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Original article

Prescription trends of disease-modifying treatments for multiple sclerosis in Iran over the past 30 years

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ABSTRACT

Background: Iran, as a middle income country, is one of the places with high and rising prevalence of multiple sclerosis (MS). Regarding the substantial economic burden, reviewing the trend in prescribed disease modifying treatments (DMTs) could be of help. Here we studied the DMT information of nearly 14000 MS cases and its trends change for 30 years to improve health services to patients.

Methods: The population base of this descriptive-analytical (cross-sectional) study consisted of all MS patients in the nationwide MS registry of Iran (NMSRI), up to August 1, 2021. Registrars from 15 provinces, 24 cities, 13 hospitals,8 MS associations, 16 private offices, and 7 clinics had entered the data.

Results: Overall, 14316 cases were enrolled. The majority (76.1%) were female. The youngest and eldest patients were 5 and 78 years old, respectively. Diagnosis delay was under one year in most cases (median: 0, IQR: 0 – 1). Most (61.4%) had RRMS. Generally, platform injectables (IFN beta, glatiramer acetate) were the most used DMTs until 2010. It seems that introduction of newer agents (antiCD20s and oral DMTs) resulted in a decrease in the use of former drugs since around 2015. Some unusual practices are prominent such as using not approved DMTs for PPMS over the years, or administering high efficacy drugs like natalizumab for CIS. The results indicate the remaining popularity of first line injectable DMTs in female and pediatric patients.

Discussion: Mean age (SD) at onset in our study (29 ± 8.8) is near the statistics in Asia and Oceania (28 ± 0.7). Concerns about COVID-19 had a noticeable impact on administering high efficacy drugs like rituximab and

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fingolimod. However, in male patients this approach has not been the case. It may be related to more aggressive disease course in this group. The other possible explanation could be planning for pregnancy in female cases. The popularity of platform injectable drugs in pediatric MS may be related to its favorable safety profile over the years. Another point in this group, is the superiority of rituximab over other highly efficient medications.

1. Introduction

For nearly 150 years, since the first introduction of multiple sclerosis (MS) by Charcot (Charcot, 1965), attempts have been made to overcome the disease and its disabling consequences. In 1951, cortisone was found to be effective in controlling MS relapses (Glaser and Merritt, 1951). The first approved disease-modifying treatment (DMT) for the cases with relapsing-remitting MS (RRMS) was interferon beta-1b that was approved by Food and Drug Administration (FDA) in 1993, and by European Medicines Agency (EMA) in 1995 (Finkelsztejn, 2014). Since then, notable treatments with various mechanisms of actions have been established. Selecting the best option for an individual patient has become a state of art. Iran, as a middle income country, is one of the places with high and rising prevalence of MS (Azami et al., 2019). Its prevalence is estimated to be 100/ 100000 which is considered notable (Mirmosayyeb et al., 2021). Regarding the substantial economic burden (Hartung, 2021), and the superimposed impact of international sanctions that has limited the Iranian patients' access to numerous drugs (Sahraian et al., 2021), some Iranian pharmaceutical companies has attempted to manufacture DMTs inside the country. Many of these drugs have been approved by Iranian Food and Drug Administration (IFDA), after a comprehensive review based on regulatory guidelines. Reviewing the trend in prescribed DMTs could be of help in understanding the status, appraising, and finally promoting it. Here we studied the MS treatment information of nearly 14000 Iranian MS cases since 1990.

2. Material and methods

The population base of this descriptive-analytical (cross-sectional) study consisted of all MS patients in nationwide MS registry of Iran (NMSRI) (Shahin et al., 2019), up to August 1, 2021. This validated dataset has enabled researchers and subsequently policy makers to get a better image of different aspects of the condition in a national level. Registrars from 15 provinces, 24 cities, 13 hospitals, 8 MS societies, 16 private offices, and 7 clinics had entered the data. MS diagnosis was confirmed by a neurologist based on Mc Donald criteria 2017 (Thompson et al., 2018). Information on demographic (age, gender), disease characteristics (MS type (RRMS, secondary progressive (SP), primary progressive (PP), clinically isolated syndrome (CIS)), age at onset and diagnosis, the Expanded Disability Status Scale (EDSS) calculated by neurologists), and prescribed DMT were extracted. Diagnostic delay was defined as the time lag between disease onset and final diagnosis of MS. The time was categorized to five-year intervals. Admins had to check for and resolve any upcoming problem. Incomplete files were not included. Duplication was controlled by national code number.

For further investigation, the patients were categorized based on their age at onset (before 18, 18 to 50, after 50 years of age). Those with age at onset under 18, who were still under 18 were separated in order to exclusively investigate the prescription pattern in pediatric MS. The patients with the age of onset after 50 were also analyzed for used DMTs.

In cases with SPMS the exact time of progression may not be clear so it may be difficult to indicate which drug was used in relapsing period and which in progressive course. Therefore this group was not evaluated separately.

