ABSTRACT

Introduction: Multiple sclerosis (MS) is a chronic inflammatory and demyelinating disease of the nervous system accompanied by a progressive neurodegenerative process. The disease involves multifocal damage to the central nervous system (CNS), causing a variety of neurological symptoms. It is estimated that there are 2.9 million people with MS worldwide. In Poland, there are around 51,000 patients, with an estimated prevalence of 134 per 100,000 inhabitants. MS is the leading cause of non-traumatic disability in young adults.

Improved diagnostic criteria, the widespread use of MRI scans, and the growing availability of effective pharmacological treatments have led to significant advances in the management of MS over the past few decades. The current approach to the treatment of multiple sclerosis focuses on predicting the course of the disease, the initial choice of treatment and the assessment of early response to treatment in order to identify the need for a change in therapy. Early prediction of response to treatment remains one of the main challenges in the management of patients with multiple sclerosis. There are no clear parameters that allow us to assess the likelihood of a positive or negative response to treatment. There is also no clear evidence that the response to treatment during the first 12 months of DMT use determines its effectiveness in subsequent years or can serve as a prognostic factor for untreated patients.

Objective: The aim of this study is to assess the early response to treatment and to analyse the correlation between clinical and radiological activity during the first year of immunomodulatory therapy in patients with RRMS, and the treatment's efficacy over the subsequent four years of follow-up. A further aim of the study is to investigate whether clinical and radiological measures of disease activity can predict response to treatment in RRMS patients.

Materials and methods: The study included 165 patients (107 women and 58 men) with relapsing-remitting multiple sclerosis, diagnosed in accordance with the 2010 McDonald criteria. All patients commenced and continued immunomodulatory treatment under medication programmes between 2013 and 2022. The study participants were aged between 19 and 70 years old, with an average age of 39.3 years (SD = 11.1).

The total follow-up period was five years (60 ± 3 months). All patients gave their consent to participate in the study.

During the initial stage of the study, baseline demographic, clinical, and radiological data were collected.

Subsequently, the patients' neurological status was assessed using the EDSS scale at 3-monthly clinical visits. Brain MRI scans were performed every 12 months during treatment, in accordance with the applicable protocol.

After the first 12 months of treatment, selected parameters were evaluated, including clinical and radiological activity, the EDSS score, changes in the EDSS score, and the proportion of patients without signs of disease activity (i.e. maintaining the NEDA-3 parameter). Data from the first 12 months were considered baseline data.

After a further 48 months of treatment, the following were assessed in each group: cumulative clinical and radiological activity, EDSS, changes in EDSS, annual relapse rate (ARR),

changes in treatment, the proportion of patients with NEDA-3 and time to six-month confirmed disability progression (6-mCDP).

The results obtained were subjected to statistical analysis. The Kaplan–Meier estimation method was used to analyse time to 6-month CDP, while the Cox proportional hazards model was used to examine the impact of individual factors on disability progression.

Results: Participants began immunomodulatory treatment at an average age of 32.2 years (SD = 10.9) and 28.9 months (SD = 32.1) after the onset of their first disease symptoms. Prior to treatment, the ARR in the study group was 1.26 and the median EDSS score was 1 (range 0–3.5).

The study group received treatment available under the National Health Fund's (NFZ) medication programme. Injection therapies (interferons and glatiramer acetate) were administered to 92% of patients, while 8% received oral dimethyl fumarate.

During the first year of treatment, 47% of patients in group I showed no disease activity (no relapses, no new lesions on MRI, no progression in EDSS (6-month CDP), and all participants continued their current treatment.

A suboptimal response to treatment was observed in 48% of patients (group II), of whom 30% experienced only relapses, 40% only radiological activity and 30% both.

In the remaining 5% of patients (group III), both clinical and radiological activity were observed. Treatment was escalated to HET for all subjects in this group after 12 months.

Over the following 48 months, relapses were observed in patients in groups I and II, whereas no relapse activity was recorded in group III. The highest relapse activity was observed in patients with a suboptimal response to treatment in the first year (group II), particularly in those exhibiting both radiological and clinical activity (88% of whom had at least one relapse). The lowest relapse rate was observed in patients with radiological activity alone during the first year of therapy. Overall, 70% of patients with a suboptimal response experienced at least one relapse within 4 years, in contrast to patients who maintained NEDA-3 status during the initial year of treatment (group I). Among these patients, only 30% experienced at least one relapse during the four-year follow-up period.

