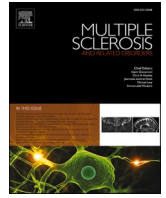




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## Current international trends in the treatment of multiple sclerosis in children—Impact of the COVID-19 pandemic

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## ABSTRACT

**Background:** Only recently has the first disease-modifying therapy been approved for children with multiple sclerosis (MS) and practice patterns including substantial off-label use have evolved. Understanding attitudes towards treatment of paediatric MS and whether this has changed due to the ongoing COVID-19 pandemic is vital to guide future therapeutic trials and for developing guidelines that reflect practice.

**Methods:** We performed an online survey within the International Paediatric Multiple Sclerosis Study Group between July and September 2020. The survey was sent to 130 members from 25 countries and consisted of five sections: demographic data, treatment, disease modifying therapies and COVID-19, outcome and three patient cases.

**Results:** The survey was completed by 66 members (51%), both paediatric neurologists and adult neurologists. Fingolimod and  $\beta$ -interferons were the most frequently used disease-modifying therapies, especially among paediatric neurologists. Almost a third (31%) of respondents had altered their prescribing practice due to COVID-19, in particular at the beginning of the pandemic.

**Conclusions:** The survey results indicate a tendency of moving from the traditional escalation therapy starting with injectables towards an early start with newer, highly effective disease modifying therapies. The COVID-19 pandemic only slightly affected prescribing patterns and treatment choices in paediatric MS.

**Abbreviations:** DMT, disease modifying therapy; IFN- $\beta$ ,  $\beta$ -interferons; GA, glatiramer acetate; TFL, teriflunomide; DMF, dimethyl fumarate; FGL, fingolimod; ALZ, alemtuzumab; OCR, ocrelizumab; RTX, rituximab; NTZ, natalizumab; EDSS, Expanded Disability Status Scale; IPMSSG, International Paediatric Multiple Sclerosis Study Group; CHI3L1, Chitinase-3-like-1 protein; CXCL13, Chemokine C-X-C motif ligand 13; WISC, Wechsler Intelligence Scale for Children; SDQ, Strengths and Difficulties Questionnaire; WIAT, Wechsler Individual Achievement Test; MUSICADO, Multiple Sclerosis Inventory of Cognition for Adolescents; PedsQL, Paediatric Quality of Life Inventory; Beery VMI, Beery-Buktenica Developmental Test of Visual-Motor Integration; MOG, myelin-oligodendrocyte glycoprotein; POMS, paediatric-onset multiple sclerosis; Ped-MSSS, Paediatric Multiple Sclerosis Severity Score.

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## 1. Introduction

Until recently, and despite more than 14 disease modifying therapies (DMTs) approved for adult multiple sclerosis (MS), none were approved for children with MS. This has led to a substantial off-label use, often following adult guidelines. Traditionally, injectable DMTs such as  $\beta$ -interferons (IFN- $\beta$ ) and glatiramer acetate (GA) have been used and appear safe and effective in children (Banwell et al., 2006; Chitnis et al., 2012; Ghezzi et al., 2016; Hacoheh et al., 2020; Kormek et al., 2003). Oral and intravenous DMTs, together referred to as newer DMTs, have been less frequently used and data on their efficacy and safety in paediatric patients are scarce (Krysko et al., 2018, 2020). Several clinical safety and efficacy trials are ongoing (ClinicalTrials.gov; ClinicalTrials.gov; ClinicalTrials.gov) following the approval of fingolimod (FGL) for paediatric MS by the Food and Drug Administration and the European Medicines Agency in 2018 (Chitnis et al., 2018).

Understanding the clinical practice and attitudes towards treatment among clinicians treating children with MS is vital to guide future therapeutic trials and develop guidelines that reflect practice. We therefore performed an online survey within the International Paediatric Multiple Sclerosis Study Group (IPMSSG) with the aim of studying how treatment of paediatric MS is organized internationally, whether there is a consensus in treatment choices and if these have been affected by the COVID-19 pandemic.

