Disease-modifying therapy for multiple sclerosis in Slovenia: analysis of 20 years of treatment

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Abstract
Introduction: Disease-modifying therapy (DMT) dramatically influenced the management of relapsing-remitting multiple sclerosis (RRMS). Novel medicines have been developing constantly and therapeutic strategy has changed. We aimed to analyse the development of DMT for MS in Slovenia with a special emphasis on contemporary approaches to the patient management.

Materials and Methods: Prescriptions of all DMT in Slovenia from 2001-2021 were analysed as well as referrals to the Committee for MS DMT the Centre for MS in Ljubljana in the last three years (2019-2021).

Results: Altogether approximately 360 patients were on DMT in 2001 and 1839 in 2021. The total number of patients on injectable therapies decreased through time while the number of patients on oral therapies increased. Dimethyl fumarate is currently the most frequently used medicine with 505 patients on the drug in 2021. The number of patients on potent medications increased from 28 (3%) in 2012 to 763 (41%) in 2021. Highly active medicines represented 52%, 62% and 69% of all DMT approvals in 2019, 2020 and 2021, respectively.

Conclusions: The number of treated MS patients has been increasing steadily in Slovenia as well as the number of patients on potent DMT which proves that neurologists follow the modern concept of MS treatment.

Keywords: multiple sclerosis, treatment, disease-modifying therapy

Sažetak:
Terapija multiple skleroze u Sloveniji koja modificira bolest: analiza 20 godina liječenja

Uvod: Terapija koja modificira bolest (TMB) dramatično je utjecala na liječenje relapsno-remittentne multiple skleroze (RRMS). Novi lijekovi se neprestano razvijaju i mijenja se terapijska strategija. Cilj nam je bio analizirati razvoj TMB-a za MS u Sloveniji s posebnim naglaskom na suvremene pristupe liječenju bolesnika.

Materijali i metode: Analizirani su recepti svih TMB-a u Sloveniji od 2001.-2021., kao i upućivanja Povjerenstvu za MS Centra za MS u Ljubljani u posljednje tri godine (2019.-2021.).


Zaključci: The number of treated MS patients has been increasing steadily in Slovenia as well as the number of patients on potent DMT which proves that neurologists follow the modern concept of MS treatment.

Ključne riječi: multiple skleroza, liječenje, terapija koja modificira bolest
**Introduction**

The most important milestone in multiple sclerosis (MS) management was the positive outcome of a clinical study with interferon beta-1b which demonstrated improvement in clinical course of relapsing-remitting (RR) MS (1). The field of disease-modifying therapy (DMT) for MS developed very fast afterwards. Currently, more than 10 different drugs, from injectable medicines to monoclonal antibodies and oral preparations are available for RRMS (2). In addition, ocrelizumab, an anti-CD20 monoclonal antibody is effective also in primary progressive (PP) MS and siponimod slows the progression of secondary progressive (SP) MS (3,4). Different efficacy, safety and tolerability profile of these drugs are making the treatment of MS more and more challenging. However, the consequences of modern disease management are impressive (5). In the 90s, epidemiological studies showed a median time from the diagnosis of RRMS to SPMS was 9 years while in 15 years most of the patients required unilateral walking support (EDSS 6.0). According to contemporary epidemiological studies only 10% of patients reach EDSS 6 in 15 years of follow-up (6).

In addition the MS treatment paradigm has changed recently towards more aggressive treatment after real-life studies showed better long-term outcome in comparison to the platform therapies (7,8). One of the greatest obstacles for the world-widespread of MS treatment are costs of the individual’s therapy which may reach 50,000 euros per year (9). Obviously, this can be an issue for low and medium-income countries.

Slovenia is a developed country with GDP of approximately 22,000 € per resident. In the 2 million population around 3,000–3,500 people have MS which corresponds to high prevalence of 150 patients per 100,000 people (10). There are three MS centres in Slovenia, the largest at the Department of Neurology, UMC Ljubljana and two others in Maribor and Celje. Altogether 7 neurologists, 4 in Ljubljana, 2 in Maribor and 1 in Celje work mainly in the field of MS and in addition neurologists from other regional hospitals in Slovenia take care for some patients with the diagnosis. All approved medications for MS are available for Slovenian patients. The first disease modifier that came to our patients was interferon beta-1b in 1995 and all other drugs followed regularly. The major milestones of the MS-treatment in Slovenia include introduction of natalizumab in 2010, fingolimod in 2012, the first-line oral drugs in 2014, ocrelizumab for PPMS in 2018 and siponimod for SPMS in 2020. In February 2022 ofatumumab, a fully human anti-CD20 monoclonal antibody was approved as a first-line agent for active RRMS.

Due to high costs of DMT neurologists are not allowed to freely prescribe medications to MS patients. From 1995 to 2011 DMT needed to be approved by a committee of three MS specialists at the National Health Insurance Institute and as from 2011, this approval is given by experts from MS Centres in Ljubljana and Maribor.

