The Efficacy of Natalizumab versus Fingolimod for Patients with Relapsing-Remitting Multiple Sclerosis: A Systematic Review, Indirect Evidence from Randomized Placebo-Controlled Trials and Meta-Analysis of Observational Head-to-Head Trials

Georgios Tsivgoulis, Aristeidis H. Katsanos, Dimitris Mavridis, Nikolaos Grigoraidis, Efthymios Dardiotis, Ioannis Heliopoulos, Panagiotis Papathanasopoulos, Theodoros Karapanayiotides, Konstantinos Kiilidireas, Georgios M. Hadjigeorgiou, Konstantinos Voumvourakis

1 Second Department of Neurology, “Attikon” Hospital, School of Medicine, University of Athens, Athens, Greece, 2 Department of Neurology, The University of Tennessee Health Science Center, Memphis, Tennessee, United States of America, 3 International Clinical Research Center, Department of Neurology, St. Anne’s University Hospital in Brno, Brno, Czech Republic, 4 Department of Neurology, School of Medicine, University of Ioannina, Ioannina, Greece, 5 Department of Primary Education, University of Ioannina, Ioannina, Greece, 6 Department of Hygiene and Epidemiology, School of Medicine, University of Ioannina, Ioannina, Greece, 7 Second Department of Neurology, “AHEPA” University Hospital, Aristotleion University of Thessaloniki, Thessaloniki, Macedonia, Greece, 8 Department of Neurology, University Hospital of Larissa, University of Thessaly, Larissa, Greece, 9 Department of Neurology, Alexandroupolis University Hospital, Democritus University of Thrace, Alexandroupolis, Greece, 10 Department of Neurology, University of Patras Medical School, Patras, Greece, 11 First Department of Neurology, “Egnition” Hospital, School of Medicine, University of Athens, Athens, Greece

¶ The complete membership of the author group can be found in the Acknowledgments.
* tsvgoulisgiorg@yahoo.gr

Abstract

Background

Although Fingolimod (FGD) and Natalizumab (NTZ) appear to be effective in relapsing-remitting multiple sclerosis (RRMS), they have never been directly compared in a randomized clinical trial (RCT).

Methods and Findings

We evaluated the comparative efficacy of FGD vs. NTZ using a meta-analytical approach. Data from placebo-controlled RCTs was used for indirect comparisons and observational data was utilized for head-to-head comparisons. We identified 3 RCTs (2498 patients) and 5 observational studies (2576 patients). NTZ was associated with a greater reduction in the 2-year annualized relapse rate (ARR; SMD\textsubscript{indirect} = -0.24;95% CI: from -0.44 to -0.04; p =
0.005) and with the probability of no disease activity at 2 years (OR_{indirect} = 1.82, 95% CI: from 1.05 to 3.15) compared to FGD, while no differences between the two therapies were found in the proportion of patients who remained relapse-free (OR_{indirect} = 1.20; 95% CI: from 0.84 to 1.71) and those with disability progression (OR_{indirect} = 0.76; 95% CI: from 0.48 to 1.21) at 2 years. In the analysis of observational data, we found no significant differences between NTZ and FGD in the 2-year ARR (SMD = -0.05; 95% CI: from -0.26 to 0.16), and 2-year disability progression (OR: 1.08; 95% CI: from 0.77 to 1.52). However, NTZ-treated patients were more likely to remain relapse-free at 2-years compared to FGD (OR: 2.19; 95% CI: from 1.15 to 4.18; p = 0.020).

Conclusions

Indirect analyses of RCT data and head-to-head comparisons of observational findings indicate that NTZ may be more effective than FGD in terms of disease activity reduction in patients with RRMS. However, head-to-head RCTs are required to independently confirm this preliminary observation.

Introduction

Available disease modifying drugs (DMDs) have been proved to be effective in reducing disability progression in patients with relapsing remitting multiple sclerosis (RRMS) [1]. High-risk RRMS patients with active or progressive disease while on treatment with a first-line agent are candidates for treatment escalation to a second-line agent, which is expected to have a more potent effect on both clinical and MRI outcomes [2]. Second-line therapy should thus be chosen after careful risk-benefit ratio stratification [3,4]. Although the second-line agents Fingolimod and Natalizumab appear to be efficacious for patients with high disease activity and generally manageable side effects [2], their comparative efficacy in patients with RRMS has never been tested within the setting of a randomized clinical trial (RCT).