## 2. Methods

A web-based questionnaire was developed in the SurveyMonkey platform (SurveyMonkey, San Mateo, CA, USA). The questionnaire consisted of 84 questions in total but the number of questions each respondent was asked depended on previous answers and was in practice lower. The questions were divided into five sections: a background section with demographic data, treatment, DMTs and COVID-19, outcome and finally three patient cases. A preliminary version of the survey was tested by the authors of this article. After some minor adjustments, the survey was carried out between July and September 2020. The full survey is found in Appendix S1. The 130 members of the IPMSSG, an international network including adult and paediatric neurologists as well as researchers in the field, were e-mailed an introduction letter with a link to the survey. To increase the response rate, a subsequent reminder was sent. The survey was administered in English only.

Data were tabulated descriptively. For each result, only the respondents completing that specific question were included in the denominator. For relevant variables, categorical data were analysed with Fisher's exact test. P-values lower than 0.05 were considered statistically significant. Analyses were performed using Stata, version 16 (StataCorp. 2019. Stata Statistical Software: Release 16. College Station, TX: StataCorp LLC).

## 3. Results

### 3.1. Background section with demographic data

Out of the 130 members of the IPMSSG who were invited to participate in the survey, 66 (51%) responded. Of these, 59 completed the entire survey. The respondents were distributed over 25 countries, where US was by far the most represented (supplementary Table 1).

In this context, the term "paediatric" varies between different countries, with the upper age generally varying from 16 to 22 years (range 7–22). Almost all (65/66, 98%) of the respondents answered that children with MS were referred to their hospital from other hospitals. Most of the respondents (47/66, 71%) were paediatric neurologists while 20% (13/66) were adult neurologists. A majority (45/66, 68%) had at least a 10-year experience taking care of children with MS (range 2–41). Almost half (32/66, 48%) worked at a site with at least 30

children with MS (range 2–200) at the time of the survey. Two thirds (45/66, 68%) answered that they had specialized paediatric MS teams which mostly consisted of paediatric neurologists and neuropsychologists (supplementary Table 2).

A majority (38/66, 58%) had a specialized transition service starting at the age of 17 (range 12–21) (Table 1).

### 3.2. Treatment

Among DMTs used for paediatric MS, IFN- $\beta$ , FGL and natalizumab (NTZ) were most frequently prescribed while teriflunomide (TFL) and alemtuzumab (ALZ) were least frequently prescribed. FGL and rituximab (RTX) were more commonly used among paediatric neurologists compared to adult neurologists ( $p = 0.03$  and  $p = 0.04$ , respectively). As a first choice, IFN- $\beta$  and FGL were the most common answers, while none answered that they used ALZ. GA and NTZ were more often prescribed by adult neurologists whereas RTX was more often prescribed by paediatric neurologists ( $p = 0.03$  for all, respectively). NTZ was more frequently prescribed in hospitals with at least 30 children with MS currently being followed ( $p = 0.01$ ). Among the anti-CD20 therapies, RTX was more often prescribed compared to ocrelizumab (OCR) in general and as first choice (Fig. 1).

Not using a certain DMT due to limited access was most commonly reported for OCR (23/62, 37%) followed by TFL (15/63, 24%), dimethyl fumarate (DMF, 13/62, 21%), ALZ (12/62, 19%) and RTX (11/62, 18%). This was less of a problem for NTZ (4/62, 6%), GA (4/63, 6%) and FGL (3/62, 5%) and none reported that they did not use IFN- $\beta$  due to limited access. With the exception of FGL and NTZ, access to the newer DMTs was more limited compared to the injectable therapies. Limited access to DMTs was rarely reported from U.S. respondents, whereas limited access to anti-CD20 therapies appears common in parts of Europe and particularly in Italy.

