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ORIGINAL ARTICLE

Global Adherence Project to Disease-Modifying Therapies in Patients With Relapsing Multiple Sclerosis: 2-Year Interim Results

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KEYWORDS
Multiple sclerosis;
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Abstract
Background: In this article we report adherence data from the first 2 years in a subset of patients from the Global Adherence Project (GAP; n=2,648) in Spain.
Methods: A questionnaire assessing adherence to Disease-modifying therapies (DMTs), was distributed annually to patients and their treating neurologists. Non-adherence was defined as missing a DMT injection or changing a dose in the four weeks prior to completing the survey. Patients signed informed consent and Ethics Committees approved annual follow-ups, visit 1 (V1) and visit 2 (V2) in 15 out of 18 centres in Spain.
Results: A total of 254 patients were enrolled in Spain. Patients had a mean age of 37.9 years and 70.4%were female, and had been on their treatment for a median time of 28 months, and the overall adherence rate was 85.4%. Patients taking intramuscular interferon beta (IFNB)-1a (Avonex®) were significantly more adherent (94.6%) compared with patients taking subcutaneous (s.c.) IFNB-1a 22μg (Rebif®22) (79.1%; p=0.0064), s.c. IFNB-1a 44μg (Rebif®44) (79.6%; p=0.0064) and glatiramer acetate (GA) (82.7%; p=0.0184). At V1 (n=142), the overall adherence rate was 86.6% and patients on Avonex® were significantly more adherent than patients on Rebif®22 (93.9%versus 66.7%; p=0.0251). At V2 (n=131), the overall adherence rate was 82.4% (Avonex®, 87.5%; Rebif®22, 80%; Rebif®44, 77.8%; Betaferon®, 85.2%, and Copaxone®, 80%) without significant differences.
Conclusions: Adherence remained high over the first 2 years of the study. It was highest with Avonex®, being significant on first assessment, after 40.5 months of therapy, on average compared with other DMTs and at year 1 compared with Rebif®22.

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PALABRAS CLAVE
Esclerosis múltiple;
Tratamientos inmunomoduladores;
Enfermedades crónicas;
Adherencia

Estudio global de adherencia a los tratamientos inmunomoduladores en pacientes con esclerosis múltiple remitente recidivante: resultados a 2 años

Resumen
Introducción: En este artículo comunicamos resultados de adherencia a los 2 años en la subpoblación de pacientes del estudio Global de Adherencia GAP (n=2.648) en España.
Métodos: Pacientes y neurólogos completaron cuestionarios anuales para evaluar la adherencia a los tratamientos inmunomoduladores (IMA). Se definió la falta de adherencia como la pérdida de una inyección o el cambio de dosis en las últimas 4 semanas previas a completar el cuestionario. Los pacientes firmaron el consentimiento informado. Estudio aprobado en 15 de 18 centros en los seguimientos anuales de la visita 1 (V1) y la visita 2 (V2) por los comités éticos.
Resultados: Se incluyó a 254 pacientes en España; la media de edad fue 37,9 años y el 70,4%eran mujeres; la mediana de tiempo en tratamiento fue 28 meses y la tasa de adherencia conjunta, del 85,4% Los pacientes en tratamiento con interferón beta (IFNB)-1a intramuscular (Avonex®) fueron significativamente más cumplidores (96,4%) que los pacientes tratados con IFNB-1a 22µg subcutáneo (s.c.) (Rebif®22) (79,1%; p=0,0064), IFNB-1a 44µg s.c. (Rebif®44) (79,6%; p=0,0064) y acetato de glatiramero (Copaxone®) (82,7%; p=0,0184). En V1 (n=142), la tasa de adherencia fue del 86,6%; los pacientes con Avonex® fueron significativamente más cumplidores que aquellos con Rebif®22 (el 93,9 frente al 66,7%; p=0,0251). En V2 (n=131), la tasa de adherencia fue del 82,4%(Avonex®, 87,5%; Rebif®22, 80%; Rebif®44, 77,8%; Betaferon®, 85,2%, y Copaxone®, 80%) sin diferencias significativas.
Conclusiones: La adherencia permaneció alta los 2 años observados. Avonex® mostró mayor adherencia frente al resto; esta diferencia fue significativa en la visita basal, tras 40,5 meses de media en tratamiento y en V1 frente a Rebif®22.