The aim of the present systematic review and meta-analysis is to compare the relative efficacy of Natalizumab and Fingolimod in RRMS patients by estimating an indirect effect using available randomized placebo-control trials and by estimating an effect from observational studies on the reported efficacy outcomes.

Methods

Trial identification and data abstraction

This meta-analysis is presented according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews and meta-analyses [5]. We performed a comprehensive literature search in MEDLINE, SCOPUS and the CENTRAL Register of Controlled Trials databases to identify: 1. all eligible placebo-control RCTs of Natalizumab or Fingolimod in RRMS patients and 2. all eligible observational studies comparing Natalizumab to Fingolimod in RRMS patients. The following keywords were used in all database searches: “relapsing-remitting multiple sclerosis”, “RRMS”, “fingolimod” and “natalizumab”. We imposed no language or other restrictions. Last literature search was performed on April 16th, 2016. We examined reference lists of all retrieved articles to identify studies that may have been missed by the initial database search. References to studies were also sourced...
from international trials registers via the World Health Organization's (WHO) trials portal (http://apps.who.int/trialsearch/); regulatory agencies; drug companies; the hand-searching of key journals, conference proceedings and other (non-Cochrane) systematic reviews and meta-analyses.

Database search was performed independently by three reviewers (GT, AHK, KV), while all emerging disagreements were resolved with consensus. We excluded from further quantitative/qualitative analysis all: 1. case series/ case reports, 2. RCTs without placebo arms, 3. studies reporting combination therapy in the treatment arm, 4. studies not reporting the outcomes of interest and 5. Phase II core study protocols with inadequate follow-up time (<1 year), since in multiple sclerosis the clinically relevant endpoint, which documents the presence or absence of progressive disability, consists of structured observations with validated imaging assessment over a long period of time (usually 2 years) [6], while the differences in the annualized relapse rate (ARR) are considered to be evident after an observational period of at least 1 year [7].

Data on the ARR, percentage of patients with disability progression, percentage of patients who were free of relapses and percentage of patients with no evidence of disability progression (NEDA) during the study period were extracted independently by the same authors who performed the literature search (GT, AHK, KV) for all arms in both randomized and observational study protocols that were included for the quantitative synthesis. NEDA was defined as the occurrence of no relapses, no progression of disability sustained for 12 weeks, no gadolinium-enhanced lesions and no new or enlarging T2-hyperintense lesions on MRI scan [8].

We calculated odds ratios (ORs) to express the comparison of the reported dichotomous outcomes for each available subgroup in each study protocol. The equivalent z-test was performed for each OR, and if \( p < 0.05 \) it was considered statistically significant. We expressed the unadjusted mean differences of reported continuous outcomes between subgroups as standardized mean differences (SMDs). SMD estimates were calculated as the mean differences divided by the corresponding pooled standard deviations and were subsequently interpreted using a general rule of thumb reported by Cohen, in which an SMD of 0.2 represents a small effect, an SMD of 0.5 represents a medium effect, and an SMD of 0.8 or larger represents a large effect [9,10]. To make the interpretation of SMDs more clinically relevant we additionally re-expressed all SMDs as ORs using the formula \( \text{OR} = \exp\left(\frac{\text{SMD} \times \pi}{\sqrt{3}}\right) \) and after assuming that the underlying continuous measurements in each group follow a logistic distribution and that the variability of the outcomes is the same in both FGD and NTZ group [11].

We performed meta-analysis for all the aforementioned outcomes of the included RCTs that reported treatment arms with any of the two drugs (Natalizumab or Fingolimod) versus the corresponding placebo arms, and meta-analysis for the same outcomes among patients receiving Natalizumab versus those receiving Fingolimod in the included observational studies. For the included RCTs we performed subsequent subgroup analyses, dichotomizing studies according to the reported treatment arm (Natalizumab or Fingolimod) in each study protocol. The mixed-effects model was used to calculate both the pooled point estimate in each subgroup and the overall estimates in all occasions. According to the mixed-effects model, we used a random effects model (DerSimonian Laird) to combine studies within each subgroup and a fixed effect model (Mantel–Haenszel method) to combine subgroups and estimate the overall effect. We assumed the between-study variance (tau-squared) to be the same for all subgroups. Tau-squared was first computed within subgroups and then pooled across subgroups [12]. We assessed heterogeneity between studies with the Cochran Q and \( I^2 \) statistics. For the qualitative interpretation of heterogeneity, \( I^2 \) values of at least 50% were considered to represent substantial heterogeneity, while values of at least 75% indicated considerable heterogeneity, as per the Cochrane Handbook [13].
In RCTs we compared the pooled effect sizes (SMDs or ORs) for each outcome of interest between Natalizumab and Fingolimod treatment arms by calculating the indirect effect sizes (indirect SMDs and indirect ORs), with their corresponding 95% confidence intervals, using the Bucher’s Method [14]. As transitivity assumption is a key assumption for the indirect effect to be valid, we compared the baseline characteristics of RRMS patients included in the corresponding RCTs that were treated with natalizumab and those treated with fingolimod to explore if effect modifiers are similarly distributed across the two comparisons [15].

