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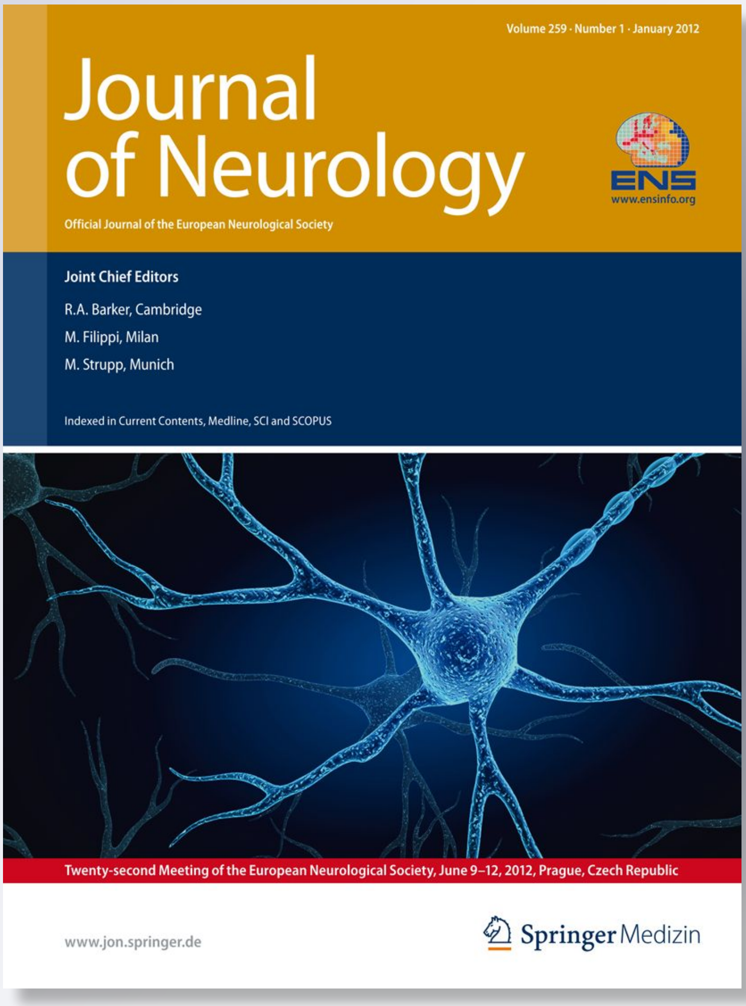

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ORIGINAL COMMUNICATION

Background information on multiple sclerosis patients stopping ongoing immunomodulatory therapy: a multicenter study in a community-based environment

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Absract Adherence to an immunomodulatory therapy still needs to be improved in MS patients. We analyzed the data of 396 MS patients of 40 German MS outpatient centers who had stopped an ongoing immunomodulatory treatment. Items analyzed were among others adherence data, reasons for the interruption and willingness to start a new therapy. It became obvious that 74.6 % of the patients made the decision to withdraw from therapy on their own. The most commonly mentioned reasons for the withdrawal were proven or putative lack of efficacy (51.4 %), side effects (58.1 %), and complaints of fatigue and depression. There was no difference concerning sex, duration of the treatment and medication taken. The expectations correlated with the empathy of the treating physician and the setting with MS nurses taking care of the patient. A total of 199 patients (51.8 % of the females, 48.9 % of the males) wanted to restart another IMT. Reasons for not wanting to restart were lack of conviction that a therapy may influence the disease (29.4 %), fear of injection (18.7 %), fear of bringing the disease to mind regularly (17.9 %) and doubt about the diagnosis (11.2 %). The results suggest that adherence is most effectively promoted by cultivating an appropriate and individual therapeutic setting for each MS patient on a medical, organizational and last but not least psychological level.

Keywords Multiple sclerosis · Adherence · Immunomodulatory therapy · Interferons · Drug therapy

Introduction

Immunomodulatory and immunosuppressive agents are widely used today in multiple sclerosis (MS) treatment to influence the natural course of the disease. A reduction in the number of relapses and in the cumulative number of new T2-weighted white matter lesions has consistently been demonstrated in patients with relapsing-remitting multiple sclerosis (RRMS) for beta-interferons [1–3], glatiramer acetate [4] with early treatment, and natalizumab [4, 5] as an escalating therapy. The efficacy of a drug, however, is critically dependent on its continuous application. Interruptions in drug therapy or improper administration may reduce the efficacy of treatment and cause the disease to progress more rapidly [6–8].