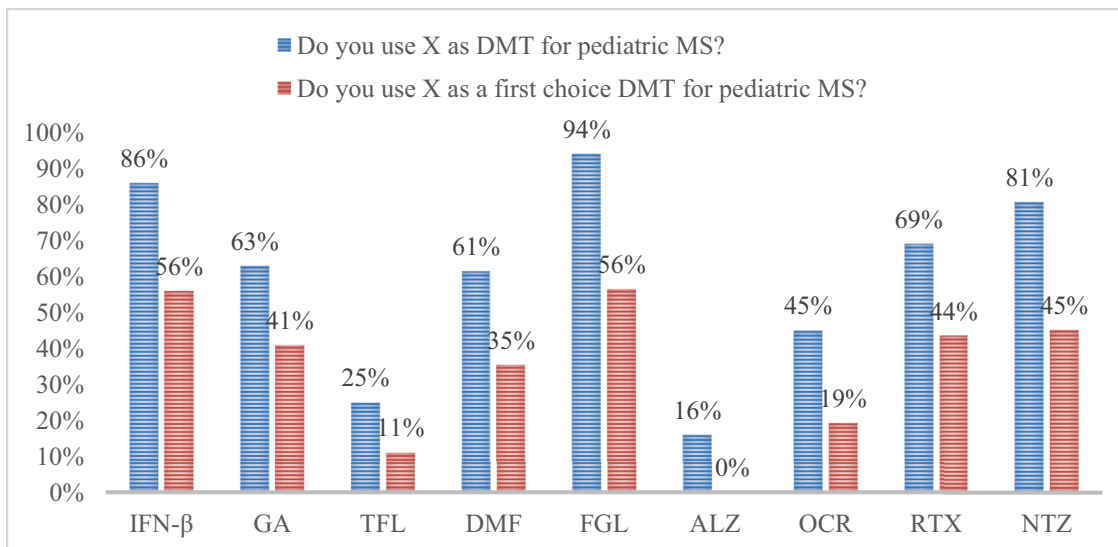
When switching from a first choice DMT, inadequate treatment response was the most common reason given for all DMTs except for RTX and OCR (adverse events) and NTZ (due to John Cunningham virus antibody positivity) (Fig. 2).

The most common go-to DMTs when switching were FGL, NTZ and RTX. Those answering "other" specified that the choice was made based on the individual situation (Fig. 3).

Almost half (27/61, 44%) started treatment with a high efficacy DMT (in the survey defined as an induction approach) while 54% (33/61) used an escalation approach but considered induction therapy an interesting option. Only 2% (1/61) did not consider induction therapy an interesting option at present. Stem cell transplant therapy was indicated as a possible option in their country by 36% (22/61) of respondents whereas 52% (32/61) answered it was not available and 11%

**Table 1**  
Demographics of respondents.

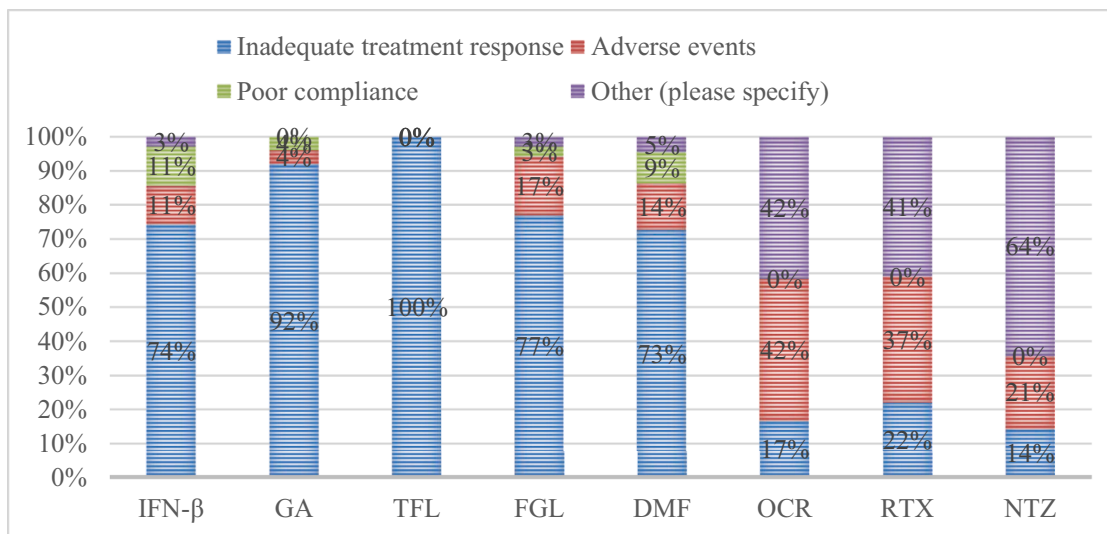
(n = 66)	n (%)
Speciality	
Paediatric neurologists	47 (71)
Adult neurologists	13 (20)
Paediatric and adult neurologists	3 (5)
Other	3 (5)
Experience of care of children with MS	
< 10 years	21 (32)
$\geq 10$ years	45 (68)
Number of children with MS currently being followed at hospital	
< 30	33 (50)
$\geq 30$	32 (48)
Don't know	1 (2)
Geographical location	
Asia	7 (11)
Australia	3 (5)
Europe	28 (42)
North America	21 (32)
South America	7 (11)



DMT: disease modifying therapy, MS: multiple sclerosis, IFN-β: β-interferons, GA: glatiramer acetate, TFL: teriflunomide, DMF: dimethyl fumarate, FGL: fingolimod, ALZ: alemtuzumab, OCR: ocrelizumab, RTX: rituximab, NTZ: natalizumab.