Descriptive analysis (frequency, percentage, mean) was applied in SPSS® IBM version 26.

2.1. Ethical issues

To guarantee the privacy of the patients' data, limited access to the registry was defined for each neurologist/registrar. Study goals were explained to the patients. Enrollment was optional. The study protocol was accepted by the institutional review boards (IRB) of ethics committee of Tehran university of medical sciences (Ref. no. IR.TUMS.VCR.REC.1397.361).

3. Results

Overall, 14316 cases were enrolled. The majority (76.1%) were female. The youngest and eldest patients were 5 and 78 years old, respectively. MS onset was before the age of 18 in 1015 (7%) of cases. Late-onset MS (the appearance of symptoms after 50 years of age) was detected in 203 (1.4%). Diagnosis delay was under one year in most cases (median: 0, IQR: 0 – 1). Most (61.4%) had RRMS. The basic characteristics are summarized in Table 1.

The schema of DMT trend in general is shown in Fig. 1. Generally, platform injectables (IFN beta, glatiramer acetate) were the most used DMTs until 2010. It seems that introduction of newer agents (antiCD20s and oral DMTs) resulted in a decrease in the use of former drugs since around 2015.

Regarding special groups, Fig. 2 demonstrates prescription attitude in PPMS and Fig. 3 contains information on prescription attitude in CIS cases over time. Some unusual practices are prominent such as using not approved DMTs for PPMS over the years, or administering high efficacy

Table 1
Basic characteristics of Iranian MS patients.

Variable	N (%)
Gender	
Female	10891 (76.1)
Male	3425 (23.9)
Mean age at present (SD)	36.5 (9.7)
Mean age at disease onset (SD)	29.0 (8.8)
Disease onset before 18	1015 (7.0)
Disease onset between 18 to 50	12059 (84.2)
Disease onset after 50	203 (1.4)
Disease onset after 60	13
Mean age at diagnosis (SD)	30.1 (9.0)
Median diagnostic delay (IQR)	0 (0 - 1)
MS type	
CIS	1027 (7.2)
RR	8795 (61.4)
SP	1771 (12.1)
PP	746 (5.2)
Missing	2007 (14)
Median EDSS (IQR)	1.5 (1 - 3)
Diagnosis time (5 year intervals)	
1975	3
1980	9
1985	13
1990	86
1995	309
2000	876
2005	1969
2010	3781
2015	5913
Missing	1357