Introduction

Multiple sclerosis (MS) is a chronic and incapacitating disease that can be controlled through the long-term use of immunomodulatory drugs (IMiDs). Among the commercially available IMiDs at the beginning of this study were Avonex®, Rebif®22, Rebif®44, Betaferon® y Copaxone®. The World Health Organization (WHO) defines adherence to a treatment as its fulfilment (taking the drug according to the prescribed dosage and program) and its persistence (taking the drug for as long as the treatment indicates), and states that non-adherence is one of the factors that contributes to the reduction of treatment efficiency in chronic diseases.[1]

Between 19%and 39%of patients with MS leave treatment with interferon beta (IFNB) within 3 years.[2,3] It has also been reported that between 10%and 20%of patients who leave the treatment do so during the first 6 months.[3,4]

In clinical trials, patients are controlled, subjected to regular periodic reviews and motivated to maintain the treatment. In addition, healthcare staff are controlled by the sponsor of the study. However, in observational studies, patients are exposed to multiple factors related with usual clinical practice that influence adherence, so the latter can be assessed more accurately.[5-7]

Patients are usually wary of starting treatment with IMiDs due to their side-effects and to the chronic administration regimes involving frequent injections.[6] It has been observed that IMiDs cannot be effective in patients with a low degree of long-term adherence.[2]

According to different authors, the main factors contributing to non-adherence are usually related to the perception of lack of efficiency of the drug, lack of information or complicated information, false hopes about recovery from the disease, difficulties in administering the treatment (such as fear of needles or of injecting oneself) and sociocultural factors.[8,9]

There are few studies that have comparatively investigated the adherence to the different IMiD drugs currently commercialised for MS.[6,10] The international, observational, multicentre, retrospective, cross-sectional phase IV GAP study[5] included 2,648 patients who had given their consent and who suffered relapsing-remitting MS (RRMS) in 22 countries. The general adherence rate was 75%, with the most important factor in non-adherence being forgetting injections (50.2%).

A 5-year follow-up study is being carried out in Spain and Portugal to evaluate long-term adherence and the factors that influence it on patients previously included in the GAP

study.[5] This article communicates the results for the first 2 years in Spain.

Patients and Methods

This is an observational, multicentre, retrospective, cross-sectional, phase IV study. Consent was obtained from patients with RRMS, and the study involved one baseline assessment (baseline visit) and five annual follow-up assessments (V1-V5).

An assessment of the patients' and healthcare staff's degree of satisfaction with the new presentation of Avonex®, as well as with the quality of life (QoL) associated with health, was one of the secondary objectives of this study in Spain. Its results will be published independently.

Non-adherence was defined as forgetting one injection or changing the dose in the 4 weeks prior to completing the questionnaire. Patients signed informed consent forms at the start and end of follow-up; the ethics research committees approved the study in 18 centres in the baseline phase and in 15 in the follow-up phase.

Patients over 18 years old with RRMS and in treatment with one of the commercialised IMiDs (according to the technical datasheet of the drug and considering the criteria of the MS Advisory Committee of their region, when applicable) were included in the study. Patients had undergone treatment for at least 6 months prior to being included in the trial. As can be seen in table 1, the mean duration of treatment with IMiDs was 28 months at the baseline visit. Specifically, it was 40.5 months for Avonex®, 40 for Rebif®22, 24 for Rebif®44, 45 for Betaferon® and 15 months for Copaxone®.

Each centre tried to include an equal number of patients in each study group. The aim was to include a minimum of 3 patients and a maximum of 6 for each treatment group; consequently, the maximum number of patients to be included at each centre was 30. Patients were included sequentially at each centre as they came for their standard follow-up visit and gave their consent for taking part in the study.

Data from the questionnaires were contrasted with clinical histories through follow-up visits carried out by an independent company.