Fig. 1. Use of disease modifying therapies.

DMT: disease modifying therapy, MS: multiple sclerosis, IFN-β: β-interferons, GA: glatiramer acetate, TFL: teriflunomide, DMF: dimethyl fumarate, FGL: fingolimod, ALZ: alemtuzumab, OCR: ocrelizumab, RTX: rituximab, NTZ: natalizumab.



DMT: disease modifying therapy, IFN-β: β-interferons, GA: glatiramer acetate, TFL: teriflunomide, DMF: dimethyl fumarate, FGL: fingolimod, ALZ: alemtuzumab, OCR: ocrelizumab, RTX: rituximab, NTZ: natalizumab.

Fig. 2. The most common reason of switching from a DMT.

DMT: disease modifying therapy, IFN-β: β-interferons, GA: glatiramer acetate, TFL: teriflunomide, DMF: dimethyl fumarate, FGL: fingolimod, ALZ: alemtuzumab, OCR: ocrelizumab, RTX: rituximab, NTZ: natalizumab.

	IFN	GA	TFL	FGL	DMF	ALZ	OCR	RTX	NTZ	Other
IFN		6%	3%	57%	3%	0%	0%	9%	14%	9%
GA	15%		4%	54%	4%	0%	0%	4%	15%	4%
TFL	17%	0%		50%	17%	0%	0%	0%	0%	17%
FGL	3%	0%	0%		0%	3%	17%	31%	31%	14%
DMF	0%	0%	0%	27%		0%	14%	27%	14%	18%
OCR	0%	0%	0%	8%	0%	25%		8%	42%	17%
RTX	0%	0%	0%	30%	0%	11%	4%		19%	37%
NTZ	0%	0%	0%	25%	0%	7%	21%	36%		11%

DMT: disease modifying therapy, IFN-β: β-interferons, GA: glatiramer acetate, TFL: teriflunomide, DMF: dimethyl fumarate, FGL: fingolimod, ALZ: alemtuzumab, OCR: ocrelizumab, RTX: rituximab, NTZ: natalizumab.

Fig. 3. Switching from one DMT (Y axis) to another DMT (X axis)  
 DMT: disease modifying therapy, IFN-β: β-interferons, GA: glatiramer acetate, TFL: teriflunomide, DMF: dimethyl fumarate, FGL: fingolimod, ALZ: alemtuzumab, OCR: ocrelizumab, RTX: rituximab, NTZ: natalizumab.