Statistical analyses were conducted using the Review Manager (RevMan) Version 5.3 software (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and the Stata Statistical Software (StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP).

Results
Study selection and study characteristics
Systematic search of MEDLINE and SCOPUS databases yielded 91 and 141 results respectively. Subsequent search in the CENTRAL Register of Controlled Trials retrieved no additional RCTs. After removing duplicates, the titles and abstracts from the remaining 225 studies were screened and 14 potentially eligible studies for the meta-analysis were retained. The complete search algorithm used in the MEDLINE search is available in the S1 File. After retrieving the full-text version of the aforementioned 14 studies, 6 studies were excluded because they either reported non-placebo control RCTs or combination therapy with interferon (INF) or short-term follow-up (6 months) or not providing data on the outcomes of interest. All excluded studies with reasons for exclusion are presented in Table A in S1 File. In the final presentation of the literature search results, there was no conflict or disagreement between the 3 reviewers and the 8 studies that met the study protocol’s inclusion criteria were included in both the qualitative and quantitative synthesis (Fig 1).

The baseline characteristics of the arms of RRMS patients that were included in available placebo-control RCTs (2498 total patients) and treated with either Natalizumab or Fingolimod are presented in Table 1 [16–18]. After comparing available variables, using t-test and chi-square statistical tests where appropriate, we found that patients randomized to receive Natalizumab in the AFFIRM trial [16] were significantly younger but had a higher pre-treatment load of gadolinium-enhancing lesions compared to the patients randomized to receive Fingolimod in the FREEDOMS I&II trials [17,18].

Similarly, the baseline characteristics of RRMS patients treated with either Natalizumab or Fingolimod in all eligible prospective observational studies (2576 total patients) are presented in Table B in S1 File [19–23]. Among studies patients receiving Natalizumab were reported to be younger than patients receiving Fingolimod [20], while patients receiving Natalizumab were reported to have more severe pre-treatment EDSS score [19–22], higher pre-treatment load of gadolinium-enhancing lesions [19] and more relapses before treatment [19–22]. Four of the study protocols reported statistical methods for either balancing the baseline characteristics between subgroups or addressing for potential confounders [19–22], while one of the studies reported only unadjusted estimates between subgroups (Table 2) [23].

Overall analysis and indirect estimates in randomized clinical trials
Natalizumab was found to be associated with a greater reduction in the 2-year ARR compared to placebo (SMD: -0.62; 95% CI: from -0.76 to -0.48; Fig 2 and OR:0.32; 95%CI: from 0.25 to 0.41; Fig A in S1 File) than the ARR reduction of Fingolimod in 2 years compared to placebo (SMD: -0.38, 95% CI: from -0.48 to -0.28; Fig 2 and OR:0.50 95%CI: from 0.42 to 0.60; Fig A in
The p-value for subgroup differences was 0.005 (SMD\text{indirect}: -0.24; 95% CI: from -0.44 to -0.04 and OR\text{indirect}: 0.64; 95%CI: from 0.45 to 0.93). No evidence of heterogeneity was found in both subgroups ($I^2 = 0$).

However, the percentage of patients with no relapse at 2 years was not found to be significantly different among the RRMS patients treated with Natalizumab and those treated with Fingolimod (OR for Natalizumab: 3.04, 95% CI: from 2.29 to 4.03 vs OR for Fingolimod: 2.54, 95% CI: from 2.05 to 3.17, p-value for subgroup differences:0.33, Fig B in \text{S1 File};

\text{S1 File}).
OR\text{indirect}: 1.20, 95% CI: from 0.84 to 1.71). No evidence of heterogeneity was present (I\textsuperscript2 = 3%, p-value for chi-square test statistic Q: 0.36). Similarly, the percentage of patients with disability progression at 2 years did not differ between RRMS patients treated with Natalizumab and Fingolimod (OR for Natalizumab: 0.51, 95% CI: from 0.37 to 0.70 vs OR for Fingolimod: 0.67, 95% CI: from 0.48 to 0.94, p-value for subgroup differences: 0.23, Fig C in S1 File; OR\text{indirect}: 0.76, 95% CI: from 0.48 to 1.21). No evidence of heterogeneity was present (I\textsuperscript2 = 30%, p-value for chi-square test statistic Q: 0.23).

