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Clinical and radiological consequences of delayed therapy escalation in patients with relapsing-remitting multiple sclerosis

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ABSTRACT

Aim of the study. To evaluate the clinical and radiological consequences of delayed escalation of therapy in patients with relapsing-remitting multiple sclerosis (RRMS), in whom, despite finding platform therapy ineffective, high-efficacy drugs were introduced with a delay.

Material and methods. We performed a single-centre, observational study evaluating patients with RRMS for ineffectiveness of disease-modifying therapies (DMTs). Depending on the time of therapy escalation to high-efficacy drugs, the patients were divided into an early escalation or a late escalation group, both of which were then observed for 48 months. All patients underwent a neurological examination every six months and a brain magnetic resonance imaging (MRI) every 12 months. The primary endpoint was a change in the Expanded Disability Status Scale (EDSS) score during the observation period. The secondary endpoint was the time to 6-month confirmed disability progression (6mCDP). In addition, we analysed the annualised relapse rate and the cumulative number of new Gd+ and T2 lesions on brain MRI.

Results. 165 patients were qualified for the analysis. On treatment initiation, mean age was 38 years (± 10.9), and mean EDSS was 1.41 ± 0.38. After 48 months, there was a statistically insignificant decrease in the EDSS score in the early escalation group (–0.17 ± 0.35; $p > 0.05$), while in the late escalation group there was an increase in the EDSS score. The highest increase was noted in the group in which the escalation was performed with a delay of more than two years (1.2 ± 0.63; $p < 0.001$), and moreover 80% of patients in this group met the 6mCDP criteria.

The median time to 6mCDP was 4.6 years (LESC1) and 4.5 years (LESC2) in the late escalation groups. In the early escalation group, zero subjects met the 6mCDP criteria after 48 months of observation.

Conclusions. In everyday practice, the long-term outcomes in patients with RRMS and disease activity, despite DMT being used, are more favourable after early implementation of high-efficacy drugs. Delaying therapy escalation results in the accumulation of permanent disability in patients with RRMS.

Keywords: multiple sclerosis, therapy escalation, treatment failure, access to therapy, highly effective disease-modifying therapy

Introduction

Multiple sclerosis (MS) is the most common autoimmune disorder of the central nervous system (CNS) among young adults. The disease is usually diagnosed between the ages of 20 and 40 and is one of the most common causes of disability in young people [1]. According to the data of the National Health Fund (NFZ) as at the end of 2021, MS was diagnosed in Poland in 54,887 people, a rate of 144 per 100,000 residents [2].

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Relapsing-remitting MS (RRMS) occurs in more than two in three MS patients [1, 3, 4]. In recent years, the treatment options for this type of disease have increased significantly due to the registration of many new disease-modifying therapies (DMT). Currently, the available therapies are commonly referred to as 'moderate efficacy DMT' (ME-DMT, platform therapy, including interferon-beta, glatiramer acetate, dimethyl fumarate, and teriflunomide) or 'high efficacy DMT' (HE-DMT, including alemtuzumab, cladribine, fingolimod, natalizumab, ocrelizumab, and newly approved ozanimod, ponesimod and ofatumumab) [5–7].

MS is incurable and no drug is fully effective. Therefore, the type and duration of therapy are crucial for inhibiting disease activity and irreversible brain damage, which translates into permanent disability. Thus far, MS treatment has been based on an escalation model, with HE-DMT following the failure of ME-DMT. This model has worked well in patients with low or moderate disease activity. Moreover, the high safety profile of platform drugs is worth underlining.

However, in patients with high clinical and magnetic resonance imaging (MRI) activity from the onset of the disease, and with unfavourable prognostic factors, such treatment does not bring the expected benefit.

Therefore, the current paradigm of MS therapy is that highly active drugs should be started as early as possible [5]. Pathophysiological studies indicate that inflammatory processes predominate in the early stages of the disease [8]. Therefore, the use of drugs with high anti-inflammatory activity in this period makes it possible to properly interrupt the immunopathological cascade, and may reduce, or even stop, the progression of the disease more effectively.

This concept has been confirmed in randomised clinical trials and recently in studies based on data from national and international registries [9–11]. Early use of high efficacy therapy has been shown to reduce disease activity and significantly delay disability progression. It also defers disease conversion to secondary progressive MS [9, 12].

The treatment model in MS changes based on new pathophysiological and clinical data, but also depends to a large extent on administrative and reimbursement regulations in the particular country. In Poland, until November 2022, based on the recommendations of the Ministry of Health, a typical escalation model of RRMS treatment was in force. This model included strictly defined clinical and radiological rules for the use of HE-DMT which significantly limited or withheld the use of highly active drugs.

To assess the consequences of delaying or not implementing escalation therapy in a group of patients with RRMS, we conducted a study evaluating patients treated with DMT according to the drug programme financed by Poland's National Health Fund (NFZ, Narodowy Fundusz Zdrowia).