Despite the improvement in long-term outcomes, patients' adherence to current MS therapies is still rather poor. This is also true for the immunomodulatory therapies (IMT), i.e., beta-interferons and glatiramer acetate. Recent studies indicate that adherence is generally lower than expected and particularly vulnerable during the first few months of IMT [9–11]. Data from the U.S., Canada and Europe show that adherence rates using different IMTs vary considerably between 75 and 36 % after 1 year, and decline to a range between 47 and 33 % after 2 years of application [8, 12–15]. Among IMTs, adherence seems to be higher with weekly intramuscular interferon (IFN)-

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On behalf of the N.T.C. study group.

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beta1a than with the subcutaneous application of IFN-beta1a, IFN-beta1b and glatiramer acetate (12,15), albeit some data deny this [13].

The main reasons for early drug withdrawal are side effects and a feeling of insufficient efficacy, since IMTs are usually purely preventive without targeting a specific clinical problem [16]. Other reasons lie in the therapeutic setting, since IMTs are applied by the patients themselves or by their relatives without involvement of the doctor or a medical institution [11]. Therefore, problems with self-organization and self-injection competence have been found to negatively influence adherence [17, 18]. This applied particularly to treatment-naïve patients [18]. Later in the course of the disease patients discontinue therapy mainly due to a real or assumed lack of efficacy. Analyzing cases of drug discontinuation motivated by lack of efficacy, it was found that the mean delay from initiation of therapy was 36 months [19]. Moreover, complex psychosocial factors (patients' perceptions, emotional status, support) exert their influence on adherence throughout the disease process [20, 21]. In this context, it is alarming that treating physicians tend to overestimate the positive adherence in their own patients due to problems of validation and interpretation of their feelings and self-reports [22].

By performing this study, we were interested in the reasons for dropping out among MS patients undergoing IMT in an ambulatory setting. Questions were whether the decisions regarding therapy are made by the patients themselves or whether and how they were influenced by other factors. Moreover, we wanted to know the reasons for stopping treatment and to which extent decisions depended on medication, disease-related aspects and/or the qualification, empathy and the availability of MS nurses taking care of the patients and teaching them how to use their medication.

The knowledge of these factors is important for optimizing existing therapies and support-giving systems, especially in the outpatient sector, and for designing future cost- and outcome-effective treatment settings in MS outpatient centers.

Methods

MS patients from 40 German practices specializing in the outpatient care of MS patients in a community environment were screened. The patients were seen regularly by the treating physician and were additionally cared for by a trained MS nurse. Inclusion criteria for the study were relapsing-remitting (RRMS), primary progressive (PPMS) or secondary progressive (SPMS) forms of MS and discontinuation of a prior IMT at least 3 months prior to the start of investigation in October 2009. Patients who had stopped therapy at any time since 1995 were included. They were identified in a medical database of MS patients available to all medical centers. The exact number of patients in the database at the time the data were retrieved was not recorded and cannot be analyzed retrospectively. All types of previous treatment, both immunomodulation and immunosuppression, were considered eligible. Patients who had been identified as stopping treatment were contacted by telephone. Those still on medication at another treating institution, e.g., due to moving or changing physicians were excluded. The others were asked about their reasons for stopping their last therapy as well as about adherence to all former therapies using a (semi)-structured interview. In addition, medication history, their current situation including demographic data and present Expanded Disability Status Scale (EDSS) values were collected and evaluated. EDSS at the time of stopping medication was not available in many of the patients, because a systematic documentation of EDSS values was not started until 2003. To provide reliable data, a telephone interview was performed using a standardized questionnaire. At the end of the interview the patients were asked how they felt about starting another MS therapy. If interested, they were invited to a personal interview to discuss restarting therapy. For all other patients, the reasons were evaluated as to why they were not interested in IMT.

All patients who were contacted by telephone and who were willing to answer the questionnaire were asked to take part in a short test to assess the quality of life (MusiQol) and to fill out the FPI (Freiburg Personality Inventory). The FPI comprises 138 items which make up the following 12 scales to describe and specify personality structure: (1) life satisfaction, (2) social orientation, (3) performance orientation, (4) inhibition, (5) excitability, (6) aggression, (7) strain, (8) somatic distress, (9) health worries, (10) social desirability, (11) extraversion and (12) neuroticism**.**