Finally, a significantly higher percentage of RRMS with NEDA at 2-years was found in patients randomized to receive Natalizumab than those randomized to receive Fingolimod in the corresponding RCTs [8,23] (OR for Natalizumab: 7.42, 95%CI: from 4.66 to 11.81 vs OR for Fingolimod: 4.08, 95%CI: from 3.04 to 5.47, p-value for subgroup differences:0.03, Fig 3; OR\text{indirect}: 1.82, 95% CI: from 1.05 to 3.15).

Overall and subgroup analyses in observational study data

In the subsequent analysis of all available observational study data no significant difference (p = 0.66) in the 2-year ARR was found among Natalizumab and Fingolimod (SMD:-0.05, 95%
CI: from -0.26 to 0.16; Fig D in S1 File and OR: 0.92; 95%CI: from 0.64 to 1.34; Fig E in S1 File). However, substantial heterogeneity was present within studies ($I^2 = 64\%$, p-value for chi-square test statistic Q: 0.06). Similarly, no significant difference in the proportion of patients with disability progression was observed between RRMS patients treated with Natalizumab and those treated with Fingolimod at both 1-year (OR: 1.37, 95% CI: from 0.95 to 1.98, p-value = 0.10) and 2-years (OR: 1.08, 95% CI: from 0.77 to 1.52; p-value = 0.36; Fig F in S1 File), with no evidence of heterogeneity among estimates ($I^2 <40\%$ for both subgroups). Finally, in another subgroup analysis patients treated with Natalizumab were found to have a significantly
higher proportion of relapse-free patients at 2-years patients compared to those treated with Fingolimod (OR: 2.19, 95% CI: from 1.15 to 4.18, p-value = 0.02; Fig G in S1 File). However, this difference was marginally not significant during the first year (OR: 1.61, 95% CI: from 0.94 to 2.78, p-value = 0.09; Fig G in S1 File) and considerable heterogeneity was observed within studies for both the 1st and 2nd year ($I^2>80$).

**Discussion**

Both the indirect analyses of available randomized data and the direct comparisons from observational data indicate that RRMS patients receiving Natalizumab have a greater reduction in the 2-year ARR and are more likely to remain relapse-free and to achieve NEDA-3 status at two years [24], when compared to those treated with Fingolimod (Fig 4).

Even though no significant differences between the two therapies were found in terms of disability progression, we should take into consideration that in baseline characteristic analyses of both RCT and observational data, patients receiving Natalizumab had a more aggressive disease profile at baseline compared to those receiving Fingolimod (higher pre-treatment EDSS score, higher pre-treatment load of gadolinium-enhancing lesions and more relapses before treatment initiation). Moreover, AFFIRM trial [16] excluded patients who were treated with DMDs for more than six months, while previous treatment with immunomodulatory agents was highly prevalent in FREEDOMS (42.6%) [17] and FREEDOMS II (74%) [18]. Consequently, it may be postulated that patients randomized to natalizumab had more active disease (due to lack of long-term pretreatment) in comparison to patients randomized to fingolimod who were treatment-naïve in 43.2% (Table 1). Apart from the aforementioned discrepancies in baseline characteristics between treatments, the lack of significant differences in disability progression could also be partially explained by the continuously declining trend of EDSS progression over time that has been observed in RCTs [25], which inevitably may lead to underpowered estimates and thus only subtle differences among subgroups.

Results of a 9-year multicenter, cross-sectional, clinical-MRI study of 241 patients with RRMS suggest that baseline EDSS and baseline MRI are the best long-term predictors of disease progression [26]. The increase in EDSS score from baseline to 2-years in RRMS patients under treatment with IFNβ-1a was found to be an independent predictor of both EDSS progression and conversion to the secondary progressive form of the disease over a 15 year period [27]. A post-hoc individual patient data analysis from a large, placebo-controlled trial of INFβ-1a in RRMS also highlighted the predictive role of emerging MRI lesions and relapses during the first year on the 2-year EDSS progression [28]. More specifically, baseline lesion number on T1 and T2 sequences and the number of new or enlarging T2 lesions were found to be independent predictors of sustained disability progression over a 12-year observation period [29]. Gadolinium-enhancing (Gd+) lesions are also considered to be surrogate markers of treatment effect on relapse rate and disability progression in RRMS patients [30], as gadolinium enhancement on MRI represents blood-brain barrier instability and thus ongoing disease activity [31]. Thus both the presence of multiple Gd+ lesions at baseline MRI evaluation and the occurrence of new lesions during the first several years of the disease have been associated with worse long-term prognosis [32, 33].