Patients and neurologists completed the questionnaires independently and blindly in a single annual visit. The questionnaire for neurologists consisted of 13 questions that included information about the workplace (infrastructure, role of nursing and/or other staff involved), questions about the treatment information given to the patient (mechanism of action, adverse reactions, method of administration) and questions about the relevance of adherence and the factors involved. The questionnaire for patients collected information from the patient's point of view about medical intervention (healthcare staff involved, value of different visits and education offered during those visits), personal view about their current MS treatment and its complications, adherence to drugs for MS treatment in the last 4 weeks and sources of support that may have an influence on adherence. In each patient questionnaire, healthcare staff answered the first 10 questions regarding duration of disease, degree of disability, treatment and history of outbreaks and their treatments.

Statistical Analysis

A statistical analysis was carried out, both descriptive and of the correlation between variables or factors that may influence adherence.

Continuous data was described using appropriate statistical tools: mean and standard deviation or median and interval. The possible differences between treatment groups were analysed through a parametric test (ANOVA) and a non-parametric test (Kruskal-Wallis); categorical data was presented by frequency distribution and percentages for each IMiD group.

Adherence rates were estimated and compared between Avonex® and the rest of IMiDs. The analyses were performed through bilateral tests with a Type I error (alpha error) of 0.05.

Frequencies and percentages of the "good adherence" variable were analysed compared to "no adherence". Possible differences between treatment settings were analysed using the $^{-2}$ test or the Fisher exact test. Factors potentially related to treatment adherence were analyzed using a log-rank test.

The dependent variable (adherence) was analysed in relation to treatment satisfaction, efficiency of current treatment, ease of treatment administration, treatment tolerability, support for the patient in delaying the disease evolution, improvement in MS symptoms, and sociodemographic variables.

Results

A total of 254 patients were included for the baseline visit of the GAP study in Spain, 142 for the first year follow-up visit (Visit 1) and 131 for the second year (Visit 2). The baseline demographic characteristics are described in table 1. The only significant differences were found in the group treated with Copaxone® (lower mean age, length of treatment and duration of disease), in the group treated with Rebif®44 (shorter length of treatment) and in the group treated with Betaferon® (longer duration of disease). The median value for time in current treatment was 28 months. The median for duration of disease was 2.3 years (table 1).

Patient Questionnaire

Rate of Adherence

The joint baseline adherence rates were 85.4% and 82.4% for the first 2 years (fig. 1). At the baseline visit, after almost 3 years of treatment, patients who were taking Avonex® were significantly more compliant (96.4%) than those treated with Rebif®22 (79.1%; $P=.0064$), Rebif®44 (79.6%; $P=.0064$) and Copaxone® (82.7%; $P=.0184$) (fig. 2). The joint adherence rate for Visit 1 was 86.6% and patients taking Avonex® were significantly more compliant than patients with Rebif®22 (93.9% vs 66.7%; $P=.0251$). In Visit 2, the joint adherence rate was 82.4%, higher for Avonex® (87.5%) than for other IMiDs (Rebif®22, 80%; Rebif®44, 77.8%;

Table 1 Baseline characteristics of patients

	Avonex® (n=56)	Rebif®22 (n=43)	Rebif®44 (n=54)	Betaferon® (n=49)	Copaxone® (n=52)	All (n=254)
Age (years)	38.8±10.1	37.2±9	38.4±10.6	40.1±11	35.1±8.2[a]	37.9±9.9
Females	78.2	62.8	68.5	67.3	73.1	70.4
Outbreaks in the last year. Patients						
0	66.1	67.4	55.6	69.4	57.7	63
1	28.6	23.3	24.1	20.4	15.4	22.4
2	5.4	4.7	11.1	10.2	17.3	9.8
> 3	0	4.7	9.3	0	9.6	4.7
Current IMA duration (months)	40.5 [6-108]	40 [6-120]	24 [6-60][b]	45 [6-124]	15 [6-42][c]	28 [6-124]
Duration of the disease (years)	8 [1-33]	7 [1-17]	5 [1-34]	7 [1-37][d]	6 [1-16][e]	6 [0-37]

IMA: immunomodulatory treatment; [ ]: range.
Data expressed as mean ± standard deviation, percentage or median [interquartile range].
[a] P=.01 compared to Betaferon®.
[b] P=.0009 compared to Avonex®; P=.0012 versus Rebif®22; P=.0003 compared to Betaferon®.
[c] P<.0001 compared to Avonex®; Rebif®22 and Betaferon®; P=.02 compared to Rebif®44.
[d] P=.05 compared to Rebif®44.
[e] P<.05 compared to Avonex® and Betaferon®.