The highest proportion of patients with no new T2 lesions identified on brain MRI scans over the following 48 months was observed in group I (64%), compared to 34% and 50% in groups II and III, respectively.

Furthermore, 79% of patients in group I and 75% in group III showed no new Gd+ lesions after an additional 4 years of follow-up.

Group II had the highest mean number of new T2 and Gd+ lesions after a further 48 months, while group I had the lowest. These differences were highly statistically significant ($p = 0.0000$). Furthermore, in the suboptimal response group, the highest number of T2 and Gd+ lesions was observed in patients with concurrent clinical and radiological activity after the first 12 months of therapy.

The highest mean EDSS scores were observed in group I (those with a suboptimal response; M=2.15; SD=0.93), and the lowest in group III (M=1.69; SD=0.37). However, these differences were not statistically significant. Subjects showing a suboptimal early response also recorded the greatest disability progression as measured by the EDSS scale: EDSS increased by 59% in this group compared to 34% in group I and 44% in group III.

Following a further 48 months of follow-up, 30% of participants met the established criteria for six-month disability progression. The highest proportion (41%) was observed in group II participants; however, 6-month CDP was also observed in 21% of group I patients and 12% of group III patients. In addition, it was found that approximately half of the patients in the groups with clinical activity and with both clinical and radiological activity reached the threshold for confirmed disability progression after 48 months of follow-up.

By 48 months after starting treatment with moderately effective drugs, patients in group I had not reached the predefined disability endpoint.

By comparison, for group II patients showing clinical activity, this threshold was reached after 36 months. For patients with a suboptimal response showing only radiological activity during the first year of treatment, time to disability progression depended on the type of lesions observed on MRI scans. In the group with new Gd+ lesions, the proportion of patients who had not reached 6-mCDP decreased as early as 24 months, whereas in the group with new T2 lesions, this occurred after 48 months. For patients with concurrent clinical and radiological activity, the time to reach 6-mCDP was 24 months.

Participants who experienced at least one relapse during the first year of treatment had a four-fold higher risk of disability progression, as measured by the 6m-CDP (HR=3.93), than patients who maintained NEDA-3 status. Similarly, participants in whom both disease relapses and radiological activity were observed had a threefold higher risk of disability progression than group I (HR = 3.01).

Among patients exhibiting radiological activity alone, no increased risk of disability was evident after four years (HR = 1.53, not statistically significant).

After five years of follow-up, 29 patients (18% of the entire study group) had maintained NEDA-3 status. Radiological activity was found to be the most common cause of loss of NEDA status, accounting for 65% of cases.

The study results suggest that patients who did not respond well to treatment after 12 months had an unfavourable prognosis. This group showed the highest proportion of patients displaying signs of disease activity over the subsequent 4 years, as well as reaching the accepted disability milestone in the shortest time.

Conclusions: Radiological activity is observed more frequently than clinical activity during the first year of treatment with platform drugs. 47% of patients maintain NEDA status after the first 12 months.

The occurrence of disease relapses and/or gadolinium-enhancing lesions during the first year of immunomodulatory therapy is associated with a higher risk of disability progression over the following four years. This indicates the need for rapid treatment escalation in patients with active disease.

Disease relapse is the strongest adverse predictor during the first year of treatment. Even a single relapse in the early stages of treatment significantly worsens the prognosis and requires therapy to be modified immediately.

The presence of T2 lesions on an MRI scan after 12 months of treatment does not predict disability progression over the following four years. This may be partly due to 'residual' activity following treatment initiation.

Assessing disease activity during the first year of treatment may help to predict how patients will respond to treatment in subsequent years, and can identify those at risk of disability progression.

Although maintaining the NEDA-3 score after the first year of treatment is associated with less disability progression after five years, it is not an ideal predictor of disease progression. This parameter needs to be supplemented with additional indicators that take into account the inflammatory process and neurodegeneration. These indicators could be used in everyday clinical practice to identify the need for a change in treatment.