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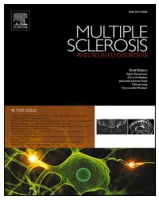

Original article

Evaluation of the use of high-efficacy treatments (HETs) in patients with relapsing-remitting multiple sclerosis in Argentina

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ABSTRACT

Background: Disease-modifying therapies (DMTs) in multiple sclerosis (MS) can be classified according to the efficacy in which they prevent inflammatory activity. To date, there are limited data regarding the use of high-efficacy treatments (HETs) in Latin America (LATAM). We aimed to analyze the use of HETs in Argentina, focusing on the clinical and sociodemographic characteristics of the patients who use these treatments and the changes in the trend of use over the years.

Methods: A retrospective cohort study was done using the Argentina MS patient registry, RelevarEM. Patients diagnosed with relapsing-remitting MS (RRMS) according to validated diagnostic criteria and under treatment with natalizumab, alemtuzumab, cladribine, rituximab or ocrelizumab were included.

Results: Out of 2450 RRMS patients under a DMT, 462 (19%) were on HETs. One third of those patients (35%) received HETs as the first treatment. The most frequent reason for switching to HETs was treatment failure to

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previous DMT (77%). The time from MS diagnosis to the first HET in treatment-naive patients was less than one year (IQR: 0–1 year) and in treatment-experienced patients it was 5 years (IQR: 3–9 years). Between 2015 and 2017 (P1), 729 patients included in RelevarEM started a new treatment, of which 85 (11.65%) were HETs. Between 2018 and 2020 (P2), 961 patients included in RelevarEM started a new treatment, of which 284 (29.55%) were HETs. When comparing P2 with P1, a significant increase in the use of HETs was observed ($p < 0.01$). The most frequently used HETs were alemtuzumab (50.59%) in P1, and cladribine (45.20%) in P2.
Conclusion: The demographic and clinical characteristics of patients under HET in Argentina were identified. Based on a real-world setting, we found a significant trend towards and a rapid increase in the use of HETs in clinical practice in patients with RRMS.

1. Introduction

Multiple sclerosis is a chronic disease that affects the central nervous system and can lead to significant disabilities (Filippi et al., 2018). In recent years, the MS treatment landscape has significantly evolved due to the introduction of increasingly effective disease-modifying therapies (DMTs). Disease-modifying therapies are commonly categorized as moderate-efficacy treatments or high-efficacy treatments (HETs) based on their ability to prevent clinical or radiological inflammatory disease (Filippi et al., 2022; Schmierer et al., 2021). Various clinical and paraclinical factors lead clinicians or treatment guidelines to recommend HETs in individuals with more aggressive forms of MS (Ransohoff et al., 2015). In those with moderately active MS, clinicians often adopt an escalation approach whereby the selected DMT is considered safer, subsequently escalating to more efficacious therapies, with more complex safety profiles, in the event of continuing disease activity (Giovannoni et al., 2015). However, in light of current knowledge, it is possible that the inevitable delay in starting a HET, imposed by escalation strategies, may result in a lost therapeutic opportunity (Harding et al., 2019). The limited effectiveness of the escalation strategy has induced some neurologists to use high-efficacy treatments (HETs) in early stages of the disease. The international scientific community consider the following approved immunomodulatory/immunosuppressive drugs as HETs: ocrelizumab, natalizumab, alemtuzumab, ofatumumab, cladribine, ozanimod, siponimod and fingolimod (Buron et al., 2020; Filippi et al., 2022). Although Rituximab is not approved for the treatment of MS, it is used off label and it was included in the analysis. Following optimal MS treatment guidelines is not always possible in real world clinical practice (Comi et al., 2017). This is especially true in developing countries such as Argentina, where access to HETs is not covered by some payers, delaying treatment initiation (Carnero Contentti et al., 2020, 2019). Despite the evidence showing that HETs are more efficacious in suppressing or delaying relapse activity when initiated early after disease onset (Rojas et al., 2022a) to date, there are few data on the characteristics of MS patients treated with HETs in Argentina. Therefore, the aim of this study was to analyze the use of HETs in Argentina, focusing on the clinical and sociodemographic characteristics of the patients who use these treatments and the changes in the trend of use over the years.

