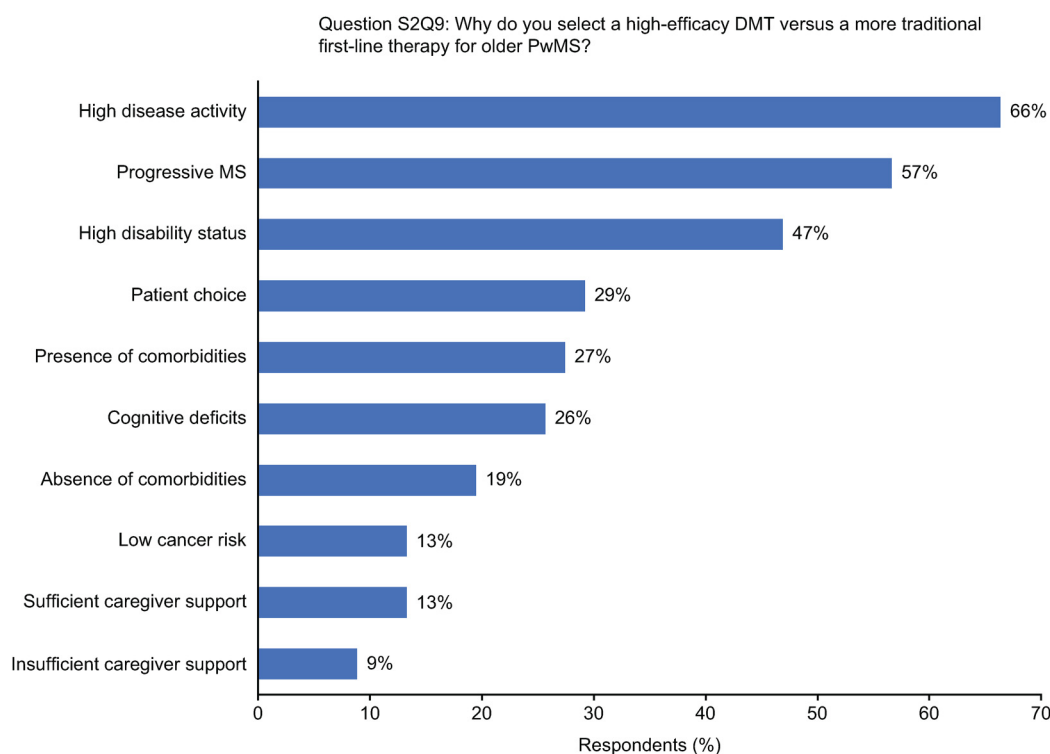


Figure 3. Use of a high-efficacy DMT in newly diagnosed, older PwMS.

DMT: disease-modifying therapy; MS: multiple sclerosis; PwMS: people with multiple sclerosis; S2Q9: Survey 2, question 9. The proportions are based on number of respondents ($n = 113$; derived from respondents who answered “yes” to S2Q8: Do you consider high-efficacy DMTs as a first option for older PwMS who are newly diagnosed?).