The aim of our study was to analyse the clinical and radiological consequences of delayed treatment escalation in patients who, despite the ineffectiveness of the current therapy, were started on high efficacy drugs after a delay. Our analysis was based on data from one centre, thus enabling a uniform assessment of patients.

Material and methods

Study design

Data from 1,008 patients with MS treated in a specialist MS centre were analysed; 537 patients with RRMS diagnosed according to the 2010 McDonald criteria and treated with DMT platforms between January 2013 and June 2022 were identified. Then, 165 patients were included in the study group according to our inclusion criteria, which were: (1) RRMS; (2) age ≥ 18 years; (3) a minimum of 12 months of treatment with IFN beta, glatiramer acetate, dimethyl fumarate or teriflunomide; (4) a confirmed lack of clinical and/or radiological treatment efficacy in any period of therapy; and (5) the ability to analyse data for 48 months after determining treatment inefficacy. Patients who had a break in treatment (e.g. withdrawal from treatment, pregnancy), or who had been previously treated in clinical trials, or those in whom clinical data was insufficient or the observation period too short, were excluded. Demographic information (age, sex) and clinical data (date of first symptoms, date of diagnosis, number of relapses in the 12 months prior to treatment initiation, date of treatment initiation) were collected. Neurological status on treatment initiation was assessed according to the Expanded Disability Status Scale (EDSS). Then, after determining the date of complete or partial therapy failure, the possible escalation of treatment was assessed. Complete failure was diagnosed if, during the 12-month period of DMT, there were two or more moderate relapses, or one severe relapse after six months of DMT, along with new lesions found on brain MRI — (> 1 change in Gd+ or > 2 changes in T2). In the drug programme financed by the NFZ, meeting such criteria made it possible to change the therapy and use a high-efficacy drug. Partial failure was diagnosed if, within 12 months of DMT, the patient had clinical and/or radiological disease activity that did not meet the criteria for complete treatment ineffectiveness. These were patients with clinical failure — they experienced only relapses, and radiological failure — they had only new T2 or Gd+ lesions on brain MRI or with clinical and radiological failure, but less than required for a complete failure. According to the criteria of the drug programme in force at that time, these conditions did not allow the use of HE-DMT. Data from any treatment period during which complete or partial treatment failure occurred was considered as reference data.

On this basis, two groups of subjects were distinguished: group A, and group B. Group A comprised patients with complete ineffectiveness of treatment. In this group, a switch to a high-efficacy drug was made immediately after treatment failure (EESC, early escalation group). Group B comprised patients with partial treatment failure. This group was divided into three subgroups: B1 — patients with only a relapse

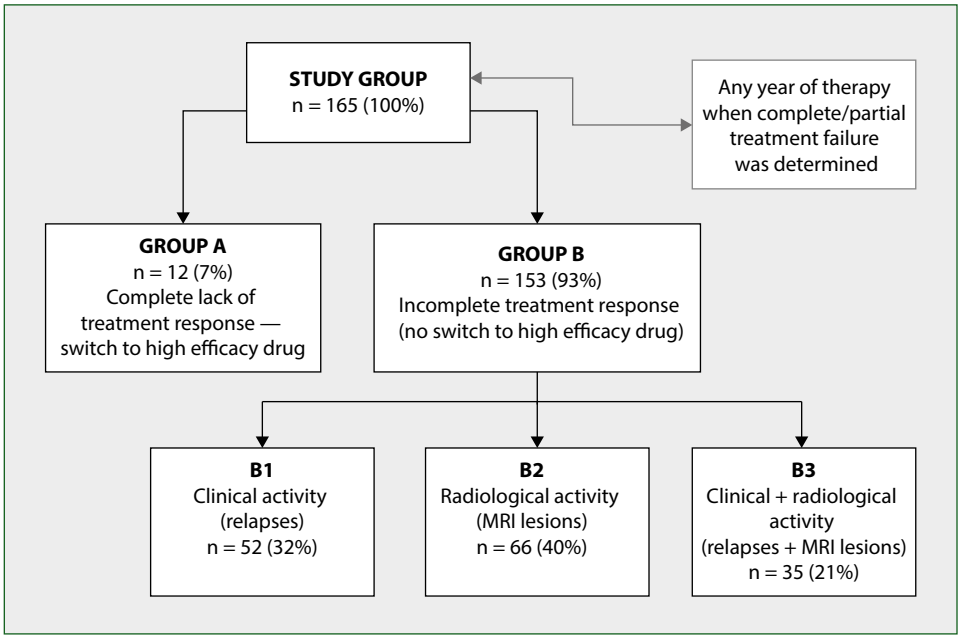

Figure 1. Flowchart of patient selection procedure. MRI — magnetic resonance imaging

during the observation period; B2 — patients with only new brain MRI lesions during the observation period; and B3 — patients with both a relapse and brain lesions in MRI during the observation period. These patients were either switched to a high-efficacy drug at a later time (LESC, late escalation group) or did not receive such therapy (NESC, no escalation group) (Fig. 1).

