**Relapses in patients treated with high-dose biotin for progressive multiple sclerosis**

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**Running title**: Biotin and multiple sclerosis' relapses

## Abstract

High-dose biotin (HDB) is a therapy used in non-active progressive multiple sclerosis (PMS). Several reports have suggested that HDB treatment may be associated with an increased risk of relapse. We aimed to determine whether HDB increases the risk of clinical relapse in PMS and describe the characteristics of the patients who experience it. We conducted a French, multicenter, retrospective study, comparing a group of PMS patients treated with HDB to a matched control group. Poisson regression was applied to model the specific statistical distribution of the annualized relapse rate (ARR). A propensity score (PS), based on the inverse probability of treatment weighting (IPTW), was used to adjust for indication bias and included the following variables: gender, primary PMS or not, age, EDSS, time since the last relapse, and co-prescription of a DMT. 2,628 patients treated with HDB and 654 controls were analyzed with a follow-up of 17±8 months. Among them, 148 validated relapses were observed in the group treated with biotin and 38 in the control group (p=0.62). After adjustment based on the PS, the ARR was 0.044±0.23 for the biotin-treated group and 0.028±0.16 for the control group (p=0.18). The more relapses there were before biotin, the higher the risk of relapse during treatment, independently from the use of HDB. While the number of relapses reported for patients with no previous inflammatory activity receiving biotin has gradually increased, the present retrospective study is adequately powered to exclude an elevated risk of relapse for patients with PMS treated with HDB.

**Key words:** Multiple sclerosis; Clinical trials Observational study; Biotin; Relapse; propensity score; Progressive multiple sclerosis

## Introduction

At least 1.3 million people worldwide suffer from progressive multiple sclerosis (PMS)(1), accounting for more than half of all MS patients(2). Until recently, few therapeutic options, other than symptomatic treatment, have been available in this indication(3). Ocrelizumab was approved in 2017 for patients with early-stage primary PMS (PPMS)(4) and siponimod in 2019 for secondary PMS (SPMS), associated with clinical or radiological inflammatory activity in both cases(5). For patients with non-active PPMS or SPMS who have been relapse-free for at least one year, regardless of disease duration and level of disability, high-dose purified biotin (i.e. 300 mg/day) was available in France in an early-access program with a special procedure that included a hospital delivery from June 2016 to April 2019. According to the MS-SPI study, the first phase III trial of high-dose biotin for PMS, 13% of patients were responders, i.e. showing an improvement in disability, albeit modest(6). The safety profile also appeared to be good(6). According to a press release from March 2020 for the second phase III trial, conducted in both North America and Europe, SPI2 failed to confirm the results of MS-SPI (NCT02936037)(7).

In the French pivotal study(6), clinical relapses were observed in the treated group (5/103, i.e. 4.9%), as in the pilot study(8). In clinical practice, the number of relapses reported with this treatment, in case reports and small cohorts, has gradually increased for patients with little or no previous inflammatory activity(9–12). Although the risk of relapse in PMS is considered to be low(13–15), this raises the question of a potential increased risk of clinical inflammatory activity associated with high-dose biotin in PMS.

The present study aimed to determine whether biotin therapy for PMS increases the risk of relapse in a large cohort. The secondary objective was to report the characteristics of the patients who had relapse, with or without biotin treatment.

## Patients and methods

### Study design

This was a French, academic, multicenter, retrospective study, analyzed in intention-to-treat, comparing a group of PMS patients treated with high-dose biotin to a control group naive to this drug. This study was carried out in MS expert centers participating in the *Observatoire Français de la Sclérose en Plaques* (OFSEP)(16) and collecting a minimal set of data prospectively at each visit in their local European Database for Multiple Sclerosis (EDMUS) database(16,17).

### Standard protocol approval, registration, and obtention of patient consent

The study was approved by the local ethics committee (Clermont-Ferrand University Hospital MR18-002). This study was registered with ClinicalTrials.gov, number NCT03552211. Patients enrolled in OFSEP provided written consent for participation. Data confidentiality and safety were ensured according to the recommendations of the French *Commission Nationale Informatique et Libertés* (CNIL). OFSEP has received approval for storing clinical, biological, and imaging data for research purpose and has been registered at clinicaltrials.gov NCT02889965.

### Participants

Participants in the study were identified from the EDMUS database of the 23 French MS expert centers who agreed to participate.