Apart from radiological findings, the number of relapses during the disease course has also been highlighted to be an independent and significant predictor of disease progression [34]. Consequently, it may be postulated that the reduced ARR that was documented in patients treated with Natalizumab (in comparison to Fingolimod treatment) may also translate into reduced rate of disability progression in a larger sample of RRMS with a longer duration of follow-up. The higher rate of NEDA-3 status in patients randomized to Natalizumab in
### A

| Outcome                        | ES (95% CI)       |
|--------------------------------|-------------------|
| **Randomized Data**            |                   |
| Annualized relapse rate        | 0.64 (0.45, 0.93) |
| Disability progression at 2-years | 0.76 (0.48, 1.21) |
| **Observational Data**         |                   |
| Annualized relapse rate        | 0.92 (0.64, 1.34) |
| Disability progression at 1-year | 1.37 (0.95, 1.98) |
| Disability progression at 2-years | 1.08 (0.77, 1.52) |

### B

| Outcome                                                  | ES (95% CI)       |
|----------------------------------------------------------|-------------------|
| **Randomized Data**                                      |                   |
| Relapse free at 2-years                                  | 1.20 (0.84, 1.71) |
| No Evidence of Disease Activity at 2 years               | 1.82 (1.05, 3.15) |
| **Observational Data**                                   |                   |
| Relapse free at 1-year                                   | 1.61 (0.94, 2.78) |
| Relapse free at 2-years                                  | 2.19 (1.15, 4.18) |
comparison to Fingolimod that was documented in the indirect comparison of RCT data lends support to the former hypothesis. In a longitudinal cohort of patients with an initial diagnosis of RRMS or clinically isolated syndrome, NEDA-3 status at 2 years was found to be a significant predictor of disease progression throughout a 7-year follow-up period [35]. These data suggest that NEDA status is of paramount importance to detect disease activity early in the course of the disease, and thus influence disease progression with a timely and optimal treatment selection [36]. To the best of our knowledge, this is the first-meta-analysis on the comparative efficacy of different DMDs that has incorporated NEDA-III status as an endpoint.

Apart from the efficacy endpoints, a comparative analysis of first-year Fingolimod and Natalizumab drug discontinuation among Swedish RRMS patients suggests that both drugs are well tolerated therapies, but fingolimod is less tolerated in the subgroup of patients switching from Natalizumab [37]. In a cost-effective analysis based on the perspective of the Swedish healthcare system Fingolimod treatment was found to be less expensive, but treatment with Natalizumab was found to be more effective, resulting in a relapse decrease and thus a better cost-to-benefit ratio, especially for patients with rapidly evolving disease [38]. The cost-effectiveness of Natalizumab in patients with highly active RRMS has also been confirmed in another cost-effective analysis based on the UK healthcare system [39].

Our results are in agreement with a very recent network meta-analysis on RCT data from immunomodulators and immunosuppressants that have been used for the treatment of RRMS, in which Natalizumab was ranked as the third more effective treatment [RR 0.56, 95% CI 0.47 to 0.66; surface under the cumulative area curve (SUCRA) 88%; high quality evidence] used in RRMS, followed by Fingolimod (RR 0.72, 95% CI 0.64 to 0.81; SUCRA 71%; moderate quality evidence) [40]. The authors also noted that Natalizumab was the only therapy to provide moderate quality evidence in the prevention of the 2-year disability progression, with all other treatments providing low to very low quality of evidence. Even though the authors of the aforementioned network meta-analysis [40] reported that they found no evidence of important variables variations across comparisons, we found significant differences in baseline characteristics between patients randomized to receive Natalizumab and those randomized to receive Fingolimod (Table 1). We also highlighted that the imbalances found in baseline characteristics from RCTs were also present in the observational studies, suggesting that all indirect analyses between Natalizumab and Fingolimod should be interpreted with caution and awareness of the population imbalances in baseline disease severity.