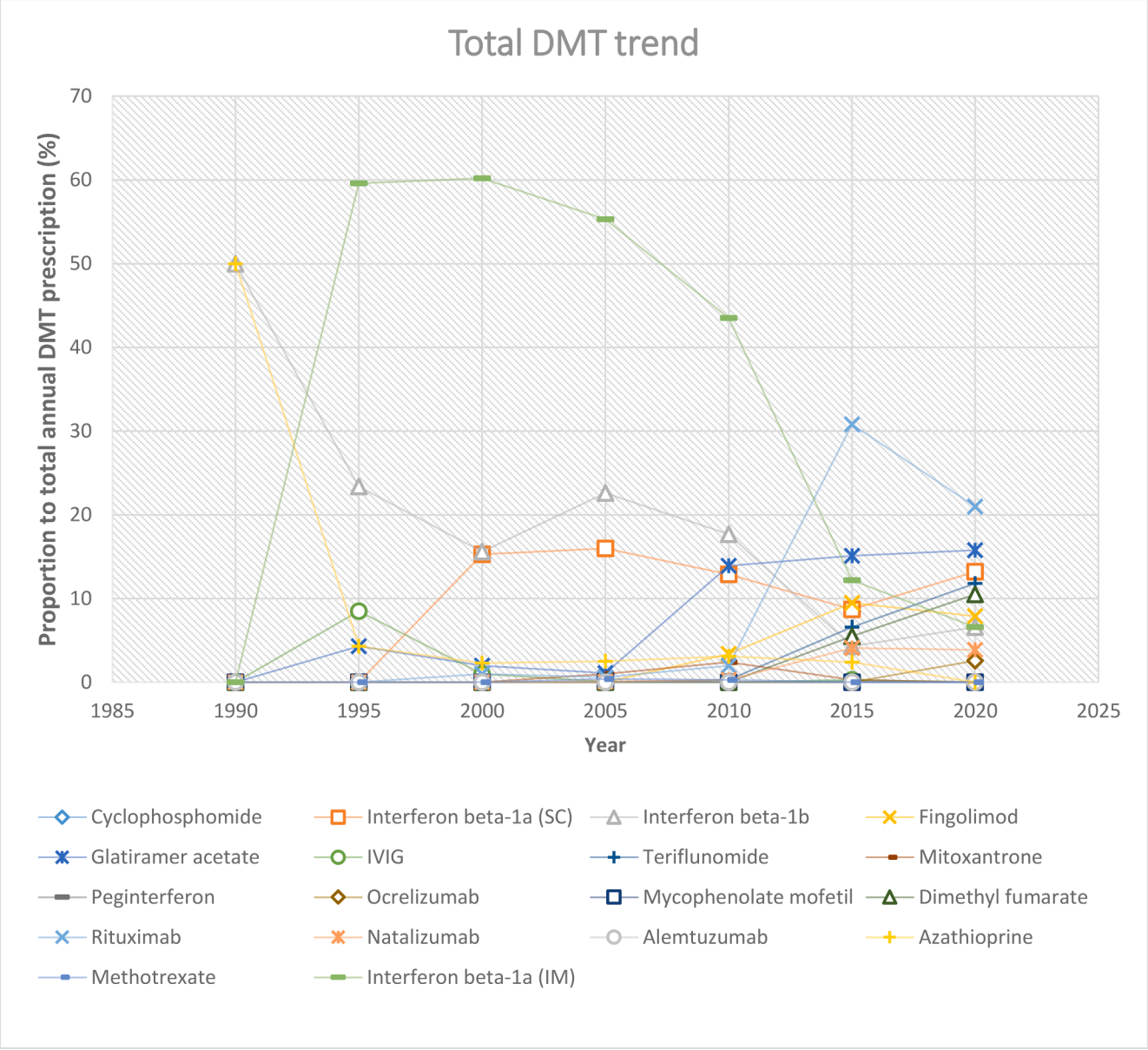

Fig. 1. Prescribed DMTs in Iranian MS population over time.

drugs like natalizumab for CIS.

The trend in females and males has some differences as shown in Fig. 4. The graphs indicate the remaining popularity of first line injectable DMTs in female patients.

Those with age at onset under 18, who are still under 18 were investigated separately (Table 2). Platform drugs (interferon-beta 1a (42%) and 1b (3%), glatiramer acetate (10%)) seem to be the most prescribed DMTs in our pediatric population.

Fig. 5 reveals the prescription attitude in late-onset MS. 13 cases with very late-onset MS (age at first symptom more than 60 years old) were identified. Of these, 8 had relapsing forms (1 RIS, 7, RRMS) and the others were in progressive phases (3 SPMS, 2 PPMS). Aside from one patient who was diagnosed in 2007, the first symptoms of the other patients manifested after 2014. Only five case of very late-onset MS received DMT (interferon beta-1b (2007), interferon beta-1a (IM) (2015), mycophenolate mofetil (2018), glatiramer acetate (2020), ocrelizumab (2021)).

4. Discussion

This study depicts the Iranian clinicians' approach to MS treatment over about 30 years by tracking the DMT prescription patterns. The results highlight the impact of newly introduced drugs and also the recent pandemic on selecting DMTs. To our knowledge, there is one previous report of DMT prescription information from Iran. The mentioned study, which was a part of a more extensive research, evaluated 2358 MS cases in about 10-year period. The administered DMT was only recorded for 250 patients (Moradi et al., 2021) which is way more limited than our study population. Besides no data on the trend during the time and in different types of MS is available.

Mean age (SD) at onset in our study 29 (± 8.8) is near the statistics in Asia and Oceania 28 (± 0.7) (Forouhari et al., 2021). Significant female predominance and higher frequency of RRMS were as anticipated.

It appears that, as predicted, the first-line injectable drugs have lost their superiority over time once drugs with higher efficacy and easier administration protocols have been introduced. Oral treatments, like teriflunemide and dimethyl fumarate (DMF), have become more popular