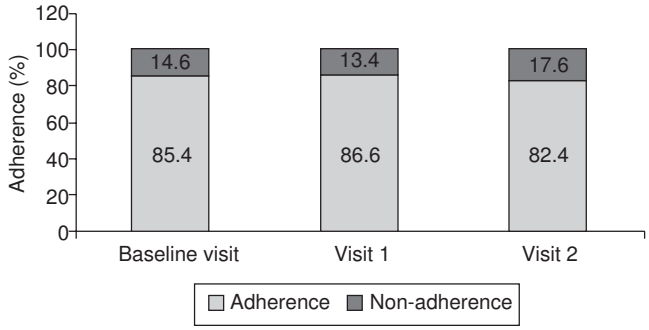


Figure 1 Rate of overall compliance in baseline visits and Visits 1-2.

Betaferon®, 85.2% and Copaxone®, 80%). At 2 years, 30.3% of all patients continued with the same treatment as in the baseline visit; 43% continued with Avonex®, significantly more (P=.0103) than with the rest of IMiDs (fig. 3).

Factors Related to Non-adherence (table 2)

Treatment-related factors. The most common reason for non-adherence during the baseline phase was forgetfulness (70.3%), followed by injection-related factors (43.2%), which included being tired of injecting oneself, skin reactions, fear of needles, pain in the area of injection, no motivation to inject and lack of help injecting. In years 1 and 2, the most common reasons for non-adherence were injection-related factors (89.5% for year 1 and 72% for year 2), followed by forgetfulness (42.1% for year 1 and 32% for year 2). After 2 years of treatment, being tired of injections was the most common injection-related reason (28%). The factors that patients scored highest at 2 years (when the MS treatment was chosen), on a scale of 0 to 5 were: the medication delays the worsening of the disease (4.61), the medication decreases the outbreaks (4.5), how the medication works (4.3) and the independence given by the treatment (4.1) (fig. 4).

Factors related to the healthcare staff. The neurologists and nursing staff of compliant patients saw patients with more frequency and regularity both in the baseline visit (89.1% and 25.7%) and at 2 years (99% and 31%). Making the decision about which type of IMiD the patient was going to receive was an activity shared between the neurologist and the patient. At the beginning of the study, the neurologist had more weight in the decision (in 13% of cases, the patient did not make a decision on the treatment). However, in the second year, the decision was taken by both equally.

Sociocultural factors. At the baseline visit, 36% of the patients worked full-time and 16% were retired or receiving some type of aid due to their MS. At 2 years, 32.2% worked full-time vs 26.3% who were retired or receiving aid for MS. The majority of patients lived with their spouse or with their family (parents or children) both at their baseline visit and at 2 years. The main sources of patient support at the beginning of the study and at 2 years were: family (87% and 85.8%), spouse (84.8% and 83.6%), doctor or nurse (80.6% and 77.4%), friends (69.6% and 69.2%), other healthcare professionals (50.2% and 54.8%) and religious beliefs (49.4% and 48.4%).