Several limitations should be acknowledged for the correct interpretation of the present report. First, even though indirect meta-analysis is very helpful in comparing the relative effectiveness and acceptability of competing treatments, several issues need to be appropriately addressed for the results to be valid and correctly interpreted [41]. Transitivity assumption, which implies that the distribution of potential effect modifiers is the same across treatment comparisons, is a key element that should be present before the conduction of all indirect analyses [41]. Although comparison of the subgroups in the included RCTs revealed imbalances in baseline characteristics between patients randomized to treatment with Natalizumab and those treated with Fingolimod (Table 1), we decided to perform indirect analyses but also take into consideration that the indirect outcomes could likely provide an underestimated effect of Natalizumab compared to Fingolimod due to the higher baseline disease severity that was present in patients randomized to Natalizumab compared to Fingolimod in the corresponding RCTs.
Moreover, only 3 placebo-control RCTs (1 with Natalizumab [16] & 2 with Fingolimod [17,18]) were available for inclusion in the present analysis and thus we were unable to reliably investigate the presence of heterogeneity between RCTs. In most of the observational study analyses, evidence of considerable or substantial heterogeneity was present. Three of the observational study protocols reported significant imbalances in patients’ baseline characteristics [19–21], one study reported no significant differences among the subgroups of patients treated with Natalizumab and those treated with Fingolimod [23], while the remaining study provided no report on potential differences between baseline characteristics [22]. However, it should be noted that all observational study protocols, except for one [20], provided adjusted outcome measures after adjusting for potential confounders. Finally, apart from the baseline disease severity and MRI burden, it should be noted that John Cunningham virus (JCV) antibody serologic testing and the corresponding risk of progressive multifocal leukoencephalopathy (PML) have a significant role in the final decision to use Natalizumab versus Fingolimod as a second-line treatment for patients with RRMS [42, 43].

In conclusion, available randomized and observational study data suggest that Natalizumab is probably more effective than Fingolimod in terms of relapse reduction and NEDA-III status increase in patients with RRMS. Head-to-head RCTs that will directly compare the two aforementioned therapeutic options are required to independently confirm this preliminary observation.

Supporting Information

S1 File. MEDLINE Search algorithm. Table A. Excluded studies with reasons for exclusion. Table B. Baseline characteristics of included observation studies. Fig A. Analysis on the annualized relapse rate odds ratios of patients with relapsing remitting multiple sclerosis included in the randomized clinical trials of Natalizumab or Fingolimod. Fig B. Analysis on the proportion of patients with relapsing remitting multiple sclerosis included in the randomized clinical trials of Natalizumab or Fingolimod who had absence of relapse reduction at 2 years. Fig C. Analysis on the proportion of patients with relapsing remitting multiple sclerosis included in the randomized clinical trials of Natalizumab or Fingolimod who had disability progression at 2 years. Fig D. Subgroup analysis on the annualized relapse rate reduction in observational studies of patients with relapsing remitting multiple sclerosis receiving treatment with Natalizumab of Fingolimod. Fig E. Subgroup analysis on the annualized relapse rate odds ratios in observational studies of patients with relapsing remitting multiple sclerosis receiving treatment with Natalizumab of Fingolimod. Fig F. Subgroup analysis on the proportion of relapsing remitting multiple sclerosis patients with disability progression receiving treatment with Natalizumab of Fingolimod in observational study protocols at both the first and second year. Fig G. Subgroup analysis on the proportion of relapsing remitting multiple sclerosis patients with no relapses receiving treatment with Natalizumab of Fingolimod in observational study protocols at both the first and second year.

S2 File. PRISMA checklist.

Acknowledgments

Founding Members of HELANI (Hellenic Academy of Neuroimmunology): Achilles Gravanis, Alexandros Papadimitriou, Anthony Rompos, Athanasia Mouzaki, Constantinos Kylintireas, Constantinos Voumvourakis, Domna Karagogeos, Efthymios Dardiotis, Georgios Tsivgoulis,
Georgios Hadjigeorgiou, Georgios Kollias, Ioannis Helliopoulos, Lesley Probert, Nikolaos Grigoriadis, Panagiotis Ioannidis, Panagiotis Papathanasopoulos, Senate-Errietta Pelidou, Socrates Tzartos, Theodoros Karapanagiotides, Villi Panoutsakopoulou.

**Author Contributions**

Conceptualization: GT AHK.

Formal analysis: GT AHK DM.

Investigation: GT AHK.

Methodology: GT AHK DM.

Project administration: GT.

Resources: AHK DM.

Software: AHK.

Supervision: GT KV.

Validation: GT DM.

Visualization: GT AHK DM.

Writing – original draft: GT AHK DM.

Writing – review & editing: NG ED IH PP TK CK GMH KV.