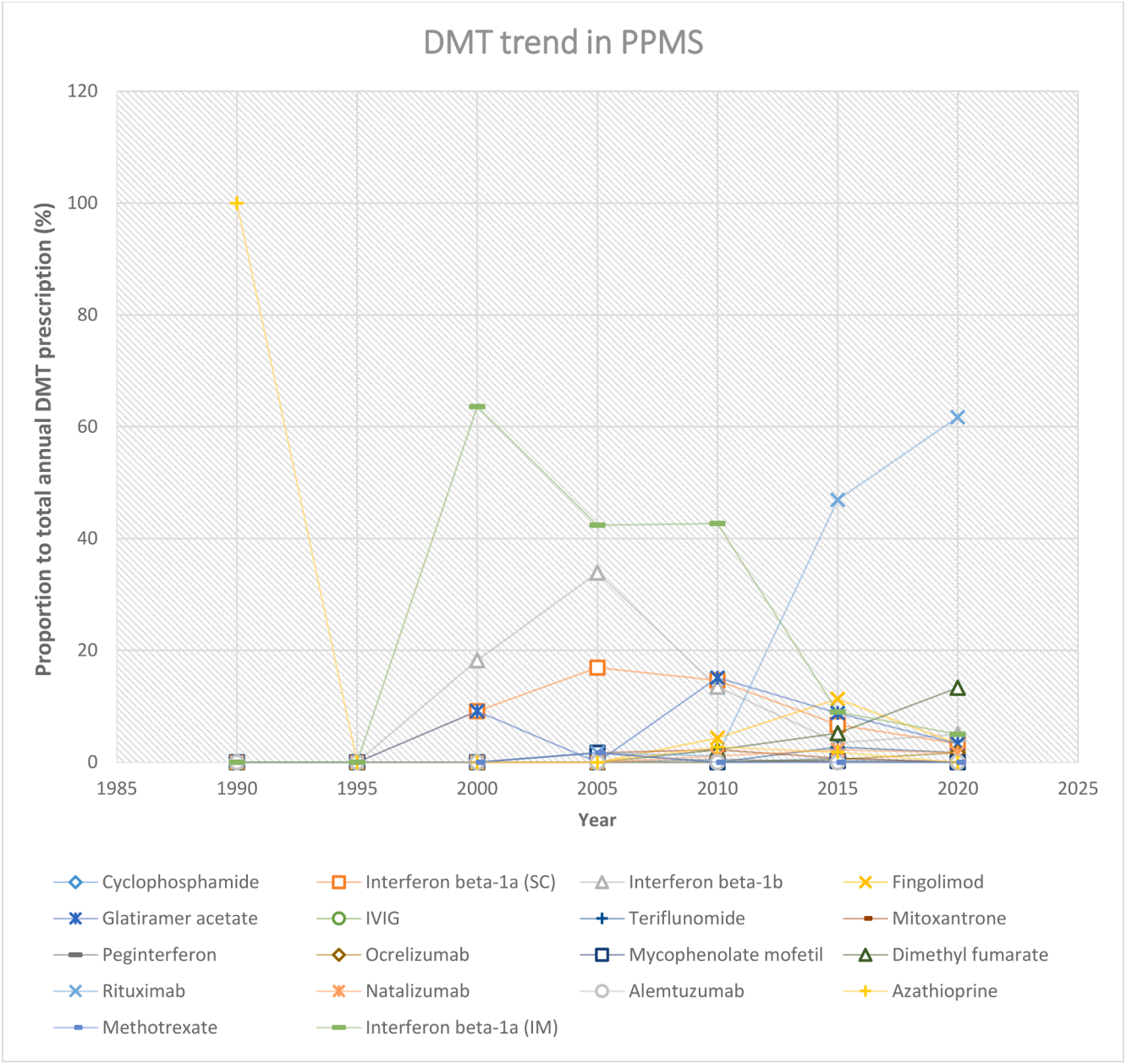

Fig. 2. The time trend of prescribed DMTs in Iranian PPMS cases.