2. Methods

This retrospective coho ed with RRMS according to validated diagnostic criteria (Thompson et al., 2018) and under treatment with natalizumab, alemtuzumab, cladribine, rituximab or ocrelizumab. HETs have been approved in Argentina in the following years: natalizumab in 2010, alemtuzumab in 2014, cladribine in 2018 and ocrelizumab in 2019. Although rituximab is not locally approved for MS treatment, it is used off-label by local neurologists, including some medical experts. Thus, patients in the MS registry treated with rituximab, an anti-CD20-antibody, were included in this study. While many in the international scientific community and various regulatory entities consider fingolimod a HET (Buron et al., 2020), there are currently 10 generic formulations of fingolimod in the Argentinian market, none of which have demonstrated efficacy and safety in clinical trials and only the minority have bioequivalence studies. For this reason, fingolimod was not included in this study group of therapies.

Taking into consideration the availability of different DMTs in Argentina, we defined two periods of time (P): from 2015 to 2017 (P1) and from 2018 to 2020 (P2). A comparative analysis between these two periods was performed to assess the tendency of DMTs use over time. The following sociodemographic variables were collected from the registry: age, sex, place of residence, disability certificate. Clinical variables: MS duration and phenotype, Expanded Disability Status Scale (EDSS) at diagnosis and at study entry, current and past DMTs and rehabilitation status at study entry. The evaluation of the presence of highly active MS risk factors (Sorensen, 2011) prior to the initiation of current HETs were evaluated and correspond to a post hoc analysis whose objective was to improve the clinical description of the patient. These data were also obtained from the anonymized registry following all relevant local regulations. The reasons for treatment switching were registered: treatment failure, adverse events, adherence issues, access issues or others. Treatment failure was defined in accordance with Argentinean consensus recommendations on treatment failure in patients with RRMS (Cristiano et al., 2018). In addition to previous studies, adherence issues for patients under oral or injectable treatments were considered if they missed one or more doses in the 28 days prior to perform the treatment change or not (Koltuniuk and Rosinczuk, 2018; Wicks et al., 2011). For those patients undergoing treatment with monoclonal antibodies (rituximab, natalizumab and ocrelizumab), there is not a universal definition of non-adherence. For this study, it was identified as non-adherent if the patients under monoclonal antibodies treatments delayed any dose for more than 15 days in the 3 months prior to making the change in treatment (Alonso et al., 2022).

2.1. Sample size calculation

The scientific committee responsible for RelevarEM reported that, approximately, 12% of RRMS patients in the registry are currently treated with HETs. Assuming that 12% of the subjects in the population have the factor of interest, the study would require a sample size of 163 for estimating the expected proportion with 5% absolute precision and 95% confidence. In order to improve the robustness of the analysis of the secondary endpoints, as this is a non-interventional and non-prospective study, all patients in the registry that fulfilled the inclusion and exclusion criteria were included in the study.

2.2. Statistical analysis

Data analysis was conducted using SPSS Statistics v22. Descriptive analyses of all variables were carried out. Results were presented as frequencies, percentages, ranges, mean and standard deviation values. Comparisons between the two groups were analyzed using Chi-square or Fisher's exact tests for categorical variables. Statistical significance was set at $p< 0.05$.

3. Results

3.1. Sociodemographic, clinical and pharmacological history of patients under HETs treatment

At data cut off (September 16th, 2021), RelevarEM included 2748 patients with a diagnosis of RRMS and 2450 (89.16%) of those patients were under treatment with a DMT. Of the treated patients, 462 (18.85%) were at the time on HETs and 315 of them were included in this analysis as they met the inclusion and exclusion criteria (Fig. 1). Of them, 67.7% were female, the mean age was 37±10.9 years at study entry, and they had a median disease duration of 6 years (IQR 4 −10). Most of the patients were residents of Buenos Aires (34.8%). Demographic and clinical characteristics are summarized in Table 1. More than one-third of patients (35%) received HETs as their first treatment, while the rest started HETs after switching from a prior DMT (Fig. 2). The treatment lines for each HET are detailed in supplementary Table 1. The most frequent reason for switching to current HETs was treatment failure to previous DMT (77%). Table 2 summarizes the most important characteristics of the pharmacological history of patients prior to the initiation of current HETs. Fingolimod was the most frequent treatment prior to current HET (32%). Additionally, the time from MS diagnosis to the first HET in treatment-naive patients was shorter than one year (IQR: 0–1 year) and in treatment-experienced patients it was 5 years (IQR: 3–9 years). Almost all patients (97.46%) presented at least one characteristic associated with high-activity MS prior to the initiation of current HETs. More than two thirds of the patients treated with HETs presented clinical or radiological activity in the previous 12 months before starting the current HET (Table 3).