The baseline corresponded to the starting date of biotin or the first clinical evaluation after 01/06/2016 for the controls, as the temporary regulatory approval for use was given at that time. At baseline, participants had to be aged between 18 and 80 years and have an Expanded Disability Status Scale (EDSS) score between 3 and 7.5 inclusive. Controls must not have been exposed to biotin before or during the follow-up. In addition, the absence of relapse in the

previous year and a diagnosis of PPMS or SPMS was mandatory for controls, as it is a condition for biotin prescription. Nonetheless, all patients who received biotin were included, even if prescription conditions had not been respected. For the control group, only patients not receiving any disease modifying therapy (DMT) other than those commonly prescribed for PMS (i.e. azathioprine, cyclophosphamide, glatiramer acetate, interferons, methotrexate, monthly corticosteroids, mycophenolate mofetil, ocrelizumab, or rituximab) were included. By contrast, all biotin-treated patients were included, regardless of the associated DMTs.

Patients in the treated group had to have taken at least one biotin tablet; treatment could be ongoing or stopped. Patients in the control group must have been actively monitored (i.e. at least three clinical evaluations over two years) to avoid a selective information bias, as biotin-treated patients were seen regularly.

**Data collection**

OFSEP gathers data on patients with MS collected by all French expert MS centers and MS networks routinely using EDMUS software as a medical file for all their MS patients(16). Patients are included when diagnosed with MS according to ongoing criteria, with no age limit. Clinical data are retrospectively collected at the first visit and prospectively thereafter during routine follow-up visits, usually at least once a year. Data collection is based on a minimal required dataset, including demographic and socioeconomic characteristics and a description of the MS and DMTs, although much more data can be collected at the investigator's discretion. Serious adverse events (SAEs) have also been systematically collected since January 2017.

The subjects for the group treated with biotin were identified directly in the local databases of each participating center. To facilitate the identification of the control group, the various inclusion and exclusion criteria were applied to the centralized data extracted from the EDMUS database on 15/06/2018. A single investigator (SM) visited each of the 23 MS expert centers to

collect and/or verify the data needed for the study using the EDMUS database and medical records.

**Definition of outcome measures**

The primary outcome was the annualized relapse rate (ARR) during the follow-up, the ARR for each patient being defined as the total number of relapses divided by the entire duration of follow-up, expressed in years. A relapse was defined as the appearance, recurrence, or worsening of neurological signs due to MS immediately preceded by a stable or improved neurological state for at least 30 days(18). The symptoms must have persisted for at least 24 hours, without fever, and been accompanied by objective neurological aggravation different from fatigue alone(18). The opinion of the treating neurologist was taken into consideration, as he/she had the best knowledge of the patient and their illness. Two MS experts blinded from treatment received (SM and XM) independently validated the relapses based on the information gathered during the study. In case of discordance, consensus was obtained after discussion.

The secondary endpoints consisted of characterizing the relapses and the patients who experienced them, both among biotin-treated patients and controls. Therefore they included, when available, relapse data (date of the event, clinical semiology, EDSS, nature of specific treatment and efficacy), demographic data (age, gender, follow-up center), disease data (PPMS or SPMS, duration of MS, duration of progression, baseline EDSS, last available EDSS, ARR before biotin initiation, date of last relapse prior to biotin initiation), and treatment data (time interval between biotin initiation and the onset of relapse, co-administration of other DMT).

**Statistical analysis**

Differences in baseline characteristics between the treated and control groups were tested using the Student-t test or the Mann-Whitney test for continuous variables (assumption of normality assessed using the Shapiro-Wilk test and homoscedasticity evaluated using Fisher-Snedecor's test) and the Chi-squared or Fisher exact test for categorical variables. For the primary outcome

(ARR), a random-effect generalized linear model was carried out to account for center effects as a random-effect. More precisely, Poisson regression was applied to model the specific statistical distribution of the ARR accounting for between- and within-center variability.

