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LEADING TOPIC

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Highly active disease and access to disease-modifying treatments in patients with relapsing-remitting multiple sclerosis in Poland

Waldemar Brola[1], Monika Adamczyk-Sowa[2], Alina Kułakowska[3], Joanna Głażewska[4], Anna Smaga[5], Halina Bartosik-Psujek[6]

[1]Collegium Medicum, Jan Kochanowski University, Kielce, Poland
[2]Department of Neurology, Faculty of Medical Sciences in Zabrze, Medical University of Silesia, Katowice, Poland
[3]Department of Neurology, Medical University of Bialystok, Poland
[4]PEX PharmaSequence, Warsaw, Poland
[5]National Institute of Public Health NIH - National Research Institute, Warsaw, Poland
[6]Department of Neurology, Institute of Medical Sciences, Medical College of Rzeszow University, Rzeszow, Poland

ABSTRACT

Introduction. In Poland, access to second-line disease-modifying treatments (DMTs) for relapsing-remitting multiple sclerosis is limited by reimbursement criteria that require evidence of more aggressive disease compared to the approved indications.

Material and methods. In a retrospective study carried out in DMT clinics across Poland, we asked neurologists to provide patient data on relapses and neuroimaging disease activity. Included were only patients with active disease, defined as one or more relapse and at least one new lesion between starting DMT and the last visit. For patients who had not received DMT, active disease was defined as at least one gadolinium-positive lesion or two or more new T2 lesions and two or more relapses within 12 months. We analysed the proportions of patients eligible for second-line DMTs based on the current reimbursement criteria and based on the broader criteria, which were in line with the approved indications.

Results. In total, 48 neurologists provided data for 641 patients (women 64%; mean age 38 years). Of the 641 patients, 610 (95%) received DMTs: 532 first-line and 78 second-line. Of the 532 patients on first-line DMTs, 40 (7.5%) were eligible for second-line treatment based on the current reimbursement criteria, and an additional 126 (23.6%) would be eligible for second-line treatment based on the broader criteria. Of the 31 patients who did not receive any DMTs, one patient was eligible for second-line treatment, and another two patients would be eligible for second-line treatment based on the broader criteria. Moreover, 13 previously treated patients would be eligible for second-line DMTs based on the broader criteria. When extrapolated to the whole of Poland, our study shows that an additional 1,581 patients would be eligible for second-line DMTs if the current reimbursement criteria were to be replaced by broader criteria complying with the approved indications.

Conclusions. An urgent change is required in the reimbursement criteria in order to expand access to second-line DMTs for patients with relapsing-remitting MS in Poland.

Key words: multiple sclerosis, highly active disease, disease-modifying treatment, reimbursement

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Address for correspondence: Waldemar Brola, Collegium Medicum, Jan Kochanowski University, Kielce, Al. IX Wieków Kielc 19, 25-317 Kielce, Poland; e-mail: wbrola@wp.pl

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Introduction

Assessment of disease activity is crucial for the management of relapsing-remitting multiple sclerosis (RRMS) in order to monitor the effectiveness of treatment and make any necessary adjustments. An absence of relapses, disease progression, and active MRI lesions [no evidence of disease activity-3 (NEDA-3)] has been proposed by some investigators as a stringent treatment goal in clinical practice [1]. When disease activity remains high, second-line disease-modifying treatments (DMTs) should be considered [2]. In particular, second-line DMTs should be offered to patients with rapidly evolving severe MS and those whose disease is not controlled by first-line DMTs [3].

A prospective study among more than 11,000 patients with MS who received DMTs in Poland reported that the median time from first symptoms to diagnosis was seven months, and that time to treatment start was 18 months; less than 10% of patients were on second-line treatments [4]. According to that study, about one-third of all patients with MS in Poland receive DMTs [4], but little is known about disease control and whether patients with high disease activity have access to second-line treatments.