3.2. Usage trend of HETs

A total of 1690 patients included in RelevarEM started some treatment in the 5 years prior to data cut off, of which 21.83% were HETs. Between 2015 and 2017 (P1) 729 patients included in RelevarEM started a new treatment, of which 85 (11.65%) were HETs. Between 2018 and 2020 (P2) 961 patients included in RelevarEM started a new treatment, of which 284 (29.55%) were HETs. When comparing P2 with P1, a significant increase in the use of HETs is observed (p <0.01). The most commonly used HETs were alemtuzumab in 43 patients (50.59%) in P1, while cladribine was prescribed in 129 patients (45.20%) in P2. Interestingly, a decrease in the prescription of natalizumab and alemtuzumab was found when comparing P2 with P1. The increase in the prescription of HETs in P2 was mainly associated with the approval of cladribine and ocrelizumab in this period. (Table 4).

Table 1
Demographic and clinical characteristics of the included patients (n=315).

Variable	Result
Gender, n (%)	
- Female	213 (67.7)
- Male	102 (32.4)
Residence, n (%)	
- Buenos Aires City	104 (33.2)
- Buenos Aires province	100 (31.6)
- Rest of Argentina	111 (35.2)
Charlson score, n (%)	
- 0	290 (92)
- ≥1	25 (8)
Mean age at study entry, SD (years)	37 (10.9)
Mean age at onset of symptoms, SD (years)	28,7±9.7
Mean age at diagnosis, SD (years)*	30,1±9.7
Median time MS duration, IQR (years)	6 (4–10)
Patients currently in rehabilitation*, n (%)	58 (18.5)
Mean EDSS score at diagnosis, SD	2,3±1,4
Mean EDSS score at study entry, SD	2,8±2
Positive OCB, n (%)	255 (81.1)
Patients with infratentorial lesions on MRI at the time of diagnosis	241 (76.6)
Patients with spinal cord lesions on MRI at the time of diagnosis	223 (70.9)
Patients with contrast-enhancing lesions on first MRI	203 (64.6)

* Mean (SD) **Median (IQR). MS: Multiple sclerosis. EDSS: Expanded Disability Status Scale. OCB: oligoclonal bands. MRI: magnetic resonance imaging. SD: standard deviation. IQR: interquartile range.

4. Discussion

A variety of pharmacological therapies for MS has become available during the last decade. In particular, several more efficacious yet possibly more hazardous DMTs, called “High Efficacy Therapies” are now widely available to treat RRMS patients (Meca-Lallana et al., 2021). The introduction of these HETs in the treatment of MS has changed the paradigm of DMTs usage worldwide. To date, reports regarding the use of HET in RRMS patients are scarce in our country (Rojas et al., 2022a). In this sense, we analyzed the largest Argentinian database that collects patients with MS. We have identified an increasing trend toward the use of HETs in Argentina in relation to the availability of the drug. Furthermore, we found a statistically significant increase in the use of HETs in the last 5 years. In the second analyzed period (from 2018 to