In our study we aimed to analyse the development of DMT treatment for MS in Slovenia with a special emphasis on contemporary approaches to the patient management.

**Methods**

Prescribed DMT in Slovenia from 2001 to 2021 were extracted from the gross sales data (units of a DMT sold in one year) for the whole country. The number of patients on an individual DMT was afterwards extrapolated taking into account the regular treatment regime. For example, 13 issued packages (56 or 28 tablets) of dimethyl fumarate or fingolimod corresponded to 1 treated patient per year. Contemporary MS treatment was determined by the analysis of 2019, 2020 and 2021 referrals to the Committee for MS DMT at the MS Centre in Ljubljana. These include treatment naïve patients and switches from previous treatments due to various reasons (lack of efficacy, adverse events, tolerability, pregnancy…). Individual patient was presented by a treating physician with a briefly written medical history together with the results of paraclinical investigations, EDSS score and MR images. The committee of two to three experts from the tertiary centre discussed the case and approved the treatment, suggested alternative medication or rejected the therapy.

**Results**

There was a steadily and marked increase of DMT from 2001 to 2021 (Figure 1). Three hundred and sixty patients were on interferons beta and glatiramer acetate up to 2009 with the first potent medication natalizumab added in 2010 and fingolimod in 2012. The use of injectables declined after 2013 when 963 patients were on interferons beta or glatiramer acetate in comparison to 384 patients with this DMT in 2021 (Figure 1). There was a rapid increase of the first-line oral treatment (teriflunomide and dimethyl fumarate) between 2015 and 2019, namely 192 and 670 patients were treated with one of these drugs in 2015 and 2019) and these numbers have plateaued in recent years (2020 and 2021) when 720 and 717 were on the first-line orals (Figure 1).

There was a rapid increase of the first-line oral treatment (teriflunomide and dimethyl fumarate) between 2015 and 2019, namely 192 and 670 patients were treated with one of these drugs in 2015 and 2019, respectively (Figure 1, Table 1), while a plateau was observed in recent years, when 717-720 patients were on first-line orals (2020-2021). Dimethyl fumarate is the most frequently prescribed medication in Slovenia with 505 patients on the drug in 2021. There was also an increase in the high-efficacy medication prescribing in Slovenia (Figure 2). In 2010 only 3% (28/842) of patients were on the second-line DMTs compared to 41% (763/1864) in 2021. Contemporary DMT treatment approach in Slovenia is shown in Figure 3. Interferon beta treatment was only exceptionally
### Table 1. DMT in Slovenia from 2001 – 2021 (number of treated patients)

<table>
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<th>Year</th>
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<th>DMF</th>
<th>TF</th>
<th>NTZ</th>
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Figure 1. DMTs in Slovenia from 2001-2021

Figure 2. Relative percentages of DMTs prescribed from 2001-2021
approved to our patients with glatiramer acetate somewhat more often in the last three years. A mild decrease of the most frequently prescribed dimethyl fumarate is observed and at the same time an increase in the high-efficacy medication prescribing. High-efficacy medicines represented 52%, 62% and 69% of all DMT approvals for 2019, 2020 and 2021, respectively. In addition 31 patients with active SMPS started siponimod therapy for secondary progressive MS in 2021.

**DISCUSSION**

In our study we aimed to analyse the development of DMT for MS in the last 20 years with the special emphasis on contemporary treatment approaches. There is a steady increase in the number of treated patients in our country. Today more than half of our MS patients (over 1,800 patients) are treated with DMTs. The number of patients on the injectables had been increasing until 2013 when nearly 1000 patients were treated with either interferon beta preparations or glatiramer acetate (Figure 1). From 2013 less injectables are prescribed every year. Interestingly, there is a faster decline in the number of MS patients treated with interferon beta compared to those treated with glatiramer acetate. This is probably due to a more frequent injection site reactions and flu-like symptoms observed with interferon beta treatment along with the availability of a higher dose lower frequency regimen of glatiramer acetate.

A major change in our treatment of MS occurred in 2014 with the availability of the first-line oral therapy. From Autumn 2014 to Spring 2016 nearly 25% of our patients switched from the injectables to the orals (unpublished observation). Today, dimethyl fumarate is the most frequently prescribed DMT in Slovenia with more than 500 patients on the drug. There are differences between teriflunomide and dimethyl fumarate prescription in our country. A major analysis which included 255 patients treated with dimethyl fumarate and 135 patients on teriflunomide was performed for our third national MS meeting held in Maribor in 2016 (11). In this survey, patients treated with dimethyl fumarate had a median age of 36 years (range 19-60), median duration of the disease 4 years, mean annual relapse-rate (ARR) 0.7 and mean EDSS score 2.1 before the introduction of the drug. Approximately 50% of patients were switchers from the injectables. On the other hand, patients who started on teriflunomide were older (mean 47 years), had longer duration of the disease (10.8 ±7.1 years) and the majority of patients (76%) were not treatment naïve before teriflunomide. Their disease course was also less active with mean ARR 0.39 before the treatment (13). Our data therefore indicate that dimethyl fumarate is given in Slovenia as a first-line drug to young people with less active MS while teriflunomide is prescribed mainly for elderly patients who are often clinically stable on the injectables but suffer from intolerable side-effects.