All patients were observed for 48 months after treatment failure. Every six months, the EDSS score was evaluated, and every 12 months the number of relapses and the new Gd+ and/or T2 lesions on brain MRI were assessed. The final review of the clinical data and the final EDSS evaluation were performed by the same investigator. Brain MRI and their evaluation were performed according to the same protocol and in the same MRI centre.

At the end of the observation stage, study endpoints were assessed. The primary endpoint was a change in EDSS score in relation to the reference score (ΔEDSS = EDSS score after 48 months – reference EDSS score). The secondary outcome was the time to a confirmed disability progression (6mCDP) defined as an increase in EDSS score confirmed on two consecutive visits at least six months apart. The required increase was defined as: ≥ 1.5 in patients with a baseline EDSS score of 0.0–0.5, ≥ 1 point in patients with a baseline EDSS score between 1.0–5.0, and ≥ 0.5 points in patients with a baseline EDSS score at least ≥ 5.5. EDSS increase had to occur in the absence of a relapse.

We defined our outcome date as the date of the confirmation of EDSS worsening. In addition, the annualised relapse rate (ARR) and the cumulative number of new Gd+ and/or T2 lesions on brain MRI compared to the reference data were assessed during the observation period in each group. Written consent to participate in the study was obtained from all patients. This study was approved by the Bioethics Committee at the University of Rzeszów (Resolution No. 3/01/2020).

Statistical analysis

Depending on the type and properties of the variable, the median test, the Mann–Whitney U test and the Kruskal–Wallis H test were used for intergroup comparisons. In addition, Cox regression analysis was used to assess progression within the groups. Linear regression analysis was used to assess the impact of individual variables on the change in EDSS over 48 months of observation. Models were adjusted for gender, age at treatment, year of DMT initiation, and year of escalation of therapy.

ARR (so-called crude ARR) in individual groups and a comparison of ARR between groups (estimating the so-called RR — relapse rate ratio) were calculated using the criteria defined by Akaishi et al. in 2022 [13].

Results

Complete or partial treatment failure according to the accepted definitions was found in 165 (31%) patients with RRMS treated with DMT. Failure occurred after a mean of 15.83 months (SD = 10.29), median 11 months (range 6–64). In this group, 12 (7%) patients met the criteria for complete failure and were switched to high efficacy drugs very quickly (Group A, EESC). The remaining 153 (93%) patients had signs of partial treatment failure in the form of clinical and/or radiological activity, but did not meet the required criteria for inclusion in HE-DMT (group B) (Fig. 1). There were no differences between groups A and B regarding sex, age, EDSS score

Table 1. Demographic and clinical characteristics of study group

Parameter	Entire group (n = 165)	Group A (complete ineffectiveness) (n = 12)	Group B (partial ineffectiveness (n = 153)	P A/B
Age at treatment initiation, mean (SD)	31.03 (10.72)	27.89 (10.71)	30.1 (10.5)	U Test
Median (range)	31 (14–62)	22 (17–47)	31 (14–62)	U = 632;
				p = 0.34
Sex – n (%)				Chi-square test:
Female	102 (62%)	8 (67%)	95 (62%)	$\chi^2(1) = 0.8$;
Male	63 (38%)	4 (33%)	58 (38%)	p = 0.78
EDSS on treatment initiation, mean (SD)	1.41 (0.68)	1.39 (0.35)	1.41 (0.69)	U Test
Median (range)	1.5 (0–3.5)	1 (1–2.5)	1.5 (0–3.5)	U = 547;
				p = 0.87
Time from first symptoms to treatment (months), mean (SD)	28.9 (32.1)	33.6 (31.7)	26.4 (32.9)	U Test
Median (range)	14 (1–120)	24.5 (1–120)	9.5 (1–120)	U = 779.5;
				p = 0.019
Number of relapses within 12 months prior to treatment, mean (SD)	1.28 (0.77)	1.44 (0.53)	1.27 (0.78)	Median test:
Median (range)	1 (0–3)	1 (1–2)	0 (0–3)	$\chi^2(1) = 0.28$;
ARR (95% CI)	1.28 (1.09–1.5)	1.44 (0.77–2.47)	1.27 (1.08–1.49)	p = 0.53
				RR (95% CI) = 1.13 (0.51–2.05)
				p = 0.8
Time (months) from treatment initiation to ineffectiveness, mean (SD)	15.83 ± 10.29	12.67 ± 3.81	16.5 ± 10.56	U Test
Median (range)	11 (6–64)	11 (6–20)	11 (6–64)	U = 628.5;
				p = 0.36
EDSS on determining treatment ineffectiveness, mean (SD)	1.57 (0.75)	2.11 ± 1.14	1.53 ± 0.7	U Test
Median (range)	1.5 (0–5)	1.5 (1.5–5)	1.5 (0–4)	U = 313;
				p = 0.032

ARR — annualised relapse rate; CI — confidence intervals;EDSS — Expanded Disability Status Scale; RR — risk ratio;SD — standard deviation

at the start of therapy, or the number of relapses during the 12 months prior to treatment. However, patients from group A had a significantly later start of treatment, and significantly higher EDSS score in the period of therapy ineffectiveness. Demographic and clinical data of individual groups are set out in Table 1.