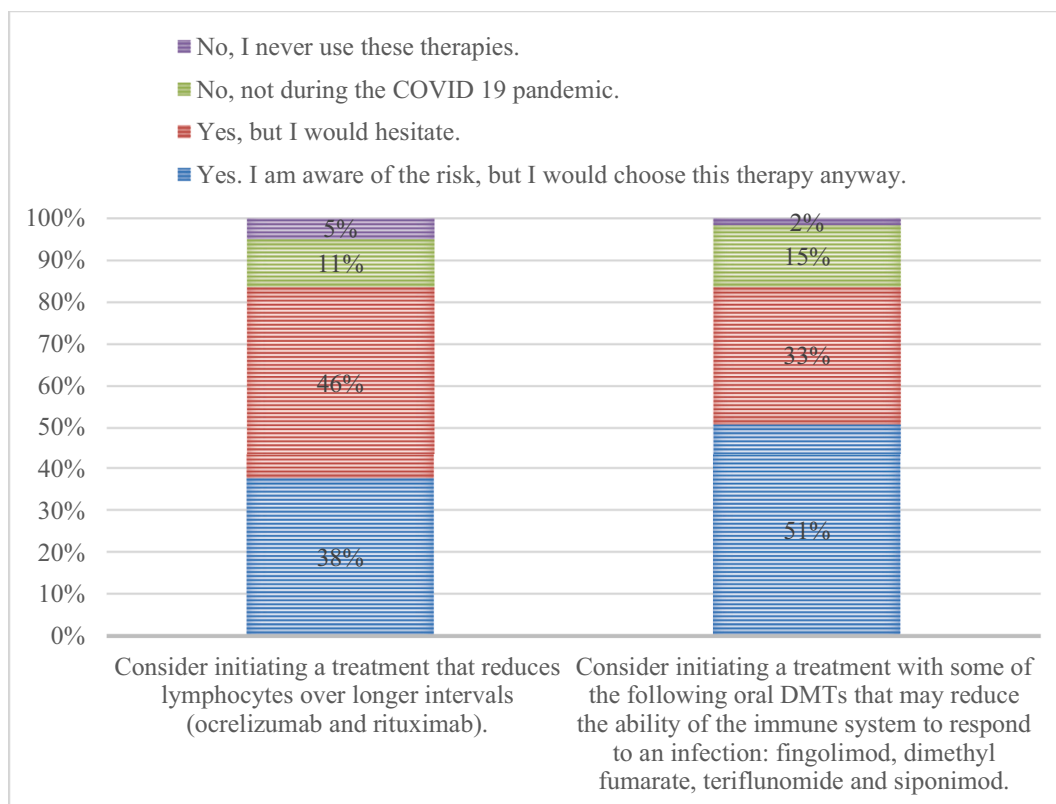


Fig. 4. Initiation of DMTs during the COVID-19 pandemic.

(7/61) did not know.

A majority of respondents (50/61, 82%) treated MS fatigue. Of those who treated fatigue, 63% (32/51) treated it pharmacologically. Modafinil and amantadine were the most frequently prescribed drugs. A fifth of the respondents (13/61, 21%) used methylphenidate, more common among paediatric neurologists compared to adult neurologists ( $p = 0.049$ ) as well as among respondents with a less than 10-year experience compared to those with at least a 10-year experience ( $p = 0.02$ ). Furthermore, 84% (42/50) of those who treated fatigue used non-pharmacological approaches where exercise and sleep hygiene were the most common forms of treatment.

### 3.3. DMTs and COVID-19

Concerning treatment in relation to the COVID-19 pandemic, 84% (51/61) of respondents indicated that they would initiate treatment with anti-CD20 DMTs, despite the pandemic. However, more than half (28/51) of these indicated that they would hesitate. Likewise, 84% (51/61) of respondents would start treatment with oral DMTs, but less than half (20/51) of these indicated that they would hesitate (Fig. 4).

Almost forty percent (24/61, 39%) of respondents “would” (6/61, 10%) or “would probably” (18/61, 30%) delay further doses of anti-CD20 treatment whereas 61% (37/61) “would not” (6/61, 10%) or “would probably not” (31/61, 51%) do so. A decision to delay was more common among adult neurologists ( $p = 0.001$ ). Only 7% (4/61) would consider discontinuing an ongoing DMT because of the pandemic. In real life, 31% (19/61) reported that they had changed their prescribing practice, especially at the beginning of the pandemic.

### 3.4. Outcome

Relapse rate, number of new T2 lesions and Expanded Disability Status Scale (EDSS) were the most commonly used measures of treatment effect while MRI brain atrophy the least used. Severity of relapses as a measure of treatment effect was more often used by respondents with a less than 10-year experience compared to those with at least a 10-year experience ( $p = 0.04$ ). In the category “other”, contrast enhancing lesions was the most frequently reported metric. (Fig. 5).

Cerebrospinal fluid (CSF) oligoclonal bands (OCB, 25/61, 41%), CSF IgG index (17/61, 28%), NTZ antibodies (17/62, 27%) and INF- $\beta$  antibodies (15/61, 25%) were the most frequently used biomarkers to measure efficacy and guide therapy. Neurofilaments were used by 11% (7/61) of respondents and CSF interleukins by 10% (6/61). None reported using Chitinase-3-like-1 protein (CHI3L1) and only 2% (1/61) used Chemokine C-X-C motif ligand 13 (CXCL13).