It is well known that patients with active disease need high-efficacy DMT which usually have more severe side-effects. Slovenian neurologists are more and more aware of negative prognostic indicators of MS. Concurrently, the rapid introduction of novel drugs has resulted in an increasing number of second-line therapies prescribed in our country. In 2013, for example, when only natalizumab and fingolimod were available, less than 10% of patients received second-line DMT (12). Today, more than 40% of patients are treated with high-efficacy DMTs (Figure 2).

The second-line drug-prescribing is also very dynamic in Slovenia. Some of the second-line-therapies, such as natalizumab or alemtuzumab, were given to fewer patients with RRMS whereas fingolimod or ocrelizumab have been more frequently prescribed. Treatment with natalizumab and fingolimod had been increasing up to 2016 and 2017 and plateaued afterwards. On the other hand, there is a steep increase in the number of patients treated with novel medications ocrelizumab and cladribine. The most plausible explanation for the observed trend in DMT prescription are severe side-effects of potent agents, such as progressive multifocal leukoencephalopathy associated with natalizumab and increased risk for infections and autoimmunity on alemtuzumab therapy. In addition, a prolonged, demanding follow-up with monthly blood-withdrawals is required for patients on alemtuzumab. Fingolimod is a relatively old second-line drug which is generally prescribed in two situations in Slovenia: for patients with moderate clinical or radiological activity on injectables or first-line orals and for the JCV-positive patients treated with natalizumab. Relative decrease of fingolimod prescribing can be explained by a novel attractive and effective immune reconstitution therapy with relatively few severe side effects. Furthermore, the real-world data demonstrate better efficacy of anti-CD20 agents after switching from natalizumab (13).

It is very important that patients on potent treatments who are at high risk of serious adverse events are monitored in specialized MS Centres as recommended by the EAN/ECTRIMS guidelines (5) and confirmed by our own experience with alemtuzumab (14). The drug was shown to be very effective in our cohort, but on the account of a substantial side-effect profile. Forty-three patients started with alemtuzumab from 2015 at the MS Centre in Ljubljana. Patients were young (31.2±7.6 years) with short disease course (2.7±2.6 years), but disabled (EDSS 3.0 ±1.4) with high relapse rate (1.6±0.8) before the medication. In 33% of patients alemtuzumab was given as a first-line medication, in 46% as a second-line and in 21% as a third-line drug. Alemtuzumab was very effective, resulted in a marked reduction of ARR to 0.1 and a reduction of the EDSS score to median 2.6 after 2 years. But there are ‘no roses without thorns’. In 70% of patients at least some side effects were observed, 41% had infusion reactions, 32% infections and 25% thyroid disorders. In addition, one patient suffered from severe and therapeutically resistant thrombocytopenia and 1 had omentum infarction.
Contemporary MS treatment in Slovenia was determined with analyses of 2019, 2020 and 2021 referrals to our Committee for MS DMT. It shows that a wide variety of medications are given to our MS patients, including siponimod for active SPMS. Our data clearly demonstrate that MS physicians in Slovenia follow modern ‘hit early hit hard’ concept of MS treatment. Namely, nearly 70% of our last-year approvals were for the high-efficacy medications, preferably drugs from the immune reconstitution groups.

There are some limitations of our analyses. Prescribed and sold medication does not necessarily mean that the medication is taken by the patient (adherence). In addition, we need to be aware that some drugs are given continually but others such as cladribine and alemtuzumab only for a limited period of time which affects the estimation of the patients being treated with these DMTs. Despite of the mentioned limitations we believe that our analysis describe very well evolution of MS treatment in Slovenia.

In conclusion our analysis showed that approximately 55% of all MS patients in Slovenia receive DMTs which is high even for western European standards (15). Because of high costs of the DMTs we never had an option to freely prescribe different medications to our patients. However, the system with individual approvals from tertiary centre experts has its benefits. The system enables discussion of treatment-options for every individual and consequently the treatment can be (and was) approved also for patients with atypical presentations or progressive course or in the transitional phase when experts believe/d it is/was worth trying it. The treatment landscape has been changing constantly and rapidly along with novel DMT options. It is also important to appreciate the increasing number of patients with potent second-line agents which indicates our physician’s awareness of importance of early high efficacy DMT when poor prognostic indicators are present.

A further increase in DMT prescription is anticipated in the future. It is also expected that more and more carefully selected patients with progressive MS will receive a proper treatment.

Figure 3. Approved DMTs at the Centre for MS, Ljubljana in 2019, 2020 and 2021
References