Indication bias is frequent in retrospective studies because the choice of treatment is generally influenced by the characteristics of the patient(19). Thus, a propensity score (PS) can be determined to adjust for these differences and recreate, as much as possible, the gold standard of a randomized trial(19). The PS corresponds to the probability of a patient receiving the treatment according to their characteristics. We used inverse probability of treatment weighting (IPTW) by assigning each participant an inverse weighting of the probability of receiving, or not, biotin treatment, estimated by the PS(19). Thus, the weight of patients who were highly likely to receive biotin based on their observable characteristics was reduced and that of patients who were unlikely to receive biotin was increased. The treated and control groups were thus rendered comparable because they would have had the same chance of being treated. Finally, the validity of the matching was tested by analyzing the standardized differences ($|d|$), with $|d| > 0.2$ considered to be an imbalance. Considering the characteristics of the subjects at baseline, the PS model included the following variables: gender, PPMS or not, age at the beginning of the progressive phase, duration of the progressive phase at baseline, EDSS at baseline, time since the last relapse to the baseline, and co-prescription of another DMT during the follow-up. The duration of follow-up was not included in the PS model because it was accounted for in the ARR. As only 2.2% of data were missing for the PS analysis (Table 1), no specific missing data approach was carried out. The characteristics of the subjects who presented relapses during the follow-up were the subject of a descriptive and comparative analysis for which the tests described above were implemented. Sensitivity analysis was performed for relapses during biotin treatment only, and not during the entire follow-up, using the methodology described above.

An effect size >0.2 was considered significant. A two-sided p value <0.05 was considered statistically significant. All analyses were performed using Stata (version 15, StataCorp, College Station, USA) software.

**Evaluation of sample size**

A sample of 1,005 subjects per group was considered to be required to show a relative difference in the ARR of 50% between the two groups, assuming an ARR of 0.05 in the control group, with a standard deviation of 0.20, a two-sided type I error equal to 0.05, and a statistical power of 80%. To account for the non-Gaussian distribution of the ARR, it was considered necessary to extend recruitment to 1,200 patients per group. However, assuming the likely unbalanced distribution between the two groups (1:4 to 1:5), 2,500 to 3,000 patients treated with high-dose biotin and 600 to 650 controls appeared to be more appropriate to show such a difference.

**Role of the funding source**

The trial was designed independently of the sponsor (i.e. MedDay Pharmaceuticals©). Data were collected, analyzed, and interpreted by the investigators and the manuscript was edited and submitted independently of the sponsor. SM had full access to the data. SM and XM were responsible for submission of the manuscript.

**Data availability statement**

All individual de-identified participant data used for this study will be shared upon reasonable request sent to the corresponding author.

## Results

### Participants

We identified 2,628 patients for whom high-dose biotin therapy had been prescribed from 06/01/2016 to 06/15/2018 and 654 controls. The average follow-up was 17±8 months. Using the IPTW method, 2,555 biotin-treated patients and 654 controls were evaluated.

Patients treated with high-dose biotin were older at baseline and had a higher EDSS (**Table 1**). There were slightly more patients with SPMS in the treated group. Treated patients had an ARR within the two years prior to baseline that was higher than that of controls. These last patients received DMT less frequently during the study ($p<0.001$).

### Risk of relapse

During the follow-up, 167 declared relapses were observed in the group treated with biotin and 40 in the control group ($p=0.78$). After blinded validation of the relapses, 148 were kept in the biotin-treated group and 38 in the control group ($p=0.62$). Before determining the PS, the ARR was 0.043±0.22 for the biotin-treated group and 0.038±0.18 for the control group ($p=0.62$, zero-inflated with center effect). After determination of the PS using the IPTW method, the ARR was 0.044±0.23 for the biotin-treated group and 0.028±0.16 for the control group ($p=0.18$; $|d|=0.07$). Sensitivity analysis was performed for relapses during biotin treatment only and not during the entire follow-up, leading to similar results ($p=0.09$; $|d|=0.09$).

### Characteristics of relapses

The 167 declared relapses in the biotin-treated group, of which 29 (17.4%) occurred after the discontinuation of treatment, occurred in 148 different subjects (5.6% of the treated population) and the 40 relapses in the control group occurred in 35 different subjects (5.4% of the control population) ($p=0.78$). Following the validation of relapses by blinded evaluators, 148 occurred

in the biotin-treated patients (139 patients, 5.3%) and 38 (32 patients, 5.1%) in the controls (p=0.82 before determination of the PS).

In the biotin-treated group, 77% (114/148) of the patients continued biotin despite the declared relapse for a mean follow-up of 12.0±8.2 months and 10 presented a second declared relapse, with a mean interval of 7.4±4.1 months between the two relapses.