In accordance with evidence-based recommendations and approved indications, the Polish Neurological Society proposes that patients with RRMS should be switched to a second-line DMT when they have one or more relapse in addition to at least one contrast-enhancing lesion or two or more new T2 lesions despite at least 12 months of first-line treatment [1, 5]. However, in practice, strict reimbursement criteria in Poland limit access to second-line DMTs to those patients who demonstrate both: (1) two or more steroid-treated moderate relapses over 12 months or one or more severe relapse occurring at least six months after treatment initiation; AND (2) two or more contrast-enhancing lesions or at least three new T2 lesions within 12 months.

In this retrospective study, we investigated the proportion of patients in Poland who have active RRMS despite treatment, and the proportion of patients who would be eligible for second-line DMTs based on the evidence-based criteria put forward by the Polish Neurological Society.

Material and methods

Study setting

We carried out a retrospective study of neurology clinics that provided DMTs for RRMS across Poland between September and November 2018. We recruited neurologists who worked in clinics with access to first-line treatment only ('first-line clinics') and others who worked in clinics with access to both first-line and second-line treatment ('second-line clinics'). The first-line and second-line clinics were selected randomly from a list of all clinics that provided DMT in Poland. Where a clinic declined to participate, we then invited the geographically closest clinic instead. Neurologists were asked to provide anonymised data on relapses and neuroimaging disease activity from medical records for the most recent, consecutive patients with RRMS seen during the previous two months (up to 30 patients per neurologist). First-line DMTs included interferon beta, glatiramer acetate, dimethyl fumarate, and teriflunomide. Second-line treatment included fingolimod, natalizumab, and alemtuzumab. Ethical approval was not required because this study was non-interventional.

Definitions

We included only patients with active disease, defined as one or more relapse regardless of severity and at least one new lesion between starting DMT and the last visit. For patients who had not received DMT, active disease was defined as at least one gadolinium-positive (Gd+) lesion or two or more new T2 lesions and two or more relapses with worsening of 1 point or more on the Expanded Disability Status Scale (EDSS) within 12 months.

The current criteria for access to second-line DMTs in Poland require two or more relapses and two or more new Gd+ lesions or three or more new T2 lesions disease over at least 12 months of first-line treatment. Second-line DMTs are also currently available to treatment-naive patients with rapidly evolving severe MS, defined as two or more moderate relapses causing disability within 12 months and two or more new Gd+ lesions or three or more new T2 lesions (and nine or more T2 lesions in total). In accordance with the recommendations of the Polish Neurological Society, the broader criteria for access to second-line DMTs were defined as follows: one or more relapse with a worsening of 1 point or more on the EDSS on current treatment and at least one new Gd+ lesion or two or more new T2 lesions within 12 months. The broader criteria for rapidly evolving severe MS were defined as two or more relapses with worsening of 1 point or more on the EDSS within 12 months, and at least one new Gd+ lesion or two or more new T2 lesions (and at least nine T2 lesions in total).

Analyses

Data was presented as counts and percentages and as mean (standard deviation, SD) or median (interquartile range, IQR). No inferential statistics were applied. Data was extrapolated to the population of patients under the care of neurology clinics in Poland that provide DMT for RRMS patients. We used three types of weight to extrapolate our data: (1) weights derived from the number of clinics included, their contracts, and the number of all DMT clinics in Poland; (2) weights derived from the frequency of patient visits to the clinics; and (3) weights derived from the proportions of patients with active disease. We compared patients eligible for second-line treatments based on the broader criteria to those who were not eligible on selected outcomes calculated for the extrapolated population. The chi-squared test and the Mann-Whitney test were used as appropriate.

Results

In total, 21 neurologists from 19 first-line clinics provided data for 277 patients, and 27 neurologists from 26 second-line clinics provided data for 364 patients. Supplemental Table 1 shows recruitment results. Of the 641 included patients, 411 (64%) were women, and the mean age was 38.39 years (SD 10.16). The mean age at diagnosis was 33.14 years (SD 9.64), the mean time from diagnosis to the start of first-line DMT was 6.94 months (SD 10.84), the median EDSS score at diagnosis was 2.00 (range 0.0–6.5), and the median EDSS score at the start of first-line DMT was 2.00 (range 0.0–5.0).