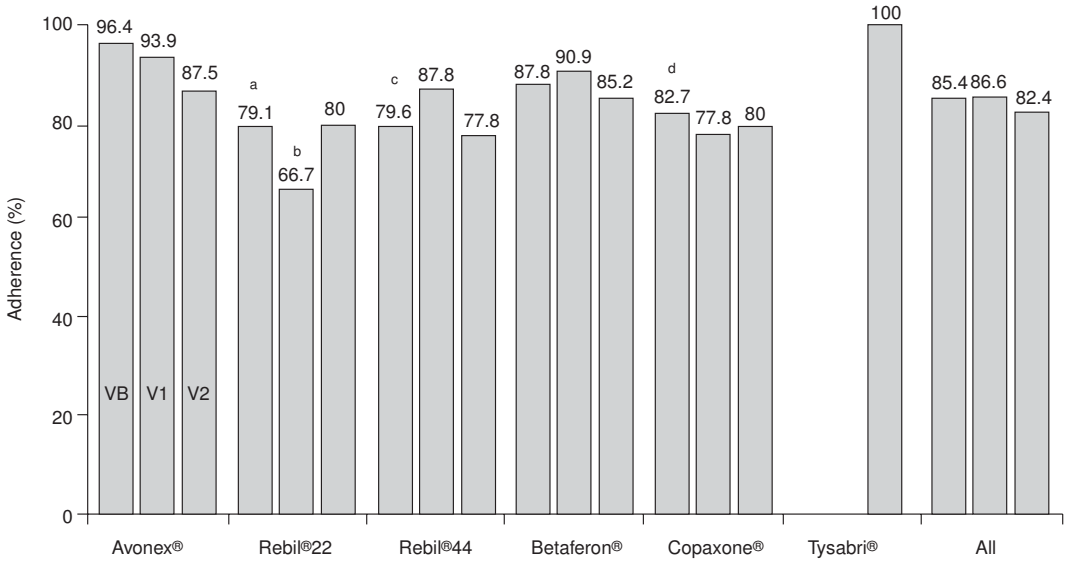
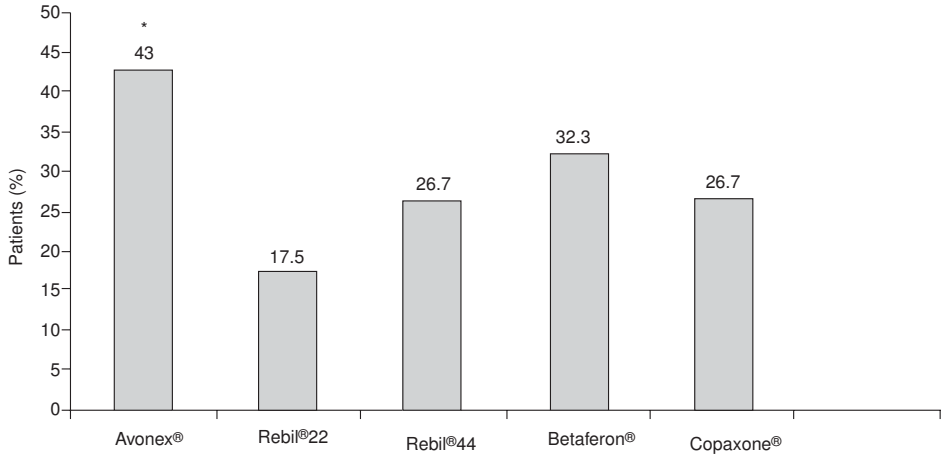


Figure 2 Rate of adherence to treatments at baseline visits and Visits 1-2. [a]*P*=.0064 compared to Avonex®. [b]*P*=.0251 compared to Avonex®. [c]*P*=.0064 compared to Avonex®. [d]*P*=.0184 compared to Avonex®.



P=.0103 compared to treatments

Figure 3 Percentage of patients who continue with the same treatment at 2 years.

Table 2 Reasons for non-adherence at baseline visit and percentage of patients: comparison among treatments

Reasons	Avonex® (n=56)	Rebif®22 (n=43)	Rebif®44 (n=54)	Betaferon® (n=49)	Copaxone® (n=52)
Forgetting	0	16.3	11.1	12.2	13.5
Injection-related	3.6	4.7	7.4	4.1	11.6
Flu-like symptoms	0	0	0	2	1.9
Weakness	0	0	0	2	1.9
Depression	0	0	1.9	2	0
Fatigue	0	0	0	2	1.9
Did not collect the medicine	0	0	3.7	0	0
Did not feel the need to inject	0	2.3	0	0	0
Lack of help for administration	1.8	0	0	0	0
No confidence in benefit of treatment	0	0	0	0	1.9