On average, all first relapses observed during the follow-up occurred 7.9±6.1 months after baseline in the biotin-treated group (range 0 to 22.8 months) versus 8.1±6.2 months in the control group (p=0.86). Overall, 77% of relapses in the biotin-treated group occurred within one year of treatment. Most of the relapses were treated with high-dose methylprednisolone (3 grams) for both biotin-treated patients and controls (88% vs 92%, respectively, p=0.51).

**Characteristics of patients treated with biotin who experienced a validated relapse**

Among patients treated with biotin, those with validated relapses were younger, more frequently had SPMS, a shorter duration of progression, a shorter time since the last relapse, and a higher ARR during the progressive phase (**Table 2**). In addition to high-dose biotin, they also received DMTs, with no disparity in the drugs used. Of note, 111 patients treated with biotin had had a relapse in the year before initiating biotin, whereas this is a contra-indication, 10 of them being noted as having relapsing-remitting MS (RRMS). Forty-three other patients were also noted as presenting RRMS. Among the 111 patients who had a relapse in the year prior to biotin initiation, 15 had at least one validated relapse during follow-up for a total of 19 relapses.

## Discussion

This nation-wide multicentric analysis showed neither an increased risk of relapse in patients treated with biotin relative to a contemporary control group nor higher severity, as evaluated by the use of methylprednisolone. Subjects within the biotin-treated group who experienced a relapse tended to more frequently have SPMS, a higher ARR during the entire progressive phase, and a more recent relapse before baseline.

Although it has now been shown with the second phase III trial that high dose biotin was ineffective to modify disease course in PMS, looking for a potential pro-inflammatory role of new drugs is relevant for any treatment used for PMS patients. The present study is the first focusing on the potential increased risk of relapse with biotin therapy and seeking to identify the profile of those concerned, involving a large number of patients, an appropriate control group, and robust statistical methods. The literature offers few chances for comparison. The low prevalence found in our study (4.4 %) is relatively close to that observed in the MS-SPI phase III study (4.9 % at 12 months)(6). The few real-life cohort studies, without control groups, that addressed this question and included at least 100 subjects produced disparate results, with a prevalence of less than 1%(20) or equal to 4.7%(10). In a recent study that included 178 prospectively evaluated patients, 2.2% had clinical relapses but 10.8% had gadolinium-enhancing lesions on the follow-up MRI(21). Moreover, in the placebo group (n=354) of the INFORMS study, regarding the effect of fingolimod in patients with PPMS, ARR was 8%(22), 7.4% in the placebo group (n=234) of the ORATORIO trial investigating the effect of ocrelizumab in PPMS(23), 16% in the placebo group (n=546) of the EXPAND trial investigating the effect of siponimod in SPMS(5), and 9% in another study evaluating the risk of relapse after treatment withdrawal in patients with SPMS(14). Of note, only 17 relapses were reported by treating neurologists in the cohort of 6,516 patients included in the early-access program via the pharmacovigilance program one year after its onset(20). This suggests

significant under-reporting of the event to the appropriate authorities and underlines the importance of our work in establishing the effect of high-dose biotin on inflammatory activity in PMS.

This analysis showed there to be no increased risk of relapse for patients treated with high-dose biotin at the group level. The patients treated with biotin who experienced a relapse during the follow-up logically exhibited inflammatory expression of their disease, as shown by a more frequent SPMS, a higher ARR during the progressive phase, a shorter duration since the beginning of the progressive phase, and a more recent relapse before baseline at a rate comparable to that of patients co-exposed to anti-inflammatory therapies.

Although this study provides new and important information for clinical practice, it had certain limitations. First, the recent negative results from the second phase 3 trial calls into question the interest of high-dose biotin in PMS. Second, the retrospective nature of the present study (based on database and medical records) may have introduced a measurement bias because it made the investigators highly dependent on the judgment of the neurologist treating the patient in terms of the veracity of the relapse, which could influence the reporting of the event, as well as the means implemented to investigate it and treat it. Nonetheless, we made efforts to minimize such bias. Indeed, the medical records of every single patient included in the present study were reviewed on each site by the same investigator and relapses were independently validated by two authors blinded to the treatment received. As the controls were selected as respecting prescription criteria for high-dose biotin treatment, none of them had had any relapse during the 12 months before study baseline. On the contrary, all biotin-treated patients were included in the present study, even if they had presented a relapse in the previous year and such an event was present in 4% (111/2628) of included patients. This fact has probably contributed to slightly increase the relapse rate in the treated group and although time since the last relapse

to the baseline was taken into account in the PS model, perfect matching was not possible on that point.