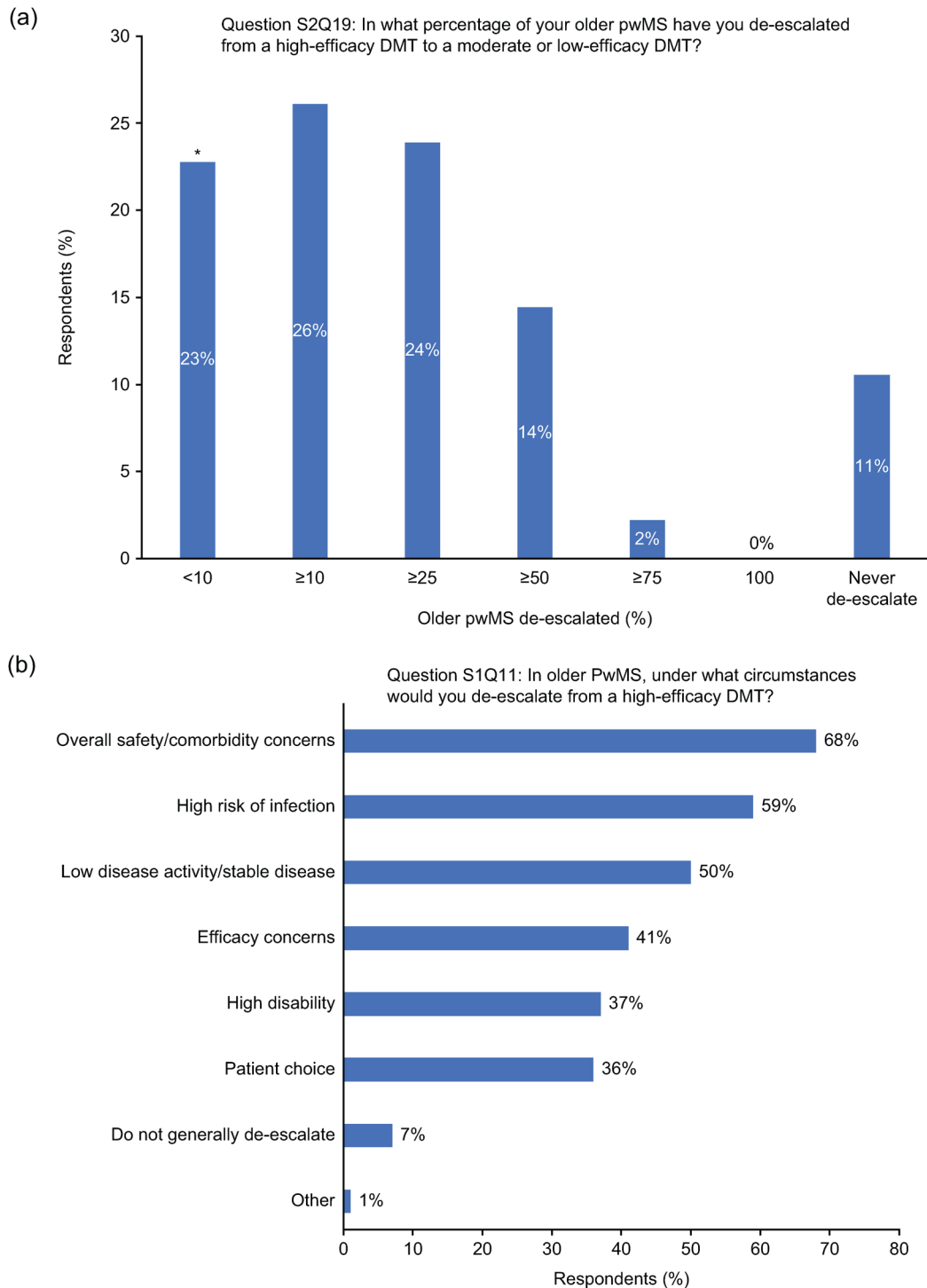


Figure 4. (a) Percentage of older PwMS de-escalated from high-efficacy DMTs and (b) reasons for de-escalation. DMT: disease-modifying therapy; PwMS: people with multiple sclerosis; S2Q19: Survey 2, question 19; S1Q11: Survey 1, question 11. The proportions are based on number of respondents (panel a: $n = 180$; panel b: $n = 224$). *A significant difference ($p < 0.05$) in proportions of respondents between South America (42%) and Europe (19%) or the US (14%).

to accommodate COVID-19 vaccination, with consensus agreement reached for glatiramer acetate (76%) and interferon beta preparations (75%) and with near consensus for

fumarates (73%). Approximately one-third of the respondents indicated that they would pause administration of anti-CD20 therapy (37%) or alemtuzumab (32%).

Table 2. Key consensus points and topics with unmet needs.

Key Consensus Points for Older Patients ^a
<ul style="list-style-type: none"> • Older patients with MS are more affected by comorbidities than younger patients (87%; S2Q3) • Patient age is useful in establishing immunosenescence (81%; S1Q3) • Generally, continue treating a patient with stable disease with their current DMT (83%; S2Q11 and S2Q13) • A COVID-19 vaccine and the influenza vaccine is recommended (85% and 78%, respectively; S1Q23) • No alterations in treatment with Glatiramer acetate or Interferons was required to accommodate COVID-19 vaccination (76% and 75%, respectively; S2Q26) • The following areas have a significant unmet need (mean score 4.0): 1) Prevention or delay of cognitive decline; 2) Treatment options for progressive disease; 3) Prevention, delay, and treatment of disability (S1Q24) • Agreement that if developed the following items would help healthcare providers be more confident in managing their older PwMS: 1) Management strategies for late- and very-late-onset MS (mean score 4.0); 2) Criteria or algorithm on when and how to start/continue/discontinue/switch DMTs for older PwMS (mean score 4.1); 3) Management strategies for older PwMS with long disease duration (mean score 4.1); 4) How to assess/measure progression on older PwMS (mean score 4.0) (S2Q27)
Critical Topics with Unmet Needs for Older Patients
<ul style="list-style-type: none"> • With no clear specific numerical age cutoff, what characteristics define an “older” patient? • How does one assess the degree and impact of immunosenescence? • Development of clearly defined strategies for DMT initiation, escalation/de-escalation/switching, and discontinuation. • How should treatment decisions be altered for patients with either long disease duration, late-onset MS, or progressive MS? • Clinical trials should recruit adequate populations of Older PwMS.
<p>^aConsensus was defined as $\geq 75\%$ of respondents selecting a categorical response or a mean score of ≥ 4.0 for questions using a 5-point Likert scale.</p> <p>S#Q# refers to survey number and question number (eg, S1Q24 is Survey 1, question 24).</p>