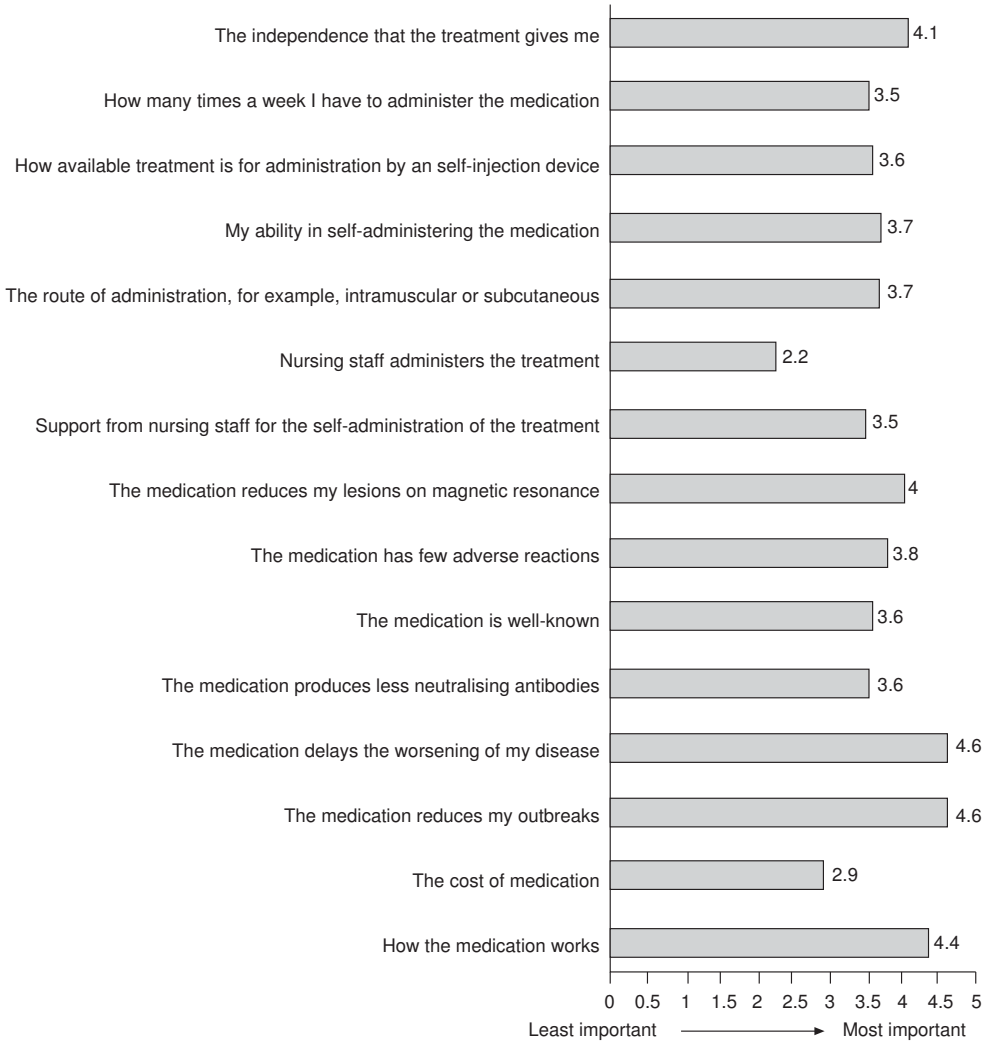


Figure 4 Evaluation factors highlighted by the patient at Visit 2.

Questionnaire for Neurologists

Rate of Adherence

The joint rates of adherence estimated by the neurologist at the baseline visit and on Visit 2 were 87.3% and 79.7%. The individual rates were Avonex®, 93.9% and 90.9%; Rebif®22, 88.5% and 81.7%; Rebif®44, 85% and 80%; Betaferon®, 82.8% and 75.4% and Copaxone®, 86.5% and 71.1%, respectively.

Factors Related with Non-adherence

Treatment-related factors. At 2 years of treatment, the reasons related to non-adherence emphasised by neurologists were the development of new outbreaks (66.8%) (fig. 5). For neurologists, the 5 most important attributes to be commented to the patient when offering a treatment for MS, in the baseline visit and in Visit 2 respectively, were: efficiency against outbreaks (94.4% and 92.9%) and against the progression of disability (77.8% and 92.9%), factors related with adverse reactions to treatment (88.9% and 92.9%), the frequency of administration (44.4% and 42.86%), ability required for administration (44.4% and 50%) and disease activity when analyzed by magnetic resonance (44.4% and 42.9%).

Factors related to the healthcare professionals. In the baseline visit and in Visit 2, the time dedicated by the neurologist to disease diagnosis, start of treatment and systematic control visits was similar. In contrast, the nursing staff dedicated more time to the patient during the baseline visit than during the follow-up visits (table 3). Among the staff helping the neurologist in clinical practice in the baseline visit and at 2 years were: nursing staff (83.3% and 85.7%), the neuropsychologist (44.4% and 71.4%), physiotherapist (27.8% and 50%) and collaborating physician (50% and 42.9%).