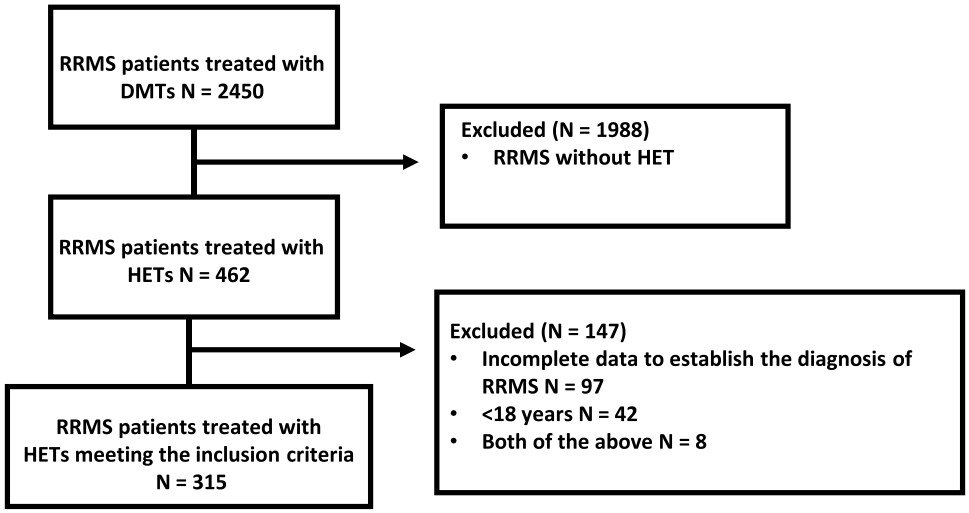

Fig. 1. Study Flowchart of Patients’ Disposition.
RRMS: relapsing-remitting multiple sclerosis. DMTs: disease-modifying therapies HETs: high efficacy therapies. * The database for this cohort study was locked in September 2021.

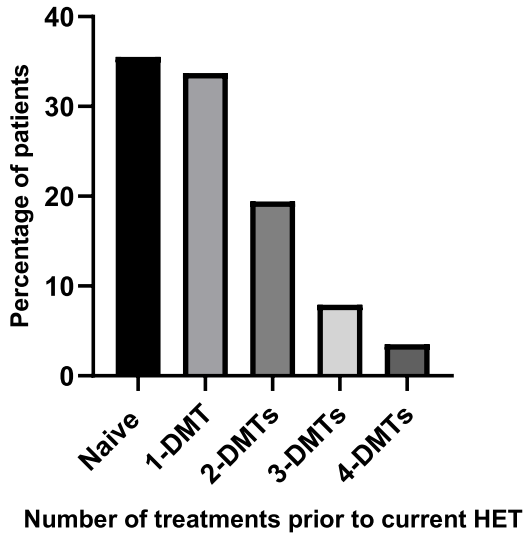

Fig. 2. Pharmacological history prior to current HET/Rituximab (*n*=315). Naive: patients without previous treatments prior current HETs. 1-DMT: patients with 1 treatment prior to current HET. 2-DMTs: patients with 2 treatment prior to current HET. 3-DMTs: patients with 3 treatment prior to current HET. 4-DMTs: patients with 4 or more treatment prior to current HET. HETs: high-efficacy treatments

Table 2
Pharmacological history prior to the initiation of current HETs/Rituximab (*n*=315).

Naïve patients	112 (35)
Patients with prior use of DMTs	203 (65)
Last treatment prior to current HETs (n 203)	
Interferon, n (%)	44 (21.7)
Glatiramer acetate, n (%)	16 (7.9)
Teriflunomide, n (%)	16 (7.9)
Fingolimod, n (%)	66 (32.5)
Dimethyl fumarate, n (%)	21 (10.3)
Natalizumab, n (%)	30 (14.8)
Alemtuzumab, n (%)	6 (2.9)
Rituximab, n (%)	1 (0.5)
Cladribine, n (%)	3 (1.5)
Main reason for switching to HETs (n 203)	
- Treatment failure, n (%)	156 (77)
- Adverse events, n (%)	12 (5.8)
- Adherence, n (%)	5 (2.4)
- Other, n (%)	30 (14.5)
Median time from MS diagnosis to the beginning of the first DMT (IQR), days	119 (45–356)
Median time from MS diagnosis to the beginning of the first HETs in naïve patients (IQR), years	0 (0–1)
Median time from MS diagnosis to the beginning of the first HETs in patients with prior use of DMTs (IQR), years	5 (3–9)
Median time from first non-HETs to first HETs treatment, (IQR) years	4 (2–8)
Median of number of DMT between the 1st DMT and 1st HET	1 (1–2)

**Median (IQR). MS: multiple sclerosis. DMTs: Disease modifying therapies. HETs: High-efficacy treatments. IQR: interquartile range.