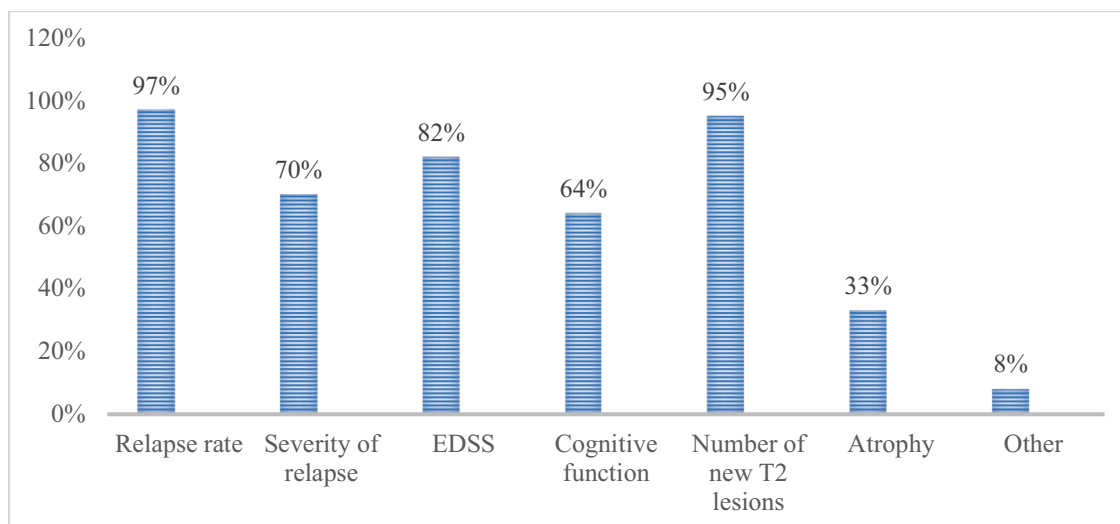
A majority (38/61, 62%) considered neuropsychological evaluation and monitoring part of routine care. A third (18/61, 30%) performed neuropsychological evaluation only when concerned about cognitive impairment. Only 8% (5/61) did not have access to neuropsychology and none thought it was not needed. Wechsler Intelligence Scale for Children (WISC), Strengths and Difficulties Questionnaire (SDQ), Wechsler Individual Achievement Test (WIAT), Multiple Sclerosis Inventory of Cognition for Adolescents (MUSICADO), Paediatric Quality of Life Inventory (PedsQL) and Beery-Buktenica Developmental Test of Visual-Motor Integration (Beery VMI) were the most frequently used scales.

### 3.5. Patient cases presented in the survey

In three patient cases, the respondents were asked either if they would start DMT in two treatment-naïve patients or switch DMT in a patient already on DMT. In addition, they were asked which DMT they would start with/switch to.

**Case 1.** “16-year-old girl with blurred vision. Eye exam and MRI show unilateral ON. On MRI also two T2 lesions (juxtacortical and spinal) without GAD enhancement. CSF-specific oligoclonal bands positive. Aquaporin-4 antibodies as well as myelin-oligodendrocyte glycoprotein (MOG) antibodies negative in serum.” A majority (49/60, 82%) would start DMT and most of these would choose FGL (15/48, 31%) or IFN- $\beta$  (13/48, 27%) followed by GA (8/48, 17%) and DMF (5/48, 10%). In contrast, OCR (1/48, 2%), RTX (1/48, 2%) and NTZ (2/48, 4%) were chosen by only few respondents.

**Case 2.** “17-year-old boy. Feeling tired most of the time. Cognitive decline. Numbness of the right arm. Eye exam and MRI show unilateral ON. On MRI also 10 T2 lesions (3 juxtacortical, 2 periventricular, 4



EDSS: Expanded Disability Status Scale.

Fig. 5. Use of outcome measures in clinical practice to measure efficacy. EDSS: Expanded Disability Status Scale.

infratentorial and 1 spinal). 3 of these (1 juxtacortical and 2 infratentorial) with GAD enhancement. CSF-specific oligoclonal bands positive. Aquaporin-4 antibodies as well as MOG antibodies negative in serum.”

All respondents (59/59, 100%) indicated that they would start DMT. FGL and NTZ were the most common choices (19/59, 32% each) followed by RTX and OCR (6/59, 10% each) and IFN- $\beta$  (5/59, 8%). Only 2% (1/59) would start with DMF, which was least common DMT response. Of those who would start DMT in both **Case 1** and **2**, 23% (11/47) would start with the same DMT in both cases.