During the observation period, 28 (17%) patients in group B had treatment escalation at a later stage (LESC, late escalation group). Fifteen (9%) patients were switched to HE-DMT within the first two years after determining treatment ineffectiveness (LESC1), and 13 (8%) more than two years afterwards (LESC2). There was no therapy escalation for 125 (82%) patients, but 15 of these patients were treated with another moderately effective drug.

53% of late escalation patients with partial ineffectiveness were recruited from the group where clinical and MRI activity occurred simultaneously. The subjects who did not undergo therapy changes constituted a group presenting only MRI activity.

The relationships between the type of partial treatment ineffectiveness and the change of therapy are set out in Figure 2.

EDSS change

Baseline mean EDSS score before starting DMT was comparable in all groups. In the EESC group it was 1.39 (SD 0.35), LESC1 — 1.36 (SD 0.81), LESC2 — 1.5 (SD 0.62), and in the NESC group 1.42 (SD 0.72) (test H $\chi^{(2)} = 0.41$ p = 0.93). The EDSS score at the moment of determining treatment ineffectiveness was in the EESC group 2.11 (SD 1.14), LESC1 — 1.68 (SD 0.64), LESC2 — 1.55 (SD 0.76) and was in the NESC group 1.55 (SD 0.76) (test H $\chi^{(2)} = 4.84$ p = 0.18). After the observation period, the mean EDSS in groups changed, and statistically significant differences were found between the EESC and LESC2 groups. (U test = 70.5, p = 0.032). Comparing the value of the EDSS change in relation to the reference values, it was found that in the EESC group the neurological status of the patients was stable, and the EDSS in this group fell insignificantly. In the remaining groups, the neurological condition deteriorated, and the EDSS score increased. The largest increase in EDSS score was noted in the LESC2 group, and the smallest in the no escalation group (Tab. 2, Fig. 3). The assessment of the change in EDSS score between groups (using Bonferroni correction for multiple testing) showed statistically

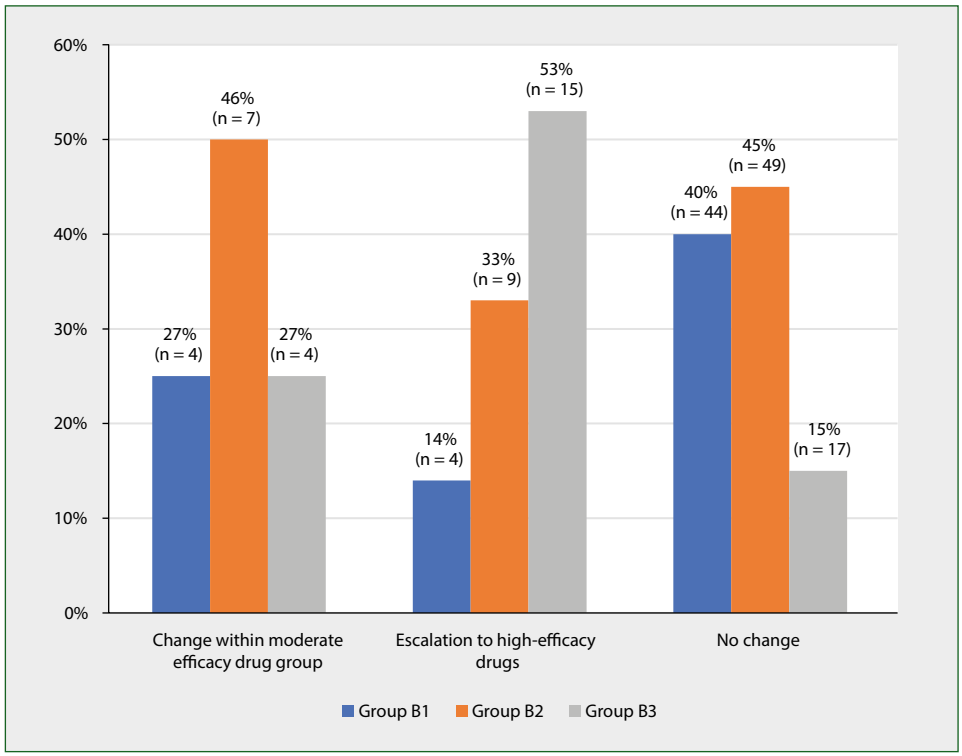

Figure 2. Change in treatment within 48 ± 3 months depending on type of partial ineffectiveness