Of 641 patients, 610 (95%) received DMTs: 532 first-line and 78 second-line. Of the 31 patients who did not receive any DMTs, 28 had discontinued treatment and three were treatment-naive. Table 1 shows the proportions of patients receiving each treatment type.

Of the 532 patients on first-line DMTs, 40 (7.5%) were eligible for second-line treatment based on the current criteria, and an additional 126 (23.7%) would be eligible for second-line treatment based on the broader criteria of the Polish Neurological Society. Of the 31 patients who did not receive any DMTs, one treatment-naive patient was eligible for second-line treatment, and another two treatment-naive patients would be eligible for second-line treatment based on the broader criteria for rapidly evolving severe MS. Moreover, 13 previously treated patients would be eligible for second-line DMTs based on the broader criteria, but none were eligible for second-line DMTs based on the current criteria. Table 2 shows the extrapolation of our data to the whole of Poland.

Based on the extrapolated data, patients in Poland who would be eligible for second-line DMTs based on the broader criteria had a mean age of 38.8 years and 62% were female (*vs.* 38.6 years, p = 0.456; 64% female, p = 0.112 in those not eligible). In the eligible patients, the median time between diagnosis and the start of first-line treatment was 4 months [IQR 1–11, *vs.* 2 months (1–7) in those not eligible based on the broader criteria, p < 0.001], the mean EDSS score at the start of treatment was 1.9 (SD 1.1 *vs.* 1.8, SD 1.0, p < 0.001), and the mean annualised relapse rate within 12 months before treatment initiation was 1.41 (SD 0.60 *vs.* 1.38, SD 0.64). At the final follow-up, eligible patients had a median treatment duration of 33 months [20–62 *vs.* 37 months (21–63), p = 0.111], a mean annualised relapse rate of 1.8 (SD 1.8), and a mean of 1.6 Gd+ lesions and 2.6 new T2 lesions.

Discussion

The course of RRMS is variable, with some patients having aggressive disease characterised by a rapid accumulation of disability. These patients require treatment escalation to prevent the progression of disability [6]. Many studies have shown that earlier treatment with highly effective DMTs reduces relapse activity and can slow the progression of disability [7]. Moreover, starting DMT early is more cost-effective [8]. Highly active RRMS is usually defined by clinical characteristics (e.g. relapses or progression) and neuroimaging data, which are currently the best biomarker of disease activity [9]. Although there are no widely accepted definitions of highly active MS, one group has proposed that highly active disease should be

Table 1. Proportions and numbers of patients receiving particular first-line and second-line disease-modifying treatments at final visit

First-line disease-modifying treatments			Second-line disease-modifying treatments		
	Raw data	Extrapolated data		Raw data	Extrapolated data
Interferon beta-1a	112 (21%)	723 (18%)	Fingolimod	44 (56%)	648 (56%)
Interferon beta-1b	116 (22%)	951 (24%)	Natalizumab	26 (33%)	406 (35%)
Peginterferon beta-1a	14 (3%)	153 (4%)	Alemtuzumab	8 (10%)	104 (9%)
Dimethyl fumarate	185 (35%)	1,342 (34%)			
Glatiramer acetate	75 (14%)	492 (13%)			
Teriflunomide	30 (6%)	267 (7%)			

Table 2. Active disease and eligibility for second-line disease-modifying treatments — extrapolated data for Poland

	Estimated number of patients in Poland
Active disease (first-line, second-line, and no treatment)	5,626
Active disease (first-line treatment)	3,928
Active disease (second-line treatment)	1,158
Active disease (untreated)	540
Patients on first-line treatment but eligible for second-line treatment	457
Patients not receiving disease-modifying treatment or on first-line treatment who are eligible for second-line treatment based on broader criteria only	1,581

characterised by an EDSS score of 4.0 or more five years after diagnosis, two or more relapses without full recovery in the current year, the accumulation of lesions on neuroimaging on the last two MRI assessments, and no response to at least one DMT within the last year [10].