**References**

1. Tsivgoulis G, Katsanos AH, Grigoriadis N, Hadjigeorgiou GM, Heliopoulos I, Papathanasopoulos P, et al. The Effect of Disease Modifying Therapies on Disease Progression in Patients with Relapsing-Remitting Multiple Sclerosis: A Systematic Review and Meta-Analysis. PLoS One. 2015; 10: e0144538. doi: 10.1371/journal.pone.0144538 PMID: 26642051

2. Freedman MS, Seichen D, Arnold DL, Prat A, Banwell B, Yeung M, et al. Treatment optimization in MS: Canadian MS Working Group updated recommendations. Can J Neurol Sci. 2013; 40:307–23. doi: 10.1017/s0317167110014244 PMID: 23603165

3. Gajofatto A, Bacchetti P, Grimes B, High A, Waubant E. Switching first-line disease-modifying therapy after failure: impact on the course of relapsing-remitting multiple sclerosis. Mult Scler. 2009; 15:50–8. doi: 10.1177/1352458508096687 PMID: 18922831

4. Torkildsen Ø, Myhr KM, Bø L. Disease-modifying treatments for multiple sclerosis—a review of approved medications. Eur J Neurol. 2016; 23 Suppl 1:1–27. doi: 10.1111/j.ene.12883 PMID: 26563094

5. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. J Clin Epidemiol 2009; 62:e1–34. doi: 10.1016/j.jclinepi.2009.06.006 PMID: 19631507

6. EMEA: Guideline on clinical investigation of medicinal products for the treatment of multiple sclerosis. Doc. Ref. CPMP/EWP/561/98 Rev. 1, 16 November 2006

7. Sormani MP, Signori A, Siri P, De Stefano N. Time to first relapse as an endpoint in multiple sclerosis clinical trials. Mult Scler. 2013; 19:466–74. doi: 10.1177/1352458512457841 PMID: 22914849

8. Havrdova E, Galetta S, Hutchinson M, Stefekos D, Bates D, Polman CH, et al. Effect of natalizumab on clinical and radiological disease activity in multiple sclerosis: a retrospective analysis of the Natalizumab Safety and Efficacy in Relapsing-Remitting Multiple Sclerosis (AFFIRM) study. Lancet Neurol. 2009; 8:254–60. doi: 10.1016/s1474-4422(09)70021-3 PMID: 19201654

9. Cohen J. Statistical Power Analysis for the Behavioral Sciences. Hillsdale, New Jersey, 1988. Lawrence Erlbaum Associates: Routledge.

10. Tsivgoulis G, Katsanos AH, Grigoriadis N, Hadjigeorgiou GM, Heliopoulos I, Papathanasopoulos P, et al. The effect of disease-modifying therapies on brain atrophy in patients with clinically isolated
syndrome: a systematic review and meta-analysis. Ther Adv Neurol Disord. 2015; 8:193–202. doi: 10.1177/1756285615600381 PMID: 26557896

11. Deeks JJ, Higgins JP, Altman DG. Chapter 9.4.6: Combining dichotomous and continuous outcomes. Cochrane Handbook for Systematic Reviews of Interventions. Available: http://handbook.cochrane.org/chapter_9/9_4_6_combining_dichotomous_and_continuous_outcomes.htm. Updated March 2011. Accessed February 23th, 2016.

12. Borenstein M, Hedges LV, Higgins JPT and Rothstein HR. Chapter 19: Subgroup Analyses, in Introduction to Meta-Analysis, John Wiley & Sons, Ltd, Chichester, UK. doi: 10.1002/9780470743386.ch19

13. Deeks JJ, Higgins JP, Altman DG. Chapter 9: Analysing data and undertaking meta-analyses. Cochrane Handbook for Systematic Reviews of Interventions. Available: http://handbook.cochrane.org/chapter_9/9Analysing_data_and_undertaking_meta_analyses.htm. Updated March 2011. Accessed February 4th, 2014.

14. Bucher HC, Guyatt GH, Griffith LE, Walter SD. The results of direct and indirect treatment comparisons in meta-analysis of randomized controlled trials. J Clin Epidemiol. 1997; 50:683–91. doi: 10.1016/s0895-4356(97)00049-8 PMID: 9250266

15. Salanti G. Indirect and mixed-treatment comparison, network, or multiple-treatments meta-analysis: many names, many benefits, many concerns for the next generation evidence synthesis school. Research Synthesis Methods 2012; 3:80–97. doi: 10.1002/jrsm.1037 PMID: 26062083

16. Polman CH, O’Connor PW, Havrdova E, Hutchinson M, Kappos L, Miller DH, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. N Engl J Med. 2006; 354:899–910. doi: 10.1056/NEJMoa044397 PMID: 16510744