**Case 3.** “11-year-old girl. Numbness and weakness right leg. Impaired balance. Fatigue. No encephalopathy. EDSS 3. On MRI 15 T2 lesions (3 juxtacortical, 4 periventricular, 4 infratentorial and 4 spinal) of which 5 with GAD enhancement (2 periventricular and 3 infratentorial). CSF-specific oligoclonal bands positive. Aquaporin-4 antibodies as well as MOG antibodies negative in serum. Starts treatment with Fingolimod. Adherent to therapy but inadequate treatment response with 2 more relapses (clinical and radiological) within 12 months.”

All respondents (59/59, 100%) would switch DMT, most often to NTZ (29/59, 49%) or RTX (18/59, 31%) followed by OCR (4/59, 7%), while only 2% (1/59) would switch to either IFN- $\beta$ , DMF or ALZ.

#### 4. Discussion

Traditionally, injectable therapies have been the most commonly used DMTs in the treatment of paediatric MS, escalating to newer or higher efficacy DMTs only when required and generally because of breakthrough disease. One important reason for this has been a lack of efficacy and safety studies in the paediatric population leading to a limited number of DMTs approved for treatment in that population. However, this survey of current practise indicates that some of the newer DMTs are used just as much or even more frequently than the injectables. This is especially true regarding FGL which was the most frequently used DMT and was also approved for use in paediatric MS in 2018. When compared to the results from a similar, unpublished survey that was undertaken in 2017, we observed a tendency towards an earlier use of newer DMTs in the current survey. Using high-efficacy DMTs early and in treatment-naïve patients is often referred to as induction therapy as opposed to an escalation model where treatment starts with lower-risk, lower-efficacy DMTs and only moves on to more aggressive treatments if the ongoing approach fails (Ruggieri et al., 2018). Such an induction approach was used by almost half of the respondents and considered it an interesting option.

Our results indicate an attitude which is in line with recent studies of children with MS or clinically isolated syndrome, where newer DMTs were increasingly used in more recent years (Krysko et al., 2018) and where initial treatment with newer DMTs led to better disease activity control compared to injectables (Abdel-Mannan et al., 2021; Krysko et al., 2020). Two recent reviews also propose that highly effective DMTs should be used during the first years post-onset, a time with a high relapse rate and rapid loss of brain tissue (Hacohen et al., 2020; McGinley and Rossman, 2017).

It is also apparent that treatment choices are influenced by access to certain DMTs, including funding issues. The current survey indicates limited access to some extent for most DMTs and with regional differences. This is an important aspect in treatment discussions and highlights the need for efficacy and safety studies in the paediatric population to resolve accessibility issues and provide children and adolescents with the best possible treatment options.

Autologous haematopoietic stem cell transplantation has been used for MS since 1995 with almost complete suppression of the disease in adult RRMS, although very few studies have been randomized and controlled (Fassas et al., 1997). However, only limited paediatric data have been published to date (Burman et al., 2017), and a possible benefit

has to be weighed against the risk of serious adverse events (Saccardi et al., 2006). In our survey, 36% of the respondents answered that stem cell transplantation is a treatment option for paediatric MS in their country.

Fatigue, described in 20% of patients with paediatric-onset multiple sclerosis (POMS) (Amato et al., 2014) was treated by a majority of the respondents and primarily non-pharmacologically. Although not significant, there was a trend for adult neurologists being more prone to treat fatigue. This may reflect more experience handling fatigue as the prevalence has been reported higher in adults than in children with MS (Rooney et al., 2019). However, it may also reflect that adult neurologists are also more likely to see older teenagers rather than younger children, and that the prevalence of fatigue is higher in that age group.