Discussion

The GAP international study has a duration of 5 years in Spain, and an intermediate analysis has been performed 2 years into the study. At 2 years, it is possible to observe a turning point in adherence, with a decline in all treatments.

Table 3 Time dedicated during consultation to a patient with multiple sclerosis

	Disease diagnosis	Start of treatment	Common control visits
Neurologist			
Baseline visit	49.17%	35.83%	21.67%
Visit 2	50.71%	35.36%	20%
Nursing staff			
Baseline visit	30.59%	49.12%	12.85%
Visit 2	12.65%	30.71%	12.14%

The adherence rate stays high with all IMiDs during the first 2 years, and is significantly higher with Avonex® than with other IMiDs after a median of more than 3 years of treatment. The number of patients who continued with the same treatment after 2 years was significantly higher with Avonex® than with other IMiDs.

The results of the baseline visit in the GAP study in Spain are coherent with the results of the international study[5], with an improvement of over 10 points in the joint adherence rate (75% in international GAP[5] vs 85.4% in Spanish GAP). The distribution of the adherence rate throughout all treatments is also higher in the GAP study in Spain. In the baseline visit, among the factors inherent to medication, forgetfulness was the most common in both studies. Differences were found in factors related to healthcare professionals and sociocultural factors. There were no significant differences related to gender and educational level in the baseline visits, which differs from the international GAP study[5]. The implication of nursing staff in patient follow up did not experience changes between the baseline visit and Visit 2, being stable around 12% (table 3). However, there was an increase at 2 years in multidisciplinary patient monitoring by the neuropsychologist and physiotherapist with respect to the baseline visit. The decrease in the joint adherence rate in Visit 2 makes it important to review the role of nursing staff in patient monitoring. It is noteworthy that the neurologists' perception of adherence is almost 3 points lower than the real patient adherence; this perception is higher only with Avonex® and Rebif®44, possibly because the neurologists underestimate the real adherence of patients with these treatments, thus dedicating less time to them. After 2 years of monitoring, it is still possible to observe a high degree of importance given to support from spouse, family and religious beliefs.

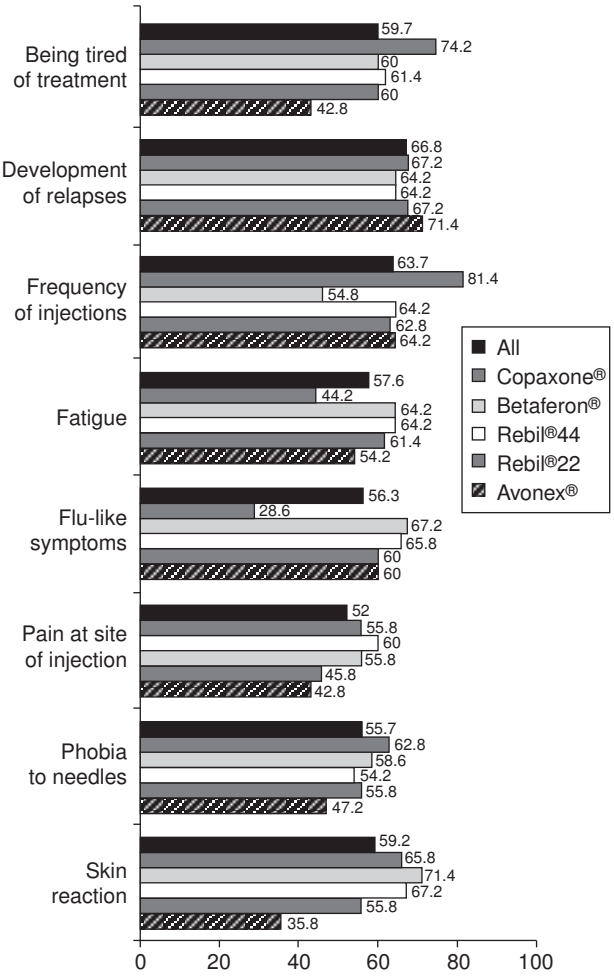


Figure 5 Adherence factors highlighted by the neurologist at Visit 2.

