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Influenza vaccination status in multiple sclerosis patients from Latin America

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Abstract

The objective of the present study was to identify the frequency of MS patients in Latin America (LATAM) that received the influenza vaccine during the most recent season and the reasons related to non-vaccination. Cross-sectional study between November and December 2020 in a large cohort of MS patients from LATAM. Patients responded about recommendation of receiving influenza vaccine and the use of it as well as reasons for not using the vaccine. Four hundred twelve MS patients were included in the analysis. 47.3% of patients were recommended to receive the vaccine from the treating physician. Nearly 54% of patients did not receive the influenza vaccine, and the most frequent cause was that it was neither recommended nor mentioned by the treating physician (27.4%). Female gender (OR = 2.3, 95%CI 1.4–3.8, p = 0.001) was associated with an increased risk of recommendation, while a progressive form of MS and higher EDSS decreased the risk (OR = 0.49, 95%CI 0.27–0.90, p = 0.023; OR = 0.65, 95%CI 0.55–0.97, p = 0.02, respectively). Despite the evidence to recommend the influenza vaccine in MS patients, a limited number of patients in clinical practice received such recommendation.

Keywords Multiple sclerosis · Vaccination · Influenza · Latin America

Introduction

Multiple sclerosis (MS) is a chronic degenerative disease that affects young adults between 18 and 45 years of age and is the first cause of physical disability of non-traumatic origin in several countries worldwide (Comi et al. 2017; Reich et al. 2018).

Previous evidence suggested that infections may trigger MS relapses, an increase in MS radiologic and immunologic activity, and the facilitation of disease progression (Buljevac et al. 2002; Correale et al. 2006; Farez et al. 2019). Likewise, select reports link immunizations to clinical or radiological activity of MS (Farez et al. 2019). At the same time, however, many studies and guidelines were developed to clarify the relationship between immunization and the possibility of MS activity, and there is currently strong evidence that it is unlikely that many immunizations predispose to MS activity while protecting patients against severe infections (Farez et al. 2019).

The influenza vaccine confers personal benefits and contributes to the well-established phenomenon of "herd" immunity for the communities in which patients with MS live[6]. Thus, vaccination of patients with MS is expected to have personal and population-level benefits (Farez et al. 2019; Fine et al. 2011).

Although influenza vaccination is recommended in MS, for reasons unknown, many patients do not receive it. The identification of the frequency in which patients receive this indicated vaccine and the causes related to the non-prescription, would allow clinicians to better deal with the problem.

The objective of the present study was to identify the frequency of MS patients in Latin America (LATAM) that

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received the influenza vaccine during the most recent season and the reasons related to non-vaccination.

Methods

We conducted a cross-sectional study with a web-based survey between November and December 2020 in a large cohort of MS patients from LATAM using a self-administered, anonymous questionnaire. Most critical questions of the survey (MS phenotype, vaccination status, expanded disability status scale [EDSS], and treatment, among others) were developed with a focus group of physicians, MS patients, and MS patient association directors (SG and PH). The preliminary version was piloted 2 times, using 3 testers each time to ensure that the questions were well-defined, clearly understood, and presented in a consistent manner. Influenza vaccination was determined in all patients. The final survey is included as Supplementary Material 1. The final Spanish language survey was later sent by e-mail to MS organizations from 12 different countries that forwarded it to potential responders diagnosed with MS. MS organizations ensured delivery of the survey to confirmed MS patients by searching their databases for patients followed and treated by neurologists and MS specialists included in their databases. Patients not followed by treating physicians included in MS organization databases were not selected to receive the survey. Treating physician was defined as the neurologist or MS specialist in charge of the affected patient. Results were collected by the Argentine Asociación de Lucha contra la Esclerosis Multiple (ALCEM; Association for the Fight Against MS). The study was approved by the Research Protocol Ethics Committee from the Hospital Universitario de CEMIC de Buenos Aires, and electronic written informed consent was obtained from all participants prior to data collection.

Statistical analysis

Continuous data were expressed with their means and ± SD. Categorical data were expressed in percentages. Descriptive measures were used to present the outcome. Patients were later stratified into those that received the recommendation to vaccine by their treating physician from those that did not receive it. Logistic regression analysis was used to identify differences between groups. Statistical analyses were performed using Stata 15 software. For all analyses, the significance level established was $p < 0.05$.