Table 2. Comparison of EDSS score and number of GD+ and T2 lesions in groups after 48 ± 3 months of observation

	EESC group (n = 12)	LESC1 group (n = 15)	LESC2 group (n = 13)	NESC group (n = 110)	
EDSS after 48 months	M = 1.94; SD = 0.85 Md = 1.5; range 1.5–4	M = 2. 23; SD = 0.75 Md = 2; range 1–3.5	M = 2.75; SD = 1.14 Md = 2.5; range 1.5–5.5	M = 2.12; SD = 0.98 Md = 2; range 1–6	Test H: $\chi^2(2) = 5.96$; p = 0.11
ΔEDSS	M = –0.17; SD = 0.35 Md = 0; range 1–0	M = 0.73; SD = 0.72 Md = 0.5; range 0–2.5	M = 1.2; SD = 0.63 Md = 1; range 0.5–2.5	M = 0.62; SD = 0.56 Md = 0.5; range 0–2.5	Test H: $\chi^2(2) = 24.32$; p < 0.001
No. of Gd+ lesions	M = 1.11; SD = 2.98 Md = 0; range (0–9)	M = 8.73; SD = 11.06 Md = 2; range (0–30)	M = 9; SD = 8.83 Md = 6; range (0–25)	M = 0.81; SD = 2.93 Md = 0; range (0–24)	Test median $\chi^2(2) = 28.31$; p < 0.001
No. of T2 lesions	M = 2.11; SD = 3.65 Md = 0; range (0–9)	M = 9.64; SD = 7.49 Md = 9; range (2–25)	M = 10.4; SD = 8.64 Md = 8; range (2–30)	M = 1.67; SD = 3.13 Md = 0; range (0–18)	Test median $\chi^2(2) = 31.64$; p < 0.001

EDSS — Expanded Disability Status Scale; M — mean; Md — median; SD — standard deviation; EESC — early escalation group; LESC1 — late escalation group 1; LESC2 — late escalation group 2; NESC — no escalation group

significant differences between the EESC and LESC2 groups (p < 0.001), between LESC1 and NESC (p = 0.001), and between LESC2 and NESC (p = 0.002). There were no significant differences between the LESC1 and LESC2 groups.

Time to confirmed 6-month disability progression (6mCDP)

In the EESC group, none of the subjects met the 6mCDP criteria after the observation period. The highest percentage

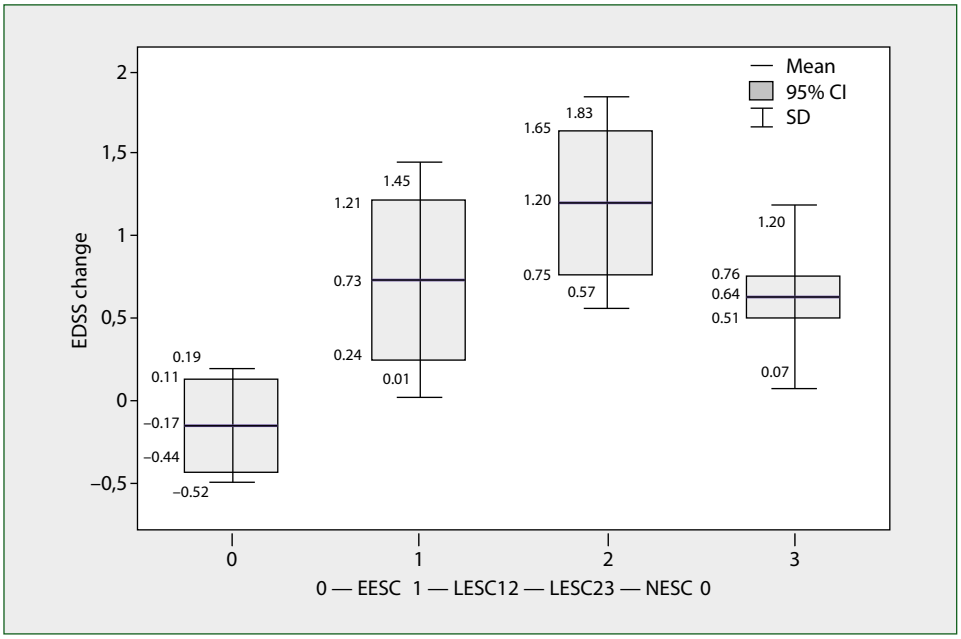

Figure 3. EDSS score change in groups after an observation period. CI — confidence intervals; EESC — early escalation group; LESC1— late escalation group 1; LESC2 — late escalation group 2; NESC — no escalation group; SD — standard deviation