Results

A total of 396 patients (89 males, 297 females) between 19 and 76 years of age entered the analysis. The mean age across both sexes was 41.3 years and the mean EDSS value was 2.7. Interestingly, the time between the first symptoms and the diagnosis and also the time between diagnosis and the start of the first IMT was rather long and exceeded 2 years when looking at the entire patient sample (means of 24.9 and 26.2 months, respectively). Basic sociodemographic and clinical data for all patients and sex-related subgroups are summarized in Table 1. Data for the subgroups (Table 2) show that patients on immunosuppressive drugs were slightly older and had EDDS values higher than in the IMT group, as expected. The duration of treatment

Table 1 Summary of sociodemographic and clinical data for the entire patient group

	Males	Females	Total
Number	89	297	396
Age	42.2 ± 10.8	41.0 ± 10.2	41.4 ± 10.3
Unable to work due to the MS	21	71	92
RR-MS	66	229	295
PP-MS	5	7	12
SP-MS	17	37	54
EDSS	3.1 ± 2.1 (median 3)	2.6 ± 2.0 (median 2)	2.7 ± 2.0 (median 2)
Time between first symptoms and establishing the final diagnosis	19.7 ± 60.4 months (median 2)	25.7 ± 51.9 months (median 5)	24.9 ± 55.4 months (median 4)
Time between diagnosis and start of the first IMT	29.3 ± 50.8 months (median 6)	26.6 ± 47.6 months (median 6)	26.2 ± 28.4 months (median 6)
Duration of the treatment	31.1 ± 31.6 (median 23)	30.4 ± 32.4 (median 19)	30.5 ± 32.1 (median 20)

Table 2 Summary of sociodemographic data related to different treatments

	Immunomodulatory		Immunosuppressive		Natalizumab	
	Males	Females	Males	Females	Males	Females
Number	80	261	7	26	2	6
Age	41.6 ± 10.7	40.4 ± 10.0	49.6 ± 0.7	47.9 ± 10.3	47 ± 14.4	41.7 ± 13.6
Unable to work due to the MS	17	55	0	5	0	3
RR-MS	63	205	3	16	1	5
PP-MS	4	6	0	0	1	0
SP-MS	13	30	3	7	0	1
EDSS	3.0 ± 2.1 (median 3)	2.5 ± 2.2 (median 2)	4.0 ± 2.4 (median 3.75)	3.5 ± 2.4 (median 3.5)	6.0	3.3 ± 2.2 (median 2.75)
Time between first symptoms and establishing the final diagnosis	20.9 ± 63.6 months (median 2.5)	27.4 ± 54.3 months (median 5)	5.6 ± 7.4 months (median 2)	26.0 ± 28.5 months (median 4)	1.0	5.5 ± 9.3 months (median 2.5)
Time between diagnosis and start of the first IMT	25.2 ± 41.2 months (median 5.5)	25.6 ± 46.8 months (median 6)	58.8 ± 123.8 months (median 1)	45.8 ± 72.9 months (median 8)	95.5	8.0 ± 15.7 months (median 3)
Duration of the treatment	30.7 ± 30.8 (median 22)	28.5 ± 27.4 (median 19)	36.6 ± 43.1 (median 23)	53.2 ± 59.5 (median 30)	13.0	8.5 ± 5.6 months (median 8.5

was longer in patients on immunosuppression due to the inclusion of patients treated for many years with azathioprine.

Sex differences were observed in the total number of patients included and concordantly in MS subgroups with females dominating due to their higher MS incidence. In EDSS, on the other hand, males scored higher than females due to a higher percentage of PPMS and SPMS cases in the male patient sample. The interval between the first symptoms of MS and the definite MS diagnosis was shorter in males than in females, but with a huge range in both groups which explains the big standard deviation. In turn, the interval between establishing the final diagnosis and the start of the first IMT was very similar in both sexes.

Table 3 shows the EDSS values in relation to the type of drug. As natalizumab and mitoxantrone are second-line therapies patients with those therapies usually have more relapses and have had the disease longer; thus, the EDSS values are higher than in the interferon and in the glatiramer acetate group. The proportion of patients using first-line therapies is representative of the whole patient sample. The high number of patients formerly treated with azathioprine is in part explained by the fact that some patients had stopped the therapy more than 10 years before being interviewed without ever starting a new therapy.

A MS nurse with special training in MS and MS therapies attended IMT in 41.6 % of the patients. In 22.2 % the therapy was initiated in a hospital during the in-patient

Table 3 Type of drug therapy in relation to EDSS value immediately before the last IMT was stopped

	Number	EDSS Mean	EDSS Standard deviation	EDSS Median	EDSS Range
Avonex®	89	2.04	1.71	2	7.5
Azathioprine	20	2.87	1.84	3	6.5
Betaferon®	65	2.96	2.23	3	8
Copaxone®	60	2.67	1.88	2.25	7
Rebif®	85	2.79	2.05	2.5	8.5
Tysabri®	6	3.75	2.23	2.75	5
Mitoxantrone®	11	4.81	2.63	4.0	7

period or in the out-patient unit of the hospital immediately following a patient's discharge.