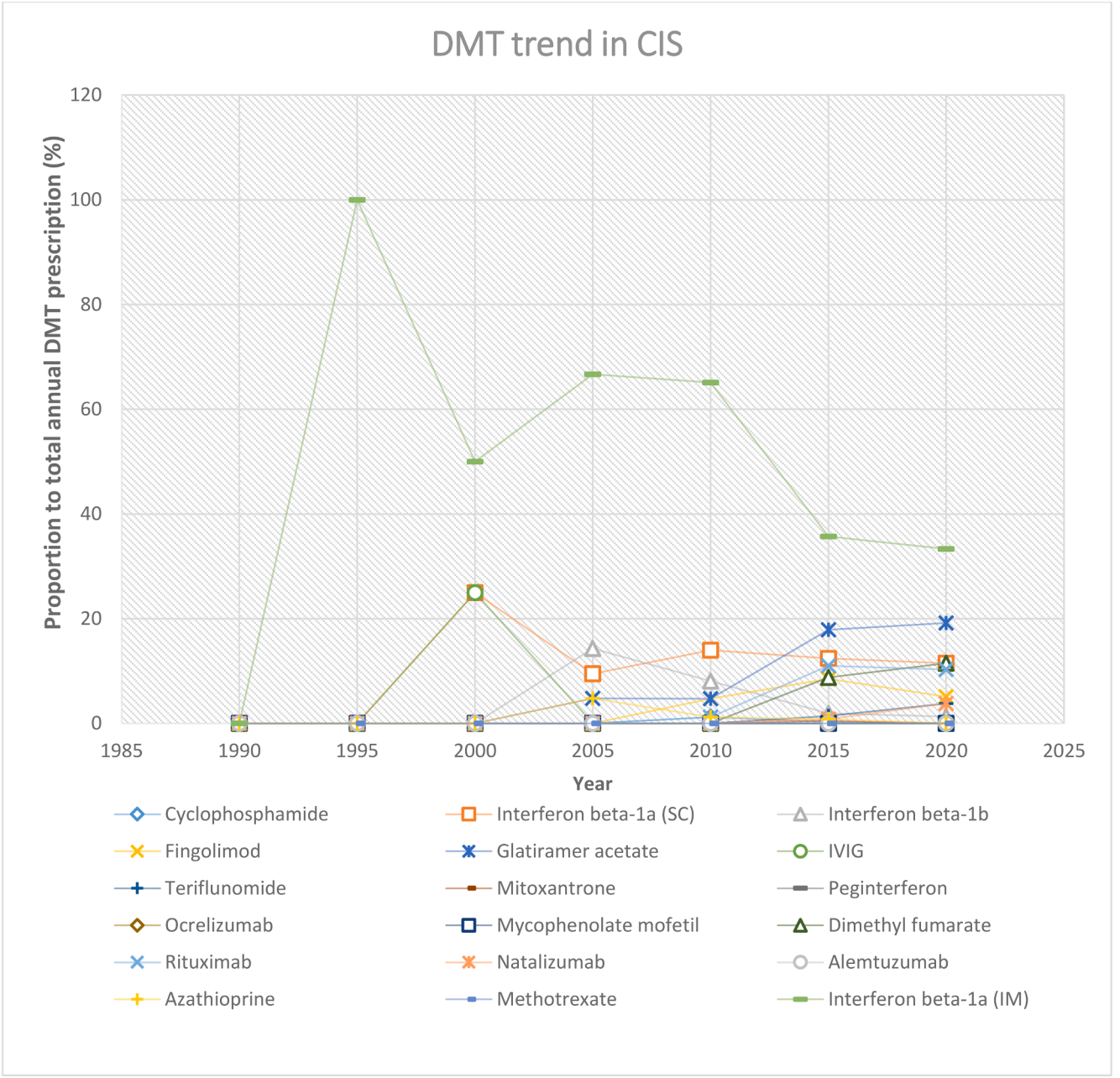

Fig. 3. The trend of prescribed DMTs in Iranian CIS cases.

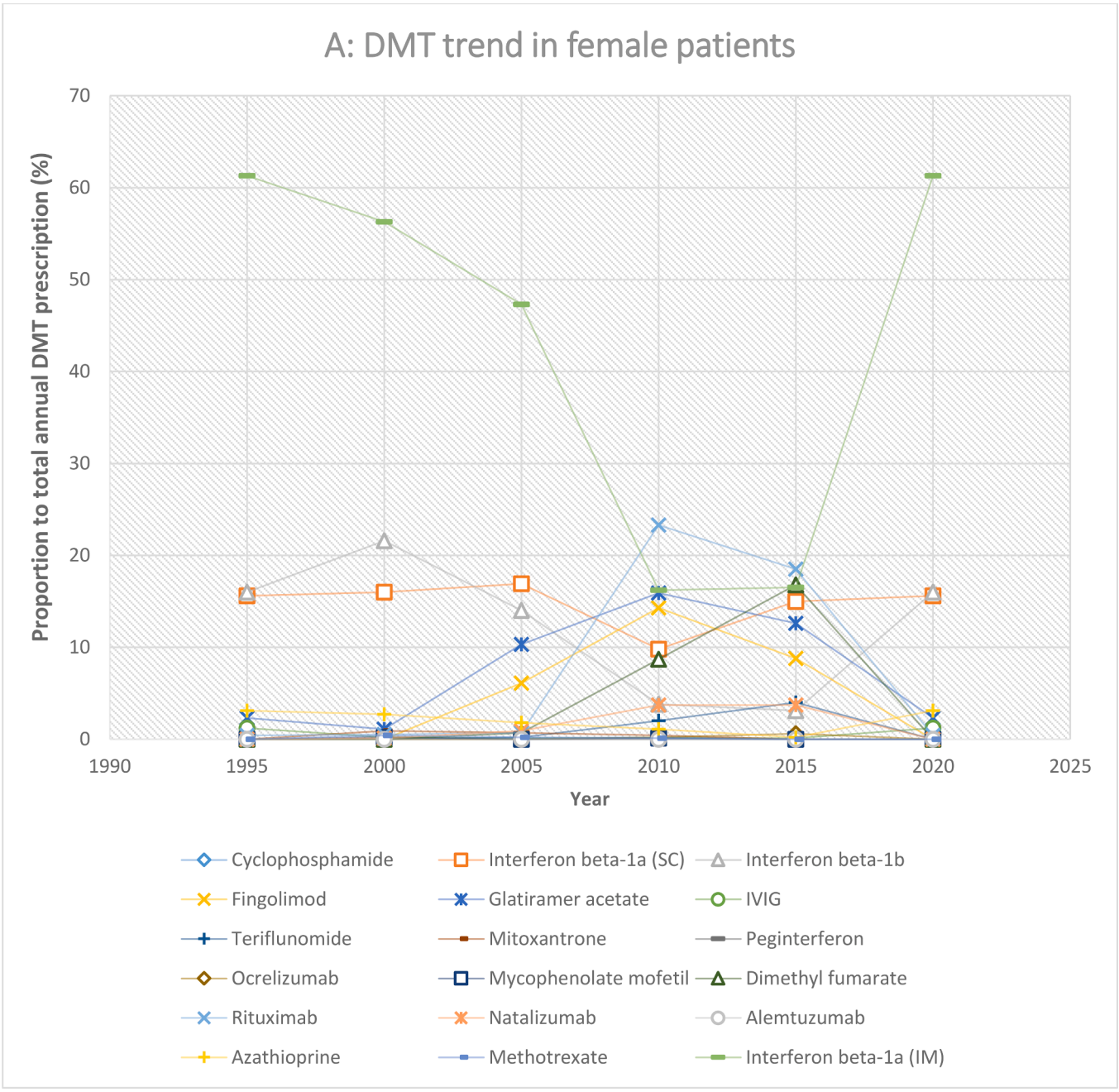

Fig. 4. DMT trend over the years in female (A) and male (B) patients.