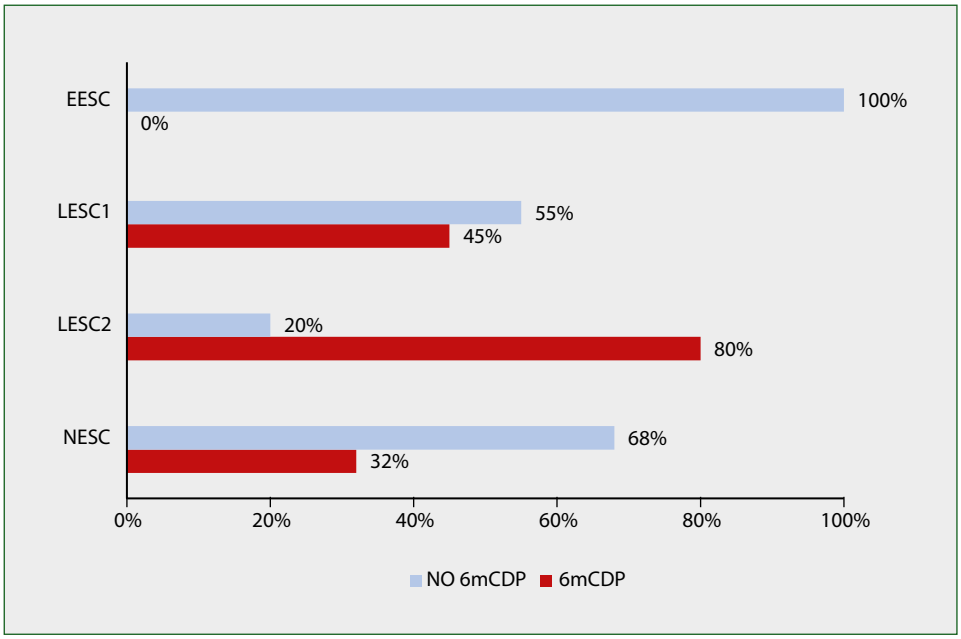

Figure 4. Percentage of patients meeting 6mCDP criteria after 48 ± 3 months of observation depending on escalation of therapy

(80%) of patients meeting the 6mCDP criteria was found in the LESC2 group (Fig. 4). In order to assess the risk of long-term accumulation of disability in the LESC1 and LESC2 groups and in the NESC group, Cox regression analysis was performed. The type of group was included in the baseline model, and the following variables were included in the adjusted model: gender, age at treatment initiation, year of treatment initiation, and time of treatment escalation during four years of observation. The median time to onset of 6mCDP in the LESC1 group was 55.5 months, (95% CI, 24–57), in the LESC2 group it was 54 months, (95% CI, 43–57), and in the NESC group it was 57 months, (95% CI, 55–57). The differences between the groups were statistically significant (log-rank test, p = 0.039). The primary model

Table 3. Cox regression model statistics

	HR (95% CI)	p-value
Baseline model		
LESC2	1.05 (0.38–2.9)	0.92
Group without change	0.463 (0.1–1.066)	0.07
Adjusted model		
LESC2	0.9 (0.323–2.511)	0.84
No escalation group	0.38 (0.16–0.9)	0.022
Age at treatment initiation	1.036 (1.003–1.069)	0.033

Note — reference group LESC1; other variables which were not included in table were not related to 6mCDP risk. CI — confidence intervals; HR — hazard ratio; LESC2 — late escalation group 2

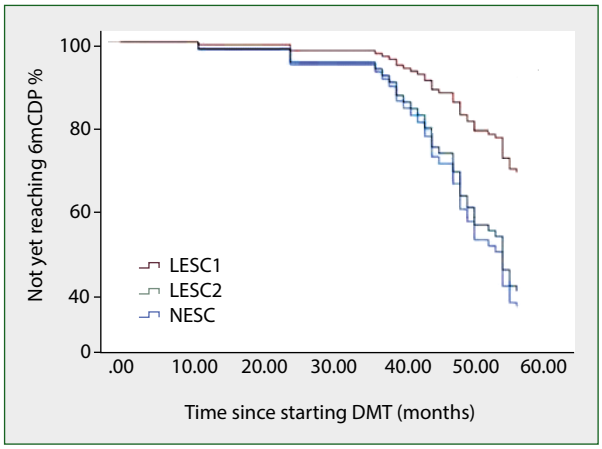

Figure 5. Time to 6mCDP depending on treatment strategy

(Cox regression analysis) showed no differences for 6mCDP risk in the compared groups. In the adjusted model, the risk of 6mCDP was lower in the NESC group (hazard ratio 0.38, 95% CI 0.16–0.9; p = 0.027). The risk was related to age at treatment initiation and was higher with older patient age (hazard ratio 1.036, 95% CI 1.003–1.069; p = 0.033). Statistical analysis for the baseline and adjusted models is set out in Table 3. The risk of reaching 6mCDP in the distinguished groups is set out in Figure 5.

Assessment of disease activity

In all study groups, a decrease in ARR was observed after DMT started, compared to the value before treatment. The largest reduction in ARR was in the EESC group (100%). In the LESC1 group, there was a decrease in ARR by 59%, and in the LESC2 group by 67%, compared to the baseline value.