Results

A total of 412 MS patients were included in the analysis. Numbers of MS patients completing the survey per country were as follows: 165 from Argentina, 25 from Chile, 24 from Colombia, 22 from Ecuador, 23 from Paraguay, 19 from Peru, 33 from Uruguay, 21 from Costa Rica, 32 from Guatemala, 19 from Honduras, 18 from Panama, and 11 from Mexico. A total of 314 (76%) MS patients were female, mean age at study entry was 42 ± 10 years, and mean disease duration was 9.5 ± 7 years. Most patients were relapsing–remitting MS (RRMS; 78.8%), and the most frequent treatment for MS identified was fingolimod

Table 1 Baseline characteristics of included patients

	N = 412
Mean age, SD, range (years)	42 ± 10 (18–68)
Mean disease duration, years	9.5 ± 7 (1–32)
Female gender, n (%)	314 (76.2)
RRMS, n (%)	325 (78.8)
SPMS, n (%)	47 (11.4)
PPMS, n (%)	40 (9.7)
Median EDSS, SD	3 (0–9)
Education, n (%)	
High school	102 (24.8)
Tertiary	90 (21.8)
University	217 (52.7)
No education	3 (0.73)
No current treatment for MS, n (%)	39 (9.5)
Current treatment, n (%)	373 (90.5)
Interferon beta	88 (24)
Glatiramer acetate	10 (2.3)
Fingolimod	111 (30)
Teriflunomide	16 (4.3)
DMF	42 (11.3)
Cladribine	20 (5.2)
Natalizumab	29 (7.6)
Ocrelizumab	30 (8)
Alemtuzumab	16 (4.3)
Rituximab	11 (2.9)

SD standard deviation; *RRMS* relapsing–remitting multiple sclerosis; *SPMS* secondary progressive multiple sclerosis; *PPMS* primary progressive multiple sclerosis; *DMF* dimethyl fumarate; *EDSS* expanded disability status scale

Table 2 Influenza vaccination status

	N = 412
Influenza vaccine prescribed by TP, n (%)	195 (47.3)
Influenza vaccinated, n (%)	186 (45.4)
Influenza unvaccinated, n (%)	226 (54.6)
Influenza reason for non-vaccination, n (%)	226 (54.6)
Neither prescribed nor mentioned by TP	62 (27.4)
Contraindicated by TP	39 (17.3)
No access to vaccine	35 (15.5)
Personal reasons	67(29.6)
Other reason	23 (10.2)

TP treating physician; *SD* standard deviation; *RRMS* relapsing–remitting multiple sclerosis; *SPMS* secondary progressive multiple sclerosis; *PPMS* primary progressive multiple sclerosis; *DMF* dimethyl fumarate

Table 3 Characteristics of vaccine recommended and not recommended patients

	Recommended by TP N = 195	Not recommended by TP N = 217	P	OR	95%CI
Mean age, SD (years)	43 ± 6	42 ± 5	0.172	1.01	0.99–1.03
Mean disease duration (years)	9.8 ± 2.5	9.3 ± 0.5	0.11	0.97	0.44–1.02
Female gender, N (%)	164 (84)	150 (69)	0.001	2.3	1.4–3.8
Progressive MS*	36 (18.4)	51 (23.5)	0.023	0.49	0.27–0.90
Median EDSS	2.5 ± 0.5	3 ± 0.5	0.02	0.65	0.55–0.97
Ongoing treatment for MS	176 (90.3)	197 (90)	0.85	0.93	0.46–1.89
Current monoclonal antibodies for MS	41 (21)	45 (20.7)	0.92	0.97	0.57–1.65

*Includes secondary progressive multiple sclerosis and primary progressive multiple sclerosis patients

TP treating physician; *EDSS* expanded disability status scale

in 30% of included patients. Distribution and baseline characteristics of included patients are displayed in Table 1. A total of 47.3% of patients were recommended to receive the vaccine from the treating physician, and almost all these patients received the vaccine during the most recent season (186 of 195). Nearly 54% of patients did not receive the influenza vaccine, and the most frequent cause for this was that it was neither recommended nor mentioned by the treating physician (27.4%), for personal reasons (29%), and for contraindication to the vaccine as determined by their treating physician (17.3%) (Table 2 and Supplementary Table 2). Patients recommended to receive the vaccine were compared in clinical and demographic aspects with patients that did not receive the recommendation. Female gender (OR = 2.3, 95%CI 1.4–3.8, p = 0.001) was associated with an increased risk of recommendation, while a progressive form of MS and higher EDSS decreased the risk (OR = 0.49, 95%CI 0.27–0.90, p = 0.023; OR = 0.65, 95%CI 0.55–0.97, p = 0.02, respectively)) (Table 3). No other significant differences were identified between groups.

Discussion

In this study we found, after analyzing 412 MS patients from different countries from Latin America, that the influenza vaccine was not recommended during the most recent season in almost 54% of patients. Additionally, in this group, most patients were not recommended to receive the vaccine, nor did they even receive a contraindication from their treating physicians. In 15.5% of patients, the reason was non-access to the vaccine. The most significant difference between patients that were recommended from those that were not to receive the vaccine was female gender, while a higher EDSS and the progressive form of MS decreased the risk of being recommended for the vaccine.