during the recent years. The "hit it hard" approach has led to more frequent prescription of newer high efficacy drugs like natalizumab and rituximab. Although, those with more side effects (cyclophosphamide, mitoxantrone) are preferentially preserved for rescue therapy, where no other safer option is beneficial (Ruggieri et al., 2018).

One noticeable issue is the trend change related to the pandemic. Concerns about COVID-19 had a noticeable impact on administering high efficacy drugs like rituximab and fingolimod. However, in male patients this approach has not been the case. It may be related to more aggressive disease course in this group (Ribbons et al., 2015). The other possible explanation could be planning for pregnancy in female cases.

As shown in Fig. 2, some patients with PPMS have received nonstandard treatments (for instance, in 2020, 16.6% was under platform injectable agents). Also, there are some CIS cases under high potency drugs like natalizumab (1.7%) and rituximab (61.7%). There may be two explanations here. Either the diagnosis was not entered correctly, or there is need to upgrade clinicians' knowledge of evidence-based approach to MS.

Considering substantial differences, the best approach to pediatric onset MS is still a matter of debate. Hence, the trend in DMT prescription in pediatric patients seems notable. New approved drugs for this age range have broaden the appropriate options for individual cases. In addition, oral drugs have made drug administration much easier for children. Still, the popularity of platform drugs (interferon-beta 1a (42%) and 1b (3%), glatiramer acetate (10%)) in our pediatric population is similar to other countries (Frahm et al., 2021; Abdel-Mannan et al., 2021; Erdal et al., 2020; Greenberg et al., 2021; Fragomeni et al., 2018). It may be related to their favorable safety profile over the years.