The EESC group had no relapses during the observation period, while in the LESC groups ARR was 0.61 (0.45–0.8; 95% CI) and in the NESC group ARR was 0.17 (0.13–0.22; 95% CI). Comparison of the ARR values revealed significant differences between the LESC groups and the NESC group: relapse rate ratio 3.59 (95% CI, 0.252–0.609); p < 0. 001. There were no differences in ARR between the LESC1 and LESC2 groups.

A comparison of the cumulative number of GD+ and new T2 lesions in groups from the entire observation period is set out in Table 2. Statistically significant differences were found when comparing the number of Gd+ lesions in the EESC group to the LESC2 group (median test $\chi^2(1) = 9.019$; p = 0.005). The highest mean number of Gd+ and T2 lesions were recorded in the LESC2 group. A comparison between the LESC groups using Bonferroni correction for multiple testing showed that there was no significant difference between the LESC1 and LESC2 groups in either T2 (p = 1) or Gd+ (p = 0.86) lesions. However, statistically significant differences occurred when comparing Gd+ and new T2 lesions in the LESC groups with the NESC (p < 0.001). The lowest number of Gd+ and new T2 lesions was found in the NESC group.

Discussion

To date, RRMS therapy has comprised mostly the escalation model, in which a drug of moderate efficacy is initially selected, and then in the case of continued disease activity despite the treatment, this therapy is escalated to one of high efficacy drugs. To achieve optimal therapeutic results, early detection and prompt response to the effectiveness of the moderately effective DMT is necessary.

For administrative restrictions, Polish patients with RRMS have had limited access to high-efficacy drugs. Consequently, escalation therapy has not been implemented despite the fact that the ongoing treatment proved to be ineffective, and many patients were kept on previously selected treatment. In our study, we compared the clinical status and brain MRI results depending on the time of therapy escalation in 165 patients with RRMS treated with platform therapy, in whom clinical and/or radiological evidence of treatment ineffectiveness was observed.

Due to the applicable reimbursement criteria, only 7% of the respondents were able to use high efficacy drugs immediately after the therapy had been found to be ineffective. The others continued platform therapy or received delayed high efficacy treatment. This confirms our previous research demonstrating that therapy escalation was rarely used (in 9% of patients), and that the most common reason for changing treatment was the prevalence of side effects [14]. In addition, the data is consistent with the results obtained by Brola et al., who assessed access to high efficacy therapy in Poland in a multi-centre study [4]. During the observation period of 48 months, another 17% of patients met the criteria for escalation to high efficacy DMT, showing the obstacles in using active treatment due to administrative reasons, which are consistent with the data of National Health Fund, which shows that in 2014–2022 in Poland 6–9% of patients received high efficacy drugs [15]. In contrast, Patti et al. and Papp et al. documented an escalating rate of 53–60% after treatment with dimethyl fumarate and teriflunomide, and in a group of

German patients 43.5% received a subsequent high efficacy DMT as a second line therapy [16–18].

Our research has shown that in patients who, despite the use of platforms DMTs, show clinical activity of the disease, the lack of early escalation of therapy leads to worsening of the neurological condition and permanent disability. Comparison of long-term treatment effects in the EESC group with the effects in the late escalation groups (LESC1 and LESC2) showed stabilisation of the neurological status and reduction of the EDSS score in patients with early escalation, while the highest increase in the EDSS score was found in the LESC2 group. When assessing the increase in the EDSS score, the difference between the groups was clear, especially when comparing the EESC group to the LESC2 group, where the escalation was made more than two years after determining ineffectiveness.

This allows us to conclude that delaying the escalation of treatment in these patients resulted in worsening of their neurological status. Similar results were obtained when evaluating permanent disability. Subjects who escalated early (immediately when therapy was found to be ineffective) showed significantly less disability progression compared to patients who escalated later. In the EESC group, none of the subjects met the 6mCDP criteria at the end of the observation. The highest progression of disability was noted in patients who were treated with high-efficacy drugs more than two years after determining ineffectiveness. After 48 months, 45% of patients in the LESC1 group and 80% of patients in the LESC2 group met the 6mCDP criteria.

In the available literature, we found papers that assessed the clinical condition of patients after delaying the escalation of therapy [9, 10]. Our results are consistent with recently published observations in groups of patients from multi-centre studies, although the concept behind these studies is completely different [9, 11, 20]. The above studies compared patients starting MS treatment with high-efficacy drugs to those who escalated therapy after having determined the ineffectiveness of previous treatment.

In our study, all patients started treatment with drugs of moderate efficacy, and the escalation options in our group were limited.

Despite different groups, the clinical consequences are the same: in patients with active disease, the late use of highly active drugs leads to a worsening of the neurological condition.