2020), we observed a decrease in the prescription of alemtuzumab and natalizumab in relation to the approval by ANMAT (Argentinian Administration of Drugs, Food and Medical Devices) of cladribine and ocrelizumab. A recent Argentinian research (Negrotto et al., 2022) has revealed an increase in the ratio of naïve/switch patients that initiated with cladribine tablets during the observational period (from April 16th 2018 to March 31st 2021). The authors suggest that, this change in cladribine tablets prescription could theoretically be related to the increasing acceptance that initiating treatment with highly effective therapies is more effective than the escalation approach in preventing disability in patients with RRMS. Additionally, treatment with

Table 3
Presence of highly active MS risk factors prior to the initiation of current HETs/Rituximab (*n*=315).

Variable	Results n, (%)
Relapses in the 12 months prior to the start of current treatment*	238 (75.3)
MRI activity in the 12 months prior to the start of current treatment (gadolinium + or new or enlarged T2 lesions)*	250 (79.1)
⩾3 EDSS points in the 12 months prior to starting current treatment*	74 (23.4)
⩾1 spinal cord injury at any time in the course and prior to the start of current treatment*	231 (73.1)
Incomplete recovery from a relapse prior to the start of current treatment*	184 (58.2)
Short interval between attacks (less than 6 months) at any time during the course and prior to the start of current treatment*	138 (43.7)
Therapeutic failure prior to the start of current treatment	156 (49.5%)

MRI: Magnetic resonance imaging. EDSS: Expanded Disability Status Scale.
* Post hoc aggregated data.

Table 4
Evaluation of the use of DMTs in different periods of time (*n*=1690).

Treatment	P1 (%)	P2 (%)	p-value
HETs + Rituximab	*85 (11.65)*¥	*284 (29.55)* ¥¥	*p < 0.01**
Natalizumab	39 (45.88) †	71 (25.0) †	p < 0.01*
Alemtuzumab	43 (50.59) †	33 (11.62) †	p < 0.01*
Ocrelizumab	–	36 (12.68) †	–
Cladribine	–	129 (45.42%) †	–
Rituximab (off label)	2 (2.35) †	15 (5.28) †	p 0.37**
No HETs	*644 (88.35)*¥¥¥	*677 (70.45)*¥¥¥¥	
Interferon	78 (12.11) ††	58 (8.57) ††	p 0.042*
Glatiramer acetate	37 (5.75) ††	30 (4.43) ††	p 0.33*
Fingolimod	338 (52.48) ††	270 (39.88) ††	p < 0.01*
Dimethyl fumarate	101 (15.68) ††	160 (23.63) ††	p < 0.01*
Teriflunomide	88 (13.66) ††	125 (18.46) ††	p 0.021*

* Chi-square.
** Fisher test. P1: Period between 2015 and 2017 P2: Period between 2018 and 2020.
¥ Percentage of patients treated with HETs over the total treatments in P1.
¥¥ Percentage of patients treated with HETs over the total treatments in P2.
¥¥¥ Percentage of patients treated with no-HETs over the total treatments in P1.
¥¥¥¥ Percentage of patients treated with no-HETs over the total treatments in P2.
† Percentage of patients treated with each HET over the total of HETs in P1 and P2.
†† Percentage of patients treated with each no-HET over the total of HETs in P1 and P2. DMTs: disease-modifying therapies. HETs: high-efficacy treatments.

cladribine has been shown to be associated with a low treatment burden and high adherence rates (Negrotto et al., 2022). Regarding the use of ocrelizumab, our findings are in line with previous reports showing an increase in the prescription of anti-CD20 drugs (ocrelizumab and ofatumumab) in Europe, the United Kingdom, and United States (Baynton, 2022). In this report, when comparing Q4 2019 and Q4 2021, note was made of an increase in the use of anti-CD20 (ocrelizumab and ofatumumab) both as 2nd line and 1st line of treatment. Admittedly, this increase is likely to be influenced partly by anti-CD20 drug availability and time on market but decreases in platform therapy usage over these same timeframes suggests a continued move towards more targeted, newer, high-efficacy treatments versus more traditional options (Baynton, 2022). Even though, the sociodemographical characteristics have led to the choice of HETs were not considered in this work, the distribution of the included patients was equitable among the different regions of Argentina. These same results were observed when we previously showed the increasing trend in the use of oral treatments for MS versus the more traditional 'platform therapies' such as interferons and glatiramer acetate (Alonso et al., 2021). These previously published data, together with data from current research, demonstrate that the

increasing trend in the use of new treatments could be due to the natural learning curve among neurologists related to knowledge and availability of drugs. Efficacy remains the primary reason for therapy choice in our reported patients initiating MS therapy.