The analysis showed that the adherence during the last therapy that had been stopped was a little bit higher in males than in females (mean %, ±SD: 85.7 %, ±22.3 vs. 79.9 %, ±28.4 in women) and in patients who had had the disease for longer compared to shorter periods of time (83.3 ± 25.9 vs. 79.8 ± 28.2).

The individual risk related to the MS that the patient expects a progression of the disease depends on the EDSS. In patients with an EDSS > 2 (median value) the risk attributed to the MS was thought to be higher than in patients with lower EDSS values.

The expectation of whether the IMT might be successfully changed during the therapy. At the start of the therapy 59 % of patients expected that IMT would positively influence the course of the disease, but at the time it was stopped only 49 % expressed this hope. There was a high correlation between the values at the beginning and at the end of the therapeutic cycle ($r = 0.62$). A positive influence on the expectation of success was found in patients being cared for by an MS nurse, in females compared with males, and in patients with lower EDSS values. Most interestingly, the rates of expectation during therapy correlated significantly with the physician's empathy ($r = 0.29$), but not with the level of expertise the patient gave the physician.

A majority of the patients (74.6 %) mentioned that it was their own decision to stop the therapy. Only very few were influenced by others (4.9 %). About half of them informed the treating neurologist about their decision. Table 4 summarizes the reasons given for stopping the last IMT. As multiple answers were allowed, most subjects gave more than one reason; the median was 6 (range 3–18). There were no differences for the reasons given related to the various drugs. Often patients expressed that they did not want to be reminded of the disease. This was not due to fear of injection but due to the psychological problem that they are confronted with the disease. This argument was expressed more often by patients injecting interferon into the muscle once a week than by patients injecting it several times a week or injecting glatiramer acetate daily. The number of patients stopping therapy due to side effects and loss of efficacy was the same in all drug subgroups.

In the different subgroups, only a few differences were found: patients with an EDSS value above the median value more often indicated lacking efficacy and more relapses as a reason for stopping the therapy. Males more often expressed doubts about the diagnosis, and, among them, more often in those who turned into a secondary progression. Females complained more often about depression and side effects, e.g., pain at the injection site.

Among subgroups of patients on immunosuppression, immunomodulation and natalizumab, differences were found according to the known side effects of medication, but not according to other factors.

Of the 396 patients, 199 (52.6 % of the females and 48.9 % of the males) wanted to initiate an IMT again. In those who said they did not want to restart IMT, males more often had doubted the efficacy of the therapy than females. This was the same in patients with EDSS values above the median EDSS.

Changes in blood tests leading to discontinuation of therapy were mostly an increase in liver enzymes followed by problems with white blood cell count.

The main reasons for restarting treatment were fear of progression (74.4 %) and hope that new drugs may be more effective than the ones formerly used (47.9 %). The advice of the treating physician was rated as important as the continuous support of an MS nurse. In addition 94 % of the patients evaluated the time the nurses provided support for them as acceptable. Comparing patients who started up treatment again with those who did not, the number of relapses (58 vs. 39 %) and the progression rate seen on the actual MRI scans (37 vs. 15 %) was higher in those who reinitiated treatment.

The patients were also asked about depression and fatigue. Both complaints were decidedly more common in females than in males (depression 23.4 vs. 16.7 % and fatigue (48.9 vs. 37.9 %).

The results of the FPI-R were similar in patients who wanted to restart IMT and those who did not. The only

Table 4 Reasons for stopping the IMT

	Total	Immunomodulation ($n = 344$)	Immunosuppression ($n = 33$)	Natalizumab ($n = 8$)
Flu-like side effects	226	212	11	0
Lack of efficacy	196	171	19	0
Relapses	121	108	10	1
Erythema	165	155	8	0
Fatigue	153	137	12	1
Feeling of ineffectiveness	91	79	7	1
Injection pain	135	128	4	0
Depression	119	111	5	1
Progression on MRI scans	63	57	4	1
Doubts regarding therapy	82	68	13	1
Psychological reasons due to repeated reminders of the disease through the therapy	68	66	2	0
Fear of injection	60	56	3	0
Change to a secondary chronic progressive state	35	29	4	1
Pregnancy	46	39	0	0
Laboratory test result changes	39	32	4	0
Local necrosis	35	33	1	0
Doubt regarding diagnosis	27	23	0	1
Loss of confidence in the physician	17	16	1	0

More reasons could be given for stopping treatment; the difference between total number and subgroups is due to some missing attributions

statistically significant difference was the difference of physical condition. Those who complained of physical signs and symptoms started a new therapy more often than those without such complaints.