In addition, the duration of follow-up of patients treated with high-dose biotin (maximum two years) was relatively short. However, 77% of the relapses in the biotin-treated group occurred during the first year of treatment and the mean time from the beginning of biotin therapy to clinical relapse was, on average, eight months for an average follow-up of nearly 18 months. This time to observed relapse is comparable to published observations(24). The duration of our study was therefore sufficient to study this event.

Moreover, certain parameters were difficult to study, such as relapse characteristics, because of the often limited description of the clinical presentation, precluding identification of the probable location of the inflammation in the central nervous system, and the absence of systematic MRI follow-up, as gadolinium-enhancing lesions are more frequent than clinical relapses(21). Additional elements in terms of the radiological inflammatory activity will probably be provided by the international MS-SPI 2 study, which includes MRI follow-up(7).

In conclusion, high-dose biotin therapy does not modify inflammatory activity in PMS. Introducing new treatments in such “non-active” patients shed light on the relapses these patients can have. As we can hope to have new drugs for modifying the course of non-active PMS in the coming years, it will be important to keep in mind that although low, relapse rate is not null in this population.

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**Table 1. Characteristics of participants before application of PS and after application of the IPTW method** *p < 0.05, |d|: standardized difference (difference is not significant when |d| < 0.20). Quantitative variables are expressed as the mean ± standard deviation and qualitative variables as numbers and associated percentages. Missing data for the propensity score analysis lead to the exclusion of 73 biotin-treated patients (73 missing data for age at the beginning of progression, 60 for the duration of progression, and 13 for the ARR before inclusion).

| | **Before PS** | | | **After IPTW** | | | |
|---|---|---|---|---|---|---|---|
| | **Biotin (n = 2,628)** | **Control (n = 654)** | **p** | **Biotin (n = 2,555)** | **Control (n = 654)** | **\|d\|** | **p** |
| **Female gender** | 1563 (59.5%) | 406 (62.1%) | 0.22 | 59.8% | 62.2% | 0.049 | 0.36 |
| **MS course:** | | | | | | | |
| SP | 1650 (62.8%) | 380 (58.1%) | < 0.001 | 65.3% | 63.0% | 0.049 | 0.61 |
| PP with relapses | 525 (20.0%) | 183 (28.0%) | | 20.4% | 21.9% | 0.035 | |
| PP without relapse | 400 (15.2%) | 91 (14.0%) | | 14.3% | 15.2% | 0.026 | |
| RR | 53 (2.0%) | 0 | | 0% | 0% | / | |
| **Age at the beginning of progression, y** | 44.7 ± 10.4 | 44.2 ± 10.2 | 0.22 | 44.7 ± 10.4 | 45.1 ± 9.9 | 0.04 | 0.41 |
| **Duration of progression at baseline, y** | 11.7 ± 8.1 | 10.8 ± 7.5 | 0.01 | 11.6 ± 8.0 | 11.6 ± 7.7 | 0.006 | 0.91 |
| **ARR during the progression to baseline** | 0.118 ± 0.24 | 0.080 ± 0.15 | 0.01 | 0.114 ± 0.229 | 0.109 ± 0.195 | 0.025 | 0.81 |
| **ARR within 2 years before baseline** | 0.058 ± 0.20 | 0.024 ± 0.12 | 0.001 | 0.047 ± 0.176 | 0.075 ± 0.272 | 0.139 | 0.49 |
| **Time from the last relapse to baseline, y†** | 10.0 ± 8.5 | 10.8 ± 8.2 | 0.005 | 10.7 ± 8.4 | 11.0 ± 8.8 | 0.036 | 0.55 |
| **Time from last relapse > 5y** | 1856 (70.6%) | 465 (71.1%) | 0.81 | 71.6% | 70.8% | 0.019 | 0.77 |
| **Age at baseline, y** | 56.3 ± 10.5 | 55.0 ± 11.4 | 0.01 | 56.2 ± 10.5 | 56.7 ± 11.2 | 0.044 | 0.43 |
| **EDSS at baseline** | | | | | | | |
| ≤4 | 339 (12.9%) | 144 (22.0%) | < 0.001 | 14.3% | 14.2% | 0.003 | 0.97 |
| 4.5-5.5 | 354 (13.5%) | 114 (17.4%) | | 14.2% | 13.9% | 0.009 | |
| ≥6 | 1935(73.6%) | 396 (60.6%) | | 71.5% | 71.9% | 0.009 | |
| **Duration of follow-up, m** | 17.5 ± 8.5 | 18.3 ± 4.6 | < 0.001 | 17.4 ± 8.5 | 17.9 ± 5.0 | 0.054 | 0.27 |
| **DMT** | | | | | | | |
| **None** | **1717 (65.3%)** | **285 (43.6%)** | **< 0.001** | **61.8%** | **63.3%** | **0.031** | **0.52** |
| Rituximab/Ocrelizumab | 305 (11.6%) | 169 (25.8%) | | | | | |
| Mycophenolate | 175 (6.7%) | 93 (14.2%) | | | | | |
| Methotrexate | 105 (4.0%) | 54 (8.7%) | | | | | |
| Azathioprine | 57 (2.2%) | 26 (4.0%) | | | | | |
| Interferon | 47 (1.8%) | 30 (4.6%) | | | | | |
| **Number of declared relapses (n patients)** | 167 (148) | 40 (35) | 0.78 | NA | NA | | |
| **ARR during follow-up (declared relapses)** | 0.051 ± 0.27 | 0.041 ± 0.19 | 0.33 | 0.049 ± 0.27 | 0.031 ± 0.16 | 0.07 | 0.14 |
| **Number of validated relapses (n patients)** | 148 (139) | 38 (32) | 0.82 | NA | NA | | |
| **ARR during follow-up (validated relapses)** | 0.043 ± 0.22 | 0.038 ± 0.18 | 0.62 | 0.044 ± 0.23 | 0.028 ± 0.16 | 0.07 | 0.18 |