In all groups, there was a decrease in ARR after the introduction of DMT, with the largest noted in the early escalation group. In the groups where the high-efficacy treatment was applied later, the reduction in ARR was not as significant. Our results are consistent with those of Harding et al. [9], who showed that an early start of high efficacy therapy lowers relapse frequency.

Many studies have evaluated T2 brain lesion counts and volumes after disease onset versus disability progression. A recent review and meta-analysis confirmed that lesion counts and volumes could be associated with disability progression [21]. Our study concentrated on the change in the cumulative number of Gd+ and T2 lesions depending on the time of therapy escalation. It is worth emphasising that during 48 months of observation in patients without treatment escalation, and with late escalation, the cumulative number of Gd+ or T2 changes increased significantly. The largest increase in MRI lesions was found in the LESC2 group. New, clinically silent lesions on MRI are 5–10 times more frequently observed than reported clinical relapses, and MRI disease activity has also been reported as a valid surrogate marker for clinical activity in relapsing MS [22]. Moreover, scoring systems combining MRI and clinical markers have been shown to predict long-term treatment non-response. Furthermore, a 1-year MRI lesion activity occurring with relapses justified the treatment outcome of EDSS worsening [23, 24].

In our study, we found a significant increase in the number of lesions, both Gd+ and T2, in the group of patients with late escalation, i.e. in patients who were constantly active despite treatment. In this group, we also found an increase in disability, which is consistent with the results of previous studies [20]. 67% of patients starting DMT did not switch therapy during the entire observation period. There was no significant increase in EDSS or brain MRI lesions in this group, and the median time to 6mCDP was 4.8 years. The only variable associated with the risk of 6mCDP in this group was patient age at the time of initiation of the first DMT. Ageing of the immune system and a worse response to DMT in patients aged over 40 is well-established [25]. A meta-analysis of randomised, blinded, DMT clinical trials showed that higher efficacy treatments exert their benefit over lower efficacy treatments, although this is observed only during the early stages of MS [26]. The relationship was not confirmed in a recent meta-analysis of clinical trials. Zhang et al. reported that DMTs for RRMS show efficacy in treating disease activity irrespective of age [27]. Furthermore, data on the importance of relapses and number of MRI lesions for predicting changes in EDSS and increasing disability are inconclusive.

An important parameter contributing to disability progression in MS, that was not taken into consideration, is brain atrophy. Brain volume loss happens independently from disease activity and cannot be prevented by early DMT implementation [28]. A previous work showed that the presence of an isolated relapse without changes in EDSS score during the first two years of treatment did not significantly impact upon an increased risk of developing marked long-term disability over a median five years [29]. But other, more recent, studies have revealed that clinical activity, defined as an EDSS score change or relapses during the first years of IFN-β treatment, had a very negative effect on the long-term prognosis [30, 31], and the same with the MRI scan. In patients treated with fingolimod, isolated MRI activity during the first year of treatment did not show a significant risk of future disease activity [32]. However, during the first year of IFN-β treatment, the

presence of substantial MRI activity increased the ability to predict treatment failure. The study concluded that substantial MRI activity during the first year of treatment with IFN-β, particularly if it is in combination with clinical relapses, indicates a significant risk of treatment failure and EDSS worsening over the short term [33]. Clinical and MRI activity in isolation may be not sufficient to determine treatment response, whereas the combination of these measures using composite scores appears preferable [34].

In our study, the patients who remained on treatment were mostly those with partial clinical or radiological failure. They were also more likely to have lower disease activity, which allowed them to maintain a good response to first-line treatment.

The limitations of our study concerned its retrospective and observational nature and the small size of the group, which are the results of it being a single-centre study. In addition, patients were included in DMT at different time periods from the onset of symptoms, which may affect disease activity and treatment response. However, in contrast to multicentre studies, EDSS was assessed by a single investigator, which significantly reduces the variability of results. This is important because EDSS is a scale characterised by high inter-rater variability and fluctuation. In addition to assessing parameters such as EDSS and ARR, the cumulative increase in the number of demyelinating lesions in brain MRI was also evaluated.

Permanent disability in the course of MS depends on many factors, including the consequences of relapses, the effects of the inflammatory and neurodegenerative process, and the effects of the treatment applied. It is likely that there is an 'early window' of therapeutic opportunity where disease modification is possible, bringing about long-term benefits. After some time a threshold is crossed, above which accumulated immune damage leads to permanent and progressive neurological disability [9].

In light of this data, we suggest it is justified to use rapid escalation of therapy in patients with suboptimal response to treatment, as a delay may result in increasing disability.

Changes in the NFZ therapeutic programme also make it much easier these days to start HE-DMT earlier in Poland, e.g. applying monoclonal antibodies in treatment-naive patients.

Article information

Data availability statement: *The original contribution presented in the study is included in the article; further inquiries may be directed to the corresponding author.*

Ethics statement: *The study protocol was approved by the local Bioethics Committee and the participants involved in the study gave their consent.*

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