Discussion

Lack of adherence to long-term medication is a very common problem in the treatment of chronic diseases, and it comprises the efficacy of treatment. This fact has also been confirmed in MS patients in various studies. We were interested in the reasons for non-adherence to current MS therapies and in patients' attitudes towards further therapies after stopping medication in MS patients being cared for in a community environment. First, demographic and psychosocial factors are known to influence adherence [23, 24]. Therefore, the patients for this study were taken from 40 different outpatient centers throughout Germany to exclude a regional or center-related influence. During appointments at regular intervals, patients were seen by the physician as well as by an MS nurse to increase medical attendance. Demographic characteristics for our patients are in accordance with previously published data concerning sex ratio, age, social and psychological status [24]. We consider our cohort representative for MS patients that are treated in an outpatient situation. As is generally known, more females suffer from MS than males, but in our cohort primary and secondary chronic MS is much more common in men than in women. This finding is echoed by other studies reporting a more favorable disease course in female MS patients compared to males [25, 26].

The time interval between first symptoms and the establishment of the diagnosis of MS, as well as between the final diagnosis and the initiation of the IMT, was rather long, spanning approximately 2 years when viewing the patient sample as a whole. Data from individual centers showed a huge range of time intervals (0–420 months) providing evidence that the standard care of MS patients in Germany is still characterized by regional differences. Especially in rural areas, the intervals between final diagnosis and patients' referrals to out-patient MS centers are longer than in urban areas resulting in a delay with long-term treatment initiation and further care.

When asking the patients about their expectations at the beginning and the end of the therapy, as expected, the hope of influencing the course of the disease was lower at the end of the therapy compared to the beginning. This may be partly explained by the fact that some patients experienced a progression of the disease and had relapses despite IMT or immunosuppression. But this did not necessarily reduce adherence. Accordingly, recent data evaluating exacerbation history show that patients experiencing higher annualized relapse rates missed fewer doses of medication and appointments than stable ones [27]. Conversely, in patients without new relapses the doubt about the necessity of a long-term, parenteral therapy may be put forward as an argument and undermine adherence [28].

It became evident that the majority of patients made the decision to stop medication by themselves. The type of therapy was not a main factor in their decision. There were only two exceptions: (1) due to the strict restrictions on the total dose of mitoxantrone it was necessary for several patients to end this therapy. (2) In women who wanted to become pregnant and in those who became pregnant during an immunotherapy the medication had to be stopped. Otherwise, there were no differences among the various therapies, including the type of application or the number of injections with respect to discontinuation of therapy. The relatively low percentage of patients who intended to start a new therapy after stopping a previous one is known from the literature [10] and shows the importance of long-term coping and caring strategies. When asked about their further expectations, the restart was mainly motivated by the fear of progression of the disease. This highlights the necessity of additional long-term mentoring of MS patients in the community environment.

Interestingly, "subjective" reasons, such as fear of injection, doubt about efficacy and others, were mentioned almost as frequently as reasons for stopping therapy as side effects and loss of efficacy. This is important since all IMT for MS is prophylactic and all types of first-line therapies are administered by injections [20]. Therefore, it is not only important to re-evaluate the patients on clinical grounds and to perform follow-up MRI scans, but also to support them psychologically. This need is highlighted by the observation that patients attached much more importance to the empathy of the physician about the patients' concerns than to his or her medical expertise. The latter was also assessed as relevant but of minor importance during therapy. Thus, our observations broaden the currently available data on the high impact of the patient–physician relationship on adherence. In addition, the support of an MS nurse was considered of great importance for initiation and continuation of therapy. This underlines the impact that disease management programs in general and nursing systems in particular have for the support of patients suffering from chronic diseases like MS [28, 29].

To improve adherence to the therapy in chronic diseases like MS, more individual support and coping strategies have to be developed. Overall, the influence of self-competence, psychosocial and organizational factors on adherence seems to be as important as the expertise of the doctor and so-called 'hard' medical facts. The patients want to feel safe with the injectable medication and emotionally accepted. As a consequence, positive adherence is not generated by an isolated factor but by the interplay of multiple factors made up of adequate organisation, psychosocial support, good medical care, and a trustful patient–physician interaction.

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Conflicts of interest None.

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