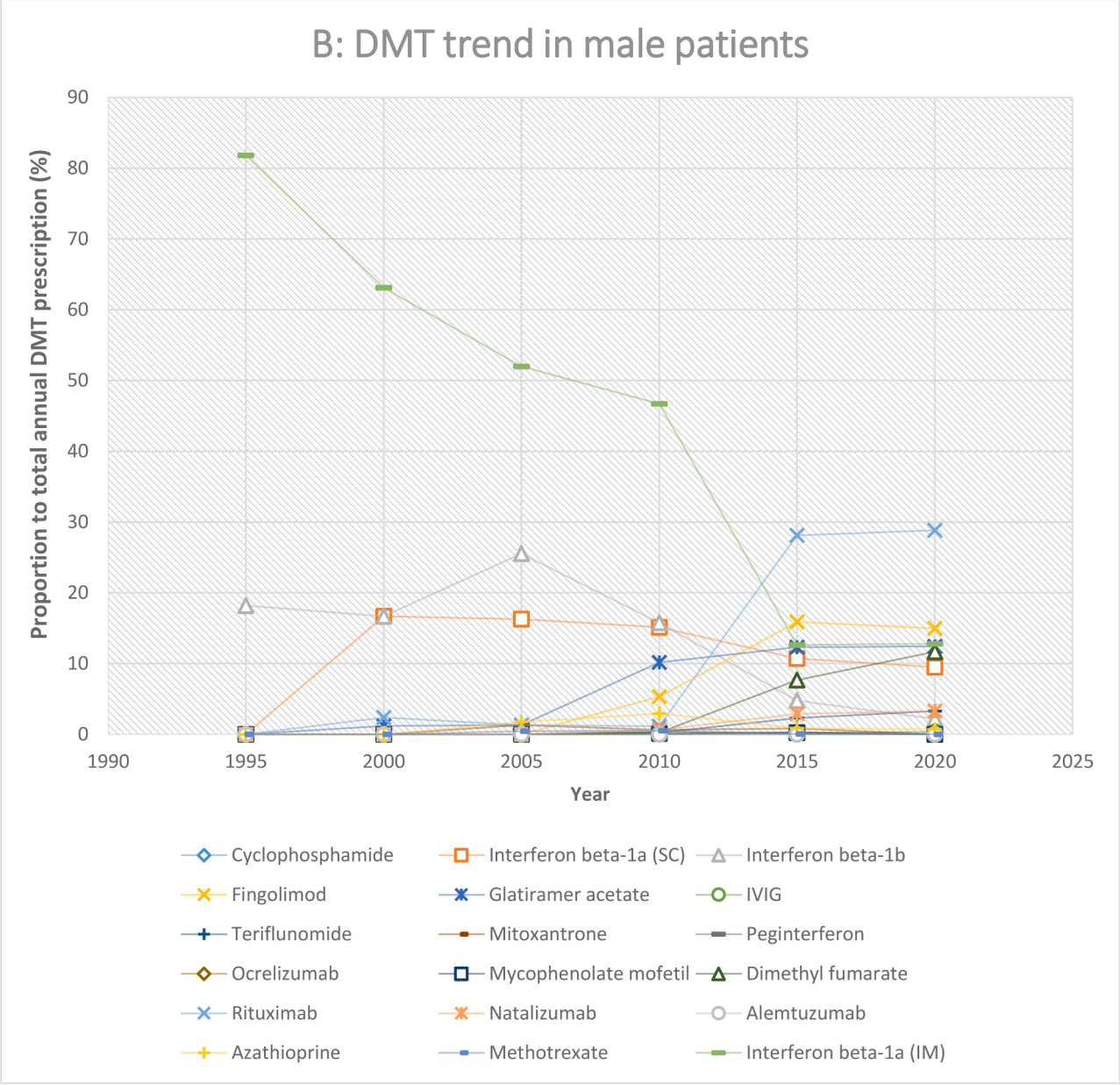

Fig. 4. (*continued*).

Table 2
DMTs prescribed in pediatric-onset MS.

Drug	2010, N (%)	2015, N (%)	2020, N (%)
Interferon beta-1a (IM)	2 (40)*	20 (34)	2 (29)
Interferon beta-1a (SC)	3 (60)	10 (17)	4 (13)
Interferon beta-1b		2 (3)	1 (3)
Glatiramer acetate		4 (7)	3 (10)
Teriflunomide		1 (2)	1 (3)
Dimethyl fumarate		1 (2)	5 (16)
Fingolimod		2 (3)	2 (6)
Rituximab		15 (26)	4 (13)
Natalizumab		1 (2)	2 (6)
Azathioprine		1 (2)	
Total	5	58	31

* The numbers in parenthesis indicate the percent of the drug relative to total DMTs prescribed in the time range.

Another point in this group, is the superiority of rituximab over other highly efficient medications. Even at time point 2020, the use of fingolimod has been further limited (due to the pandemics or availability of other DMTs like rituximab). This is not the case in some other reports where fingolimod and natalizumab are preferred (Abdel-Mannan et al., 2021; Erdal et al., 2020). Rituximab is the second most used (57/587) highly efficient drug (following natalizumab (101/587)) in the American cohort reported by Krysko et al. (2018). This study indicated that newer drugs seem safe and tolerable in pediatric population. Of note is no final consensus on the treatment of MS in cases younger than 18 years old. There are only two final approved drugs (fingolimod, and teriflunemide) in this age range. The need for further investigation into the subject seems vital as the disease activity in these patients should be halted as soon as possible (Amato et al., 2020).

The diagnosis of late-onset MS could be challenging. The disease present more in the form of progressive MS with motor features in adults older than 50 (Naseri et al., 2021). These patients tend to have fewer relapses and higher EDSS in the initial years of onset (Mirmosayyeb