In both patients and treating physicians, there are many concerns surrounding the influenza vaccine and MS. In MS patients, issues such as the immunological response to the vaccine, the risk of exacerbations in terms of clinical relapse and MRI activity, and disease progression impelled a heterogeneous approach in terms of recommendation in affected patients. Currently, data are insufficient to support or refute an association between MS exacerbation and influenza vaccination (Farez et al. 2019). Regarding effectiveness of the vaccine in this population, it is possible that MS patients have a higher likelihood of an insufficient response to influenza vaccination compared to controls (Farez et al. 2019). A meta-analysis showed that MS patients experienced increased odds of insufficient response to the influenza vaccination [OR = 1.87, 95% CI 1.07–3.27, I2 = 27%], but with CIs including values of limited clinical significance (Farez et al. 2019). Regarding the role of specific MS treatment and the response to the vaccine, it is probable that MS patients receiving interferon beta therapy do not have a meaningful reduction in the likelihood of seroprotection in response to influenza vaccination. A meta-analysis that provides class I evidence did not find meaningfully decreased odds of seroconversion [OR = 1.51; 95% CI 0.79–2.90, I2 = 55%]), suggesting its indication (Farez et al. 2019). In addition, MS patients receiving fingolimod may have a reduced likelihood of seroprotection from the influenza vaccine compared with MS patients who are not receiving treatment (OR = 0.35; 95% CI 0.21–0.57) (Farez et al. 2019). There is insufficient evidence to support or refute whether MS patients receiving natalizumab, alemtuzumab, teriflunomide, ocrelizumab, or cladribine differ in likelihood of response to influenza vaccination compared with different population of controls (Farez et al. 2019).

It is important to highlight that although some MS treatments could limit the immunological response to influenza vaccine (Farez et al. 2019), it is better to generate this response than not having it; hence, the recommendation is to prescribe it at the right time regardless the ongoing treatment (www.nationalmssociety.org).

Regarding the timing for influenza vaccination and the received MS treatment, sometimes, the best moment can be suggested (e.g., before initiation, 3 months after infusion). In real life, selecting the right moment is not always possible; consequently, it is preferable that the patient receives the vaccine instead missing the opportunity trying to find the right time.

Given that vaccination is a benefit in the general population as well as in MS patients (Fine et al. 2011), clinicians should indicate to their MS patients the influenza vaccination annually, unless there is a specific contraindication (e.g., previous severe reaction) (Farez et al. 2019). Despite this, we objectively described how this does not occur in the real-world setting. Nearly half of the patients evaluated did not receive a recommendation for vaccination. In patients in which the vaccine was recommended by a treating physician, almost all patients received the vaccine; therefore, patients generally follow recommendations provided by their physicians. In endeavoring to understand why patients are not recommended the influenza vaccine, we identified that male gender, a higher EDSS, and a progressive form of MS (secondary progressive and primary progressive MS) carry a reduced probability of being recommended the vaccine. Nonetheless, this information should be considered with caution.

Our study has many limitations. First, it was an online cross-sectional survey based on self-reported data. Second, the way that the survey was distributed (online collection) likely favored sample selection bias where younger patients, with more education and better access and use of technology, could have biased the data obtained. Third, the survey did not directly inquire treating physicians about their reasons for not recommending the vaccine; therefore, an indirect interpretation was drawn based on characteristics of patients that received a recommendation as opposed to those that did not. Fourth, although a large cohort from 12 LATAM countries was identified, it does not necessarily reflect the entire LATAM population (e.g., Brazil did not participate in the study). Related to this would be the uneven responses obtained from different countries. Another limitation to consider is the period in which the survey was delivered. It did not considered the diverse epidemiologic influenza season in the region, where a highest number of cases of influenza are observed from March to June in South America, while the highest number of cases is observed from October to March in North America. This is important due to the possibility of recall bias for those regions (or countries?) far away from the seasonal peak of influenza. However, given that most of the countries included share the seasonal peak, the risk of recall bias is low. Finally, it was MS organizations that confirmed that respondents were MS patients (see Method section); consequentially, the possibility that answers may have been derived from non-MS patients could exist, although this is low.

It is also important to note that the study was conducted in the context of isolation due to the COVID-19 pandemic and some attitudes could be consequently biased. However, the survey considered the previous year where no specific events occurred that significantly could bias the behavior towards vaccination.

In conclusion, despite the strong evidence for and recommendation of the influenza vaccine in MS patients, a limited number of patients in clinical practice received such recommendation. Causes for non-recommendation of the vaccine should be fully explored, and an increased awareness concerning this issue should be developed among treating physicians of MS patients in the region, especially during the COVID-19 pandemic.

Supplementary information The online version contains supplementary material available at https://doi.org/10.1007/s13365-021-01011-w.

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Declarations

Conflict of interest Juan Ignacio Rojas has received honoraria from Novartis as a scientific advisor. He has received travel grants and attended courses and conferences on behalf of Merck-Serono Argentina, Novartis Argentina. Liliana Patrucco has received honoraria from Novartis as a scientific advisor. He has received travel grants and attended courses and conferences on behalf of Merck-Serono Argentina, Novartis Argentina. Edgardo Cristiano has received honoraria from Novartis as a scientific advisor. He has received travel grants and attended courses and conferences on behalf of Merck-Serono Argentina, Novartis Argentina. Edgar Carnero Contentti has received personal compensation for consulting, serving on a scientific advisory board, speaking, or other activities with Biogen-Idec, Genzyme, Merck-Serono, Novartis, Teva, Roche and Bayer. Susana Giachello and Paula Henestroza has nothing to declare.

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