The demographic characteristics of our cohort were similar to those previously reported by investigators from Poland. About two-thirds of patients were female in our cohort, which is similar to the figure reported by Małecka et al. (F:M ratio 3:1) [11]. The age at diagnosis in our cohort (~ 33 years) was similar to that reported among patients diagnosed according to the McDonald criteria (~ 30–35 years) in a single-centre study from Warsaw [12].

Settling upon a definition for highly active RRMS is very important, because recognising this disease type often enables a neurologist to escalate treatment, including switching patients from first-line to second-line DMTs. The Polish Neurological Society proposes that highly active disease that justifies the use of second-line DMTs is characterised by the following criteria: one or more relapse with a worsening of disability on current treatment, and at least one new Gd+ lesion or two or more new T2 lesions within 12 months. In treatment-naive patients, highly active disease requires the occurrence of two or more relapses with a worsening of disability within 12 months, and at least one new Gd+ lesion or two or more new T2 lesions [5]. However, in practice, stricter reimbursement criteria are used for second-line DMTs in Poland, thereby reducing access to effective treatments for patients with highly active disease.

Starting a highly active DMT early after a diagnosis of MS has been shown to control the disease substantially better than escalation therapy. A registry-based study from Norway among c.700 patients with MS showed that those receiving highly active treatment as the first DMT were nearly four times more likely to achieve NEDA than were those receiving moderately effective medications [13]. In a study of Swedish and Danish real-world registries, patients in Sweden, 35% of whom started treatment with highly effective DMTs, were significantly less likely to develop 24-week confirmed disability progression than were Danish patients, of whom fewer than 8% received highly active medications as the first treatment [14].

Our study analysed current access to second-line treatment for patients with RRMS in Poland and assessed how that access would expand if evidence-based criteria were applied.

We found that nearly 8% of patients with RRMS receiving first-line DMTs were eligible for second-line DMTs, based on the current criteria. We did not ask specifically about reasons for non-escalation of treatment, but access can be limited, particularly in clinics that manage first-line treatments only. Alternatively, some patients might have declined to escalate treatment, fearing more severe adverse reactions (e.g. progressive multifocal leukoencephalopathy) or the change from oral (e.g. teriflunomide) to injectable (e.g. natalizumab) administration. A survey of 218 neurologists showed that, of patients not receiving highly active DMTs despite being eligible, one-third declined to escalate treatment [15]. In a study using semi-structured interviews, changing treatment for patients with MS was often associated with a fear of transition to a secondary-progressive phenotype and uncertainty about the effectiveness of DMT [16].

Our study showed that nearly a quarter of patients with RRMS who received first-line DMTs would be eligible for second-line treatment according to the criteria of the Polish Neurological Society. This finding underlines how a large proportion of patients with highly active RRMS in Poland do not receive effective treatment today. We estimate that this would extrapolate to more than 1,500 patients across the whole country. These patients are at risk of accumulating disability before they meet the current reimbursement criteria. Being aware of this potentially preventable disability is an additional burden on patients and neurologists. Moreover, additional disability results in higher indirect costs associated with a greater need for medical services (e.g. hospitalisation and/or rehabilitation) and greater unemployment or less effective work. Of note, the average age of patients who would be eligible for second-line DMTs based on the expanded criteria was below 40 years. Similarly to other countries, unemployment among patients with MS in Poland is strongly related to the degree of disability [17]. Moreover, the economic burden of MS has been shown to be greatest for patients with the most severe disease, which includes those with highly active disease [4, 18].

These observations justify from a public health perspective the expansion of the reimbursement criteria for second-line treatment in Poland.

Clinical implications/future directions

A large proportion of patients with RRMS receiving first-line DMTs in Poland have highly active disease that justifies switching to a more effective second-line treatment, but this is not allowed under the current reimbursement criteria. An urgent expansion of the reimbursement criteria is therefore required to prevent the accumulation of disability and resulting costs.

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