Respondents reached consensus that the following treatment approaches, if developed, would increase health care provider confidence in the management of older PwMS: management strategies for patients with long disease duration (mean ranking score 4.1); criteria or algorithms for DMT initiation, switching, or discontinuation (mean ranking score 4.1); and tools to assess disease progression (mean ranking score 4.0). There was also consensus among the respondents that prevention or delay of cognitive decline, treatment options for progressive MS, and prevention or delay of disability worsening were the areas with the greatest unmet need for older PwMS (all mean scores ≥ 4.0). Consensus points and critical topics with unmet needs are summarized in Table 2.

Regional differences in survey responses

Significant differences ($p < 0.05$) between respondents in Europe, South America, and the US were observed for three Survey 1 questions and three Survey 2 questions. An analysis of these findings is beyond the scope of this paper. A summary of

observed regional differences in survey responses is provided in Supplemental File 3.

Discussion

The prevalence of older PwMS may be attributable to a number of factors including aging of the general population, increase in age at disease onset, updated diagnostic criteria, and growing use of MRI in elderly PwMS.^{4,23,24} However, there is a lack of detailed evidence-based information on the efficacy and safety of DMTs in these patients^{25,26} and, as a result, older PwMS constitute an important underserved population in need of further exploration. In this Delphi study, a steering committee of MS specialists from Europe, North America, and South America developed questionnaires to identify areas of consensus on aspects of the management and treatment of older PwMS, including identifying and assessing older PwMS and the impact of age-related factors in making treatment decisions. Although there were varying degrees of agreement on several topics, consensus was

reached on only three questions in Survey 1 and five questions in Survey 2.

Although the majority of survey respondents agreed that management needs of older PwMS are different from those of younger patients, there was little agreement on which specific age constitutes “older”. This goes along with the lack of a consistently applied definition of “older” in scientific studies, and corresponds with the concept that numerical age alone is not sufficient to describe the biological realities of a unique aging body. Similarly, participants were divided on identification of immunosenescence and its impact on treatment decisions for older PwMS. While 81% of respondents found a patient’s age to be useful in evaluating immunosenescence, no consensus was reached on what specific age immunosenescence becomes a consideration, and only about half of the respondents found immune profiling a useful tool for evaluating immunosenescence. This could be due in part to the fact that objective measures of immunosenescence, such as altered T- and B-cell responses and naïve/memory T-cell ratios, may not be well understood, and clinical tests to establish immunosenescence are lacking. Survey participants did reach consensus on the impact of comorbidities in this population, a finding consistent with other reports on this topic.^{5,6} This was further demonstrated by majority agreements on decisions for patients with specific risks due to cardiovascular, immunological, or oncologic comorbidities.

Responses to several questions related to treatment decisions for older PwMS were varied, rarely reaching consensus. This may be due, at least in part, to the lack of clinical trial data specific to older PwMS and a lack of treatment guidelines for this patient subgroup,^{4,24–26} or regional differences in approved indications of MS DMTs. For instance, during this Delphi survey, there was regional variability in access to monomethyl or diroximel fumarate, and although rituximab is not approved in Europe or the US for the treatment of MS, it is still widely prescribed off-label.²⁷ Different prescribing regimens may have also contributed to a lack of consensus on the avoidance of specific DMTs or the use of high-efficacy DMTs.