**Table 2. Characteristics of biotin-treated patients with validated relapses versus patients without relapses**

*p < 0.05, † PPMS without relapse were excluded from this analysis. Quantitative variables are expressed as the mean ± standard deviation and qualitative variables as numbers and associated percentages.

| | At least one validated relapse (n = 139) | No relapse (n = 2,489) | p |
|---|---|---|---|
| **Duration of follow-up, m** | 20.5 ± 9.8 | 17.3 ± 9.4 | <0.001 |
| **Duration of biotin treatment, m** | 13.8 ± 9.5 | 14.3 ± 8.0 | 0.51 |
| **Age at baseline, y** | 52.8 ± 8.9 | 56.5 ± 10.6 | <0.001 |
| **Female gender** | 90 (64.8%) | 1473 (59.2%) | 0.19 |
| **SPMS** | 106 (76.3%) | 1544 (62.0%) | <0.001 |
| **Duration of progression at baseline, y** | 9.1 ± 7.8 | 11.9 ± 8.1 | <0.001 |
| **EDSS at baseline** | | | |
| ≤4 | 15 (10.8%) | 324 (13.0%) | 0.67 |
| 4.5-5.5 | 21 (15.1%) | 333 (13.4%) | |
| ≥6 | 103 (74.1%) | 1832 (73.6%) | |
| **Time from the last relapse to baseline, y†** | 7.3 ± 7.2 | 10.2 ± 8.5 | <0.001 |
| **ARR during the progression to baseline** | 0.254 ± 0.51 | 0.110 ± 0.21 | <0.001 |
| **ARR within 2 years before baseline** | 0.186 ± 0.42 | 0.051 ± 0.18 | <0.001 |
| **DMT** | | | |
| None | 54 (38.9%) | 857 (34.4%) | 0.29 |
| Rituximab/Ocrelizumab | 19 (13.7%) | 290 (11.7%) | 0.47 |
| Mycophenolate | 13 (9.4%) | 162 (6.5%) | 0.19 |
| Methotrexate | 5 (3.6%) | 100 (4.0%) | 0.81 |
| Azathioprine | 3 (2.2%) | 54 (2.2%) | 0.99 |
| Interferon | 5 (3.6%) | 43 (1.7%) | 0.11 |
| Corticosteroids | 4 (2.9%) | 71 (2.9%) | 0.99 |