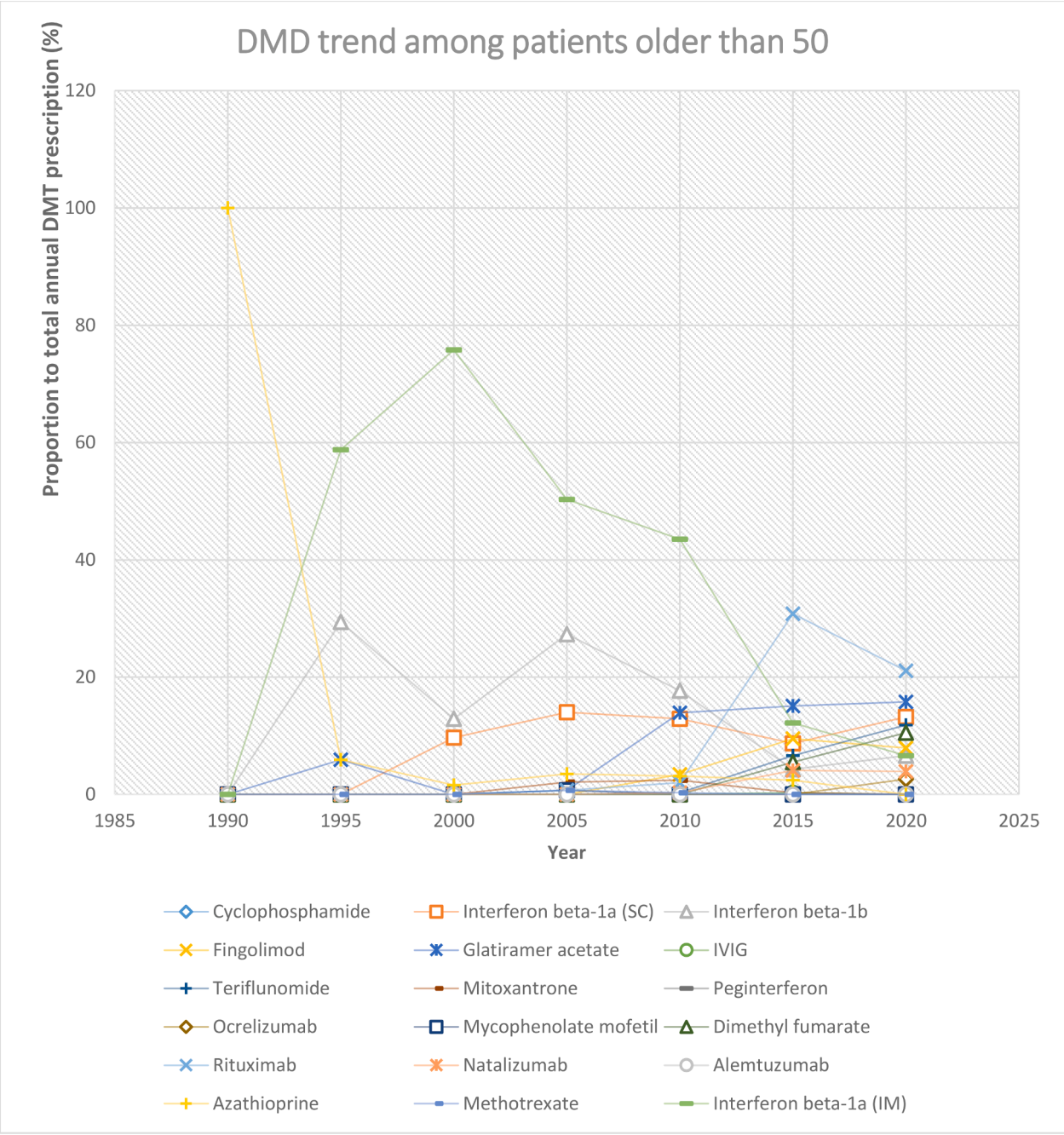

Fig. 5. Prescription attitude in late-onset MS.

et al., 2020). These feature point to a dominant degenerative pathology. Besides, treatment could be complicated by possible comorbidities (cardiovascular pathology, psychiatric disorders, diabetes, or cancer) (Ostolaza et al., 2021). Accordingly, more attention is needed in choosing the best treatment protocol. As shown in Fig. 5, oral DMTs have been frequently used during the recent years. Rituximab is another favored DMT in this group of patients. However, the recent pandemic has limited its use due to the potential association between antiCD20s and severe COVID-19 (Ghadiri et al., 2022). No detailed guideline of DMT use in older adults exists due to exclusion of such cases in most trials. Some reports suggest safety and tolerability of first-line treatments in this group (Zanghi et al., 2021; Thakolwiboon et al., 2020). Data indicate oral drugs are superior in case of efficiency in these patients (Zanghi et al., 2021). Considering the risk of faster and more pronounced disability in old-onset MS (Andersen et al., 2020), besides the aging population of MS patients calls for more research on the subject.

5. Conclusion

The observed trend in the prescribed DMTs could be of help in understanding the current approach among Iranian neurologists, find the weak points and missing data, design studies to develop evidence to fill the gaps, and finally improve the quality of care delivered to MS patients by appropriate policy making.

CRediT authorship contribution statement

Fereshteh Ghadiri: Formal analysis, Writing – original draft, Writing – review & editing, Visualization. **Mohammad Ali Sahraian:**

Conceptualization, Investigation, Validation, Resources, Supervision. **Seyed Mohammad Baghbanian:** Investigation. **Fereshteh Ashtari:** Investigation. **Nazanin Razazian:** Investigation. **Nastaran Majdinasab:** Investigation. **Maryam Poursadeghfard:** Investigation. **Hamidreza Hatamian:** Investigation. **Mohammad Hossein Harirchian:** Investigation. **Nahid Beladimoghadam:** Investigation. **Amirreza Azimi:** Investigation. **Ehsan Sharifipour:** Investigation. **Samaneh Hosseini:** Investigation. **Asghar Bayati:** Investigation. **Hoda Kamali:** Investigation. **Nahid Hosseni Nejad Mir:** Investigation. **Fardin Faraji:** Investigation. **Hossein Mozhdehipanah:** Investigation. **Farhad Modara:** Investigation. **Samira Navardi:** Investigation. **Hora Heidari:** Investigation. **Saeideh Ayoubi:** Investigation, Software, Data curation. **Abdorreza Naser Moghadasi:** Conceptualization, Validation, Resources, Supervision, Project administration, Funding acquisition. **Sharareh Eskandarieh:** Conceptualization, Methodology, Validation, Data curation, Writing – review & editing, Project administration, Funding acquisition.

Declaration of Competing Interest

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