A majority of respondents indicated that they considered high-efficacy DMTs as first-line treatment in newly diagnosed older PwMS with highly active disease which, in the absence of specific guidance for the older patient subgroup, is consistent with recommendations for the general population.²⁸ First-line use of high-efficacy DMTs is associated with improved treatment outcomes in comparison with delayed use.^{29,30} However, unrestricted early access to high-efficacy DMTs for PwMS with active

disease, while in accordance with the European Committee for Treatment and Research in Multiple Sclerosis/European Academy of Neurology and American Academy of Neurology 2018 treatment guidelines,^{31,32} may be limited owing to regional reimbursement practices.³³ There was little agreement among participants regarding de-escalation of high-efficacy DMTs in the older patients, possibly because of limited guidance on “exit strategies” for these patients.³⁴

The issue of discontinuation of DMTs among older PwMS remains unresolved. About two-thirds of respondents in our study would not discontinue a DMT in patients ≥ 55 years. Current DMTs do not appear to be as efficacious in PwMS > 55 years compared to younger PwMS.^{21,35} In addition, another consideration in making treatment decisions for older PwMS is the increased cancer risk.²⁴ It is noteworthy that a multicenter, randomized, controlled, phase 4, non-inferiority trial of PwMS ≥ 55 years (with no relapse within the past 5 years or new MRI lesion in the past 3 years) suggests that discontinuation of DMT might be a reasonable option in PwMS ≥ 55 years who have stable multiple sclerosis, although this bears a small risk of increased new MRI activity.³⁶ Clearly, further studies are needed to determine the safety of DMT discontinuation in older PwMS.

Safety considerations are important for older PwMS, and respondents were in majority agreement on specific treatment decisions to manage risk of opportunistic infections and reached consensus on the importance of vaccination for influenza and COVID-19. Though there are regional-specific guidelines for vaccination of elderly patients in general,³⁷ respondents did not reach consensus consistent with these recommendations in older PwMS. The COVID-19 pandemic has drawn attention to the possibility that some DMTs may impact the efficacy of vaccination and resulted in various regional guidelines for vaccination prior to DMT initiation, as well as with ongoing dosing. At the time of the survey, specific guidance for COVID-19 vaccinations for older PwMS receiving DMTs was still in progress.^{38,39} The Delphi survey participants recognized the possible concerns about specific DMTs, and a relatively high proportion of participants reported that COVID-19 vaccination resulted in delayed DMT initiation at least some of the time. The strategies developed to optimize COVID-19 vaccination efficacy may well apply to all vaccinations and be particularly important to consider for older PwMS.

Online Delphi surveys have inherent limitations that should be considered. Surveys are not validated for reliability (i.e., two different panels may provide

different answers and different consensus agreements).⁴⁰ The online Delphi process leads to more limited opportunities for interaction between survey participants than does an in-person meeting, possibly increasing the difficulty of obtaining consensus agreements. Furthermore, without the availability of immediate feedback for respondents, questions can lead to a broader set of interpretations than if a respondent could ask clarifying questions. For instance, the definition of high-efficacy DMTs was left up to interpretation by the respondents; therefore, the interpretation of these responses is generalized and not necessarily specific to a particular set of DMTs. Furthermore, the depth of responses could have been affected by competing demands, such as hospital or clinic obligations, vacation periods, or congress attendance. Specific to this survey about older PwMS, considerations that might be relevant only to patients diagnosed with late-onset MS were not examined in detail, though it is estimated that this subpopulation only represents a small percentage (10%)⁴ of MS incidence overall.

A strength of this survey lies in its regional diversity, with participants in different geographic locations generally providing consistent responses, suggesting broad agreement on best practices for older PwMS. There were, however, responses in both surveys that differed significantly between regions. For the results reported here, participant numbers in the different regions were insufficient to support robust statistical analysis, and a detailed exploration of regional differences is beyond the scope of this Delphi survey. While the reasons for the observed regional differences are not known, regional variation in access to MS DMTs and health care services,⁴¹ or in treatment or reimbursement practice³³ guidelines, may have played a role.

For areas of high unmet need or without detailed evidence-based information, Delphi studies are useful instruments for identifying important areas for further research and discussion. Of note, participants in this study reached consensus agreement on three areas of high unmet need for older PwMS: prevention of cognitive decline, prevention or delay of disease progression, and treatment options for progressive forms of MS. It is interesting that the prevention of cognitive decline was not commonly identified as a key unmet need by other researchers.^{42–44} This study, along with others, may be useful in informing the development of evidence-based practice guidelines for older PwMS. Such guidelines are of critical importance to ensuring that this growing and underserved segment of the MS patient population is managed appropriately, so that they receive appropriate, timely, and effective treatment to maximize patient well-being and outcomes.

In conclusion, results of the Delphi survey of MS specialists on their treatment strategies and considerations for effective management of older PwMS are generally consistent with current treatment guidelines for PwMS. However, in light of the lack of specific treatment guidelines for PwMS >55 years, this study may be useful in informing the development of evidence-based practice guidelines for older PwMS with the goal of improving elderly patient management.

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Supplemental material

Supplemental material for this article is available online.

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