One of the limitations of this study is the loss of sampling in the follow-up phase (48.4%), due to a neurologist's personal decision (at a centre) or to a decision by the centre itself (in 2 of them). This translates into a loss of statistical power and may lead to a beta type error. The groups were fairly homogeneous in the basal phase. Significant differences have been found only in the groups with Copaxone®, in the Rebif®44 group and in the group treated with Betaferon®. These differences are all explainable due to the shorter commercialisation period of Copaxone® and Rebif®44 and the longer commercialisation period of Betaferon®. However, there have been no adjustments made in the different baseline visits between groups, fundamentally due to the evident loss of sampling. Other factors that may complicate the analysis of this study are the lack of randomisation, the differences in treatment length and the suspension or change of treatment, all of which are typical situations in observational studies.

The present study has proven that the therapeutic option can directly affect the adherence of a patient to the treatment of MS with IMiDs.

The most common causes for non-adherence were forgetfulness and injection-related factors. Injection-

related factors are predominant in the monitoring of this study (especially being tired of injecting oneself), probably due to the length of both the treatment and the disease itself.

Among the treatment-related factors that influenced non-adherence were: frequency of drug administration, secondary effects inherent to the medication and the patient's perception of drug efficiency. These factors should be considered when making a decision about the treatment. Healthcare staff should approach these factors that influence adherence, maintaining good communication with the patient and controlling the aspects related to drug safety. Although these factors are dynamic, their efficient management would put more emphasis on patient education and would enhance adherence in the long run.

The results of the GAP study in Spain, along with other previous studies carried out to date,[6,10] confirm that it is necessary to be aware of the importance of adherence in treating MS with IMiDs. The use of questionnaires allows the perspectives of the neurologist and the patient to be assessed in relation with the factors that can influence adherence. This makes it possible to see that adherence is generally higher in our country than in others and that it is still higher 2 years into the treatment, decreasing only 3 points but still over the international baseline score.

Monitoring the GAP study in Spain has allowed us to verify the importance of some sanitary and sociocultural factors described previously, along with aspects of the quality of life and satisfaction, of both patients and neurologists, which will be published independently. In our country, the support of the spouse, family and healthcare staff (neurologist and nursing staff) is an important factor that affects adherence positively. In the 2 years of monitoring, an increase in the multidisciplinary staff (such as neuropsychologists and physiotherapists) treating patients with MS was observed, as well as the neurologists' continuous implication in patient follow up. We believe that these factors contribute positively to the high rate of adherence to IMiD treatment in our country. The fact that adherence to Avonex® treatment is higher could be due to the lower frequency of injections compared to other IMiDs. We wish to stress that in the 2 years of monitoring, forgetfulness has gone down from the first to the second factor (after injection-related factors), with a decrease of 38.3% That is why we feel that the awareness of the health professionals and patients included in this study has had a positive effect on remembering to inject the medication.

To the best of our knowledge, this is the only observational study on adherence to treatments with IMiDs being carried out in patients with MS in Spain to date. Observational studies with long-term monitoring have the added value of comparing the results of clinical trials with the results of clinical practice, as well as including relevant factors not normally studied. This reason has motivated us to elaborate adherence questionnaires that are published simultaneously and independently. We find it necessary to develop tools that make it easier for healthcare staff to assess immunomodulatory therapy adherence to anticipate difficulties that patients may have with specific treatment regimes and disease-modifying therapies in general. This will lead to an optimisation of results in current treatments with IMiDs. It will also provide health professionals with more adequate measures to improve the monitoring of treatments in patients with MS. This is especially true for those considered at high risk of non-adherence, such as patients with a longer disease and treatment duration, in whom lower adherence rates have been found.

During the 2 years the GAP study in Spain has lasted, it has been shown that the joint rate of adherence was higher than the rate obtained in the baseline visit in the international GAP study.[5] Avonex® showed a higher adherence rate than the rest of the medications; this difference was significant in the baseline visit, after an average 40.5 months of treatment. It would be important to increase the nursing staff's role in the monitoring of patients treated with IMiDs. Being aware of the importance of therapeutic adherence seems to be a beneficial element.

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Conflict of interests

The authors declare no conflict of interests.

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