Regarding sociodemographic characteristics of the patients under HETs, the majority reside in large cities in Argentina, with greater access to specialized centers in MS. The difficulties and inequalities in access to DMTs in Argentina were previously reported (Carnero Contentti et al., 2020, 2019). In this regard, Argentinean MS patients receiving care from the private sector reported greater access to DMTs and fewer problems obtaining them compared to those treated at public institutions. Furthermore, lack of insurance, longer MS duration, lower level of education and unemployment were independently associated with inappropriate delivery of DMTs (Carnero Contentti et al., 2020, 2019).

Unfortunately, and in line with access problems, we were able to observe that a low percentage of patients were treated with HETs as initial treatment. The early use of HETs as treatment strategy is increasing worldwide and has been shown to be beneficial in the long-term due to a lower likelihood of MS-related disability accumulation in patients who used them compared to those who started treatment with a non-HETs (Brown et al., 2019; Harding et al., 2019; Iaffaldano et al., 2021). In the present study, the most commonly used DMTs previous to HETs were oral drugs, including fingolimod (previously our group have shown that fingolimod is a widely used DMT in our country (Alonso et al., 2021).

Most patient on HETs had presented clinical or radiological activity in the 12 months prior to treatment initiation - demonstrating failures to the previous treatment. Other poor prognostic variables associated with starting HET such as incomplete recovery from a relapse at any time throughout the disease course prior to the start of current treatment, short interval between attacks (less than 6 months) at any time throughout disease course and prior to the start of current treatment were found in half of the patients currently using HET (Sorensen, 2011).

Interestingly, a large percentage of patients under HETs had at least one spinal cord lesion. These clinical and radiological characteristics have been related to a greater severity of MS (Iacobaeus et al., 2020). Both disease activity and disease severity are essential parameters when considering the right treatment for patients. Patients with highly active MS have a clear benefit if they are given rapid access to HETs (Iacobaeus et al., 2020). Different studies have shown that early intervention with HETs versus escalation therapy, regardless of MS activity, could protect patients from irreversible damage and disabilities. Additionally, this strategy might also prevent the development of a secondary progressive course, which until now lacks effective therapy (Rojas et al., 2022a; Rush et al., 2015).

We are aware this study has limitations and, therefore, results should be interpreted with caution. First, this is a retrospective study which could not evaluate all the variables related to the choice of treatments. For example, patient and/or physician preferences could not be evaluated (Rojas et al., 2022b). Second, as mentioned in the methodology section, we did not include fingolimod in the HET group due to the large number of generic formulations. This could limit the extrapolation of results and conclusions to other regions. However, there is no universally adopted classification for DMTs. According to the Association of British Neurologists in the revised guidelines for prescribing DMTs in MS (2015), fingolimod is considered a moderately effective DMT (Neil Scolding, 2015). Furthermore, observational studies comparing fingolimod and other DMTs consistently indicated clinical outcomes comparable to those of dimethyl fumarate (Fox et al., 2017; Hersh et al., 2017; Hou et al., 2021; Ontaneda et al., 2019; Vollmer et al., 2017, 2018), yet exhibiting a lower effectiveness when compared to monoclonal antibodies (Boremalm et al., 2019; Granqvist et al., 2018; Hou et al., 2021; Vollmer et al., 2020). Third, we did not have data on some potentially important patient characteristics, such as cognitive level, educational attainment, patient-reported outcomes (PROs), which may limit our ability to explore disparities in use of HETs by these factors. Finally, data on access were not collected, which may be an important factor in determining treatment decisions in patients with MS. It is important to clarify that, unlike other countries in LATAM where there are regulations for the prescription of DMTs, in Argentina, there are no government guidelines on treatments for MS. Therefore, access to DMTs directly depends on the type of social coverage.

5. Conclusion

This study evaluated the use of HETs in MS LATAM population, including drug profile and patient profile. Future research in our region is needed to demonstrate benefits in terms of disease evolution and disability accumulation as they were observed in other countries using HETs in clinical practice.

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CRediT authorship contribution statement

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Declaration of Competing Interest

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Supplementary materials

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