In light of the COVID-19 pandemic, the risk of patients with MS having a more severe infection associated with DMT use has been discussed. Given the highly inflammatory nature of paediatric MS with a high relapse rate combined with the low prevalence of comorbid risk factors, the general recommendations at the time of the survey were that the benefits of continuing MS treatment outweigh the risks of stopping therapy and potentially experiencing new relapses (Brownlee et al., 2020). In our survey, 31% of the respondents had changed their prescribing practice in real life, mostly at the beginning of the pandemic. This is lower than seen among European neurologists treating adult MS where 70% reported having altered DMT treatment as a result of the pandemic (Portaccio et al., 2021). Furthermore, delaying further doses of anti-CD20 therapies was more common among adult neurologists in the current survey, possibly reflecting more comorbid illnesses and less inflammatory disease among adults. Indeed, 80% of neurologists in USA and Canada treating adult MS would consider delaying B-cell therapy and in general, high-efficacy treatments were avoided and lower efficacy agents were preferred (Mateen et al., 2020). Whether DMTs may cause an increased risk of severe covid disease in children and adolescents is still at debate. In two recent studies of adults with MS, there was either no association between DMT exposure and COVID-19 severity (Parrotta et al., 2020) or an unclear association where patients treated with moderate-risk and high-risk DMTs (here defined as FGL, anti-CD20 therapies, cladribine, and alemtuzumab) more often had severe COVID-19 than seen in patients treated with low-risk or no-risk DMTs (Louapre et al., 2020). However, as all treatments had better outcome than the non-treated MS group, the conclusion in the latter study was that the data supported current recommendations of not stopping current DMT treatment and not delaying DMT initiation in patients with highly inflammatory MS. In contrast, a recent publication has pointed specifically to anti-CD20 agents as increasing the risk of severe COVID-19 (Sormani et al., 2021). Whether this is the case also in children and teenagers is not known.

Although physical disability is not a prominent feature in POMS, EDSS was the third most commonly used measure used by 82% of the respondents. In general, POMS score lower on EDSS compared to AOMS and the use of a Paediatric Multiple Sclerosis Severity Score (Ped-MSSS) has been proposed as an alternative (Santoro et al., 2020). Cognitive function was used as an outcome measure by almost two thirds of the respondents. A majority considered neuropsychological evaluation and monitoring part of routine care and, as children with MS can have significant cognitive dysfunction early in the disease course, this seems important to monitor although studies that suggest that specific therapies actually preserve cognitive function are scarce. One of the scales used by the respondents was the Multiple Sclerosis Inventory of Cognition for Adolescents (MUSICADO) which can serve as a brief screening instrument to assess cognitive dysfunction, fatigue and loss of health-related quality of life in POMS (Storm Van'S Gravesande et al., 2019). There is also evidence that the neurodegenerative aspect of POMS limits age-expected brain growth leading to brain atrophy (Aubert-Broche et al., 2014; Bartels et al., 2019). However, measurement of brain atrophy is challenging and among the respondents brain atrophy was the least used outcome measure.

The responses to the presented patient cases were largely in line with responses to individual questions in the survey and also had a fairly high level of agreement. In the first patient case, fulfilling the 2017 McDonald criteria but with a relatively mild disease, 18% responded that they would not start treatment. In the second case with a more inflammatory disease, all respondents would initiate treatment, and most would choose a higher efficacy DMT. Of those starting treatment in the first two cases, 23% would start with the same DMT in both cases. In the third case with an 11-year-old girl with a highly inflammatory disease already on FGL, but with inadequate treatment response, all would switch DMT.

#### 4.1. Strengths and limitations

A strength of the current study is the international approach through the use of the IPMSSG, although there was a bias towards North America and Europe among the respondents. Response rate was low which is likely in part due to the fact that many IPMSSG members are researchers not involved in direct patient care. In addition, results need to be interpreted with caution as interpretation of questions may vary among respondents.

#### 5. Conclusion

The results from this survey indicate a tendency of moving from the traditional escalation therapy starting with injectables towards an earlier start with newer, highly effective DMTs in the treatment of paediatric MS. This is in line with recent studies showing this strategy is more effective. Furthermore, the ongoing COVID-19 pandemic has only slightly affected treatment choices in paediatric MS.

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#### Ethical approval

Ethical approval through the regional ethical review board was not needed as the survey concerned clinical practice rather than individual patients.

#### Declaration of Competing Interest

None of the authors have any relevant conflicts of interest. Study sponsors indicated above had no role in study design; collection, analysis and interpretation of data; writing of the report; and the decision to submit the manuscript for publication. The first draft of the manuscript was written by the first author (FS) and all authors have been involved in manuscript preparation.

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#### Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.msard.2021.103277](https://doi.org/10.1016/j.msard.2021.103277).

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