17. Kappos L, Radue EW, O’Connor P, Polman C, Hohlfeld R, Calabresi P, et al. A placebo-controlled trial of oral fingolimod in relapsing multiple sclerosis. N Engl J Med. 2010; 362:387–401. doi: 10.1056/NEJMoa0909494 PMID: 20089952

18. Calabresi PA, Radue EW, Goodin D, Jeffery D, Rammohan KW, Reder AT, et al. Safety and efficacy of fingolimod in patients with relapsing-remitting multiple sclerosis (FREEDOMS II): a double-blind, randomised, placebo-controlled, phase 3 trial. Lancet Neurol. 2014; 13:545–56. doi: 10.1016/S1474-4422(14)70049-3 PMID: 24685276

19. Barbin L, Rousseau C, Jousset N, Casey R, Debouverie M, Vukusic S, et al. Comparative efficacy of fingolimod vs natalizumab: A French multicenter observational study. Neurology. 2016; 86:771–8. doi: 10.1212/01.wnl.0000000000002395 PMID: 26826205

20. Braune S, Lang M, Bergmann A; NTC Study Group. Second line use of Fingolimod is as effective as Natalizumab in a German out-patient RRMS-cohort. J Neurol; 2013; 260:2981–5. doi: 10.1007/s00415-013-7082-0 PMID: 24008757

21. Gajofatto A, Bianchi MR, Deotto L, Benedetti MD. Are natalizumab and fingolimod analogous second-line options for the treatment of relapsing-remitting multiple sclerosis? A clinical practice observational study. Eur Neurol. 2014; 72:173–80. doi: 10.1159/000361044 PMID: 25226868

22. Kalincik T, Horakova D, Spelman T, Jokubaitis V, Trojano M, Lugaresi A, et al. Switch to natalizumab versus fingolimod in active relapsing multiple sclerosis. Ann Neurol. 2015; 77:425–35. doi: 10.1002/ana.24339 PMID: 25546031

23. Koch-Henriksen N, Magyari M, Sellebjerg F, Soleberg Sørensen P. A comparison of multiple sclerosis clinical disease activity between patients treated with natalizumab and fingolimod. Mult Scler. 2016 Apr 7; pii: 1352458516643393. [Epub ahead of print] doi: 10.1177/1352458516643393 PMID: 27056806

24. Kappos L, De Stefano N, Freedman MS, Cree BA, Radue EW, Sprenger T, et al. Inclusion of brain volume loss in a revised measure of ‘no evidence of disease activity’ (NEDA-4) in relapsing-remitting multiple sclerosis. Mult Scler. 2015 Nov 19; pii: 1352458515616701. [Epub ahead of print] doi: 10.1177/1352458515616701 PMID: 26585439

25. Röver C, Nicholas R, Straube S, Friede T. Changing EDSS Progression in Placebo Cohorts in Relapsing MS: A Systematic Review and Meta-Regression. PLoS One. 2015; 10:e0137052. doi: 10.1371/journal.pone.0137052 PMID: 26327532

26. Lavorgna L, Bonavita S, Ippolito D, Lanzillo R, Salemi G, Patti F, et al. Clinical and magnetic resonance imaging predictors of disease progression in multiple sclerosis: a nine-year follow-up study. Mult Scler. 2014; 20:220–6. doi: 10.1177/1352458513494958 PMID: 23838177

27. Kappos L, Kuhle J, Multanen J, Kremenchutzky M, Verduin di Cantogno E, Cornelisse P, et al. Factors influencing long-term outcomes in relapsing-remitting multiple sclerosis: PRISMS-15. J Neurol Neurosurg Psychiatry. 2015; 86:1202–7. doi: 10.1136/jnnp-2014-310024 PMID: 26374702
28. Sormani MP, Li DK, Bruzzi P, Stubinski B, Cornelisse P, Rocak S, et al. Combined MRI lesions and relapses as a surrogate for disability in multiple sclerosis. Neurology. 2011; 77:1684–90. doi: 10.1212/WNL.0b013e31823648b9 PMID: 21975200

29. Uher T, Vanecovka M, Sobisek L, Tyblova M, Seidl Z, Krasensky J, et al. Combining clinical and magnetic resonance imaging markers enhances prediction of 12-year disability in multiple sclerosis. Mult Scler. 2016 Apr 6. pii: 1352458516642314. [Epub ahead of print] doi: 10.1177/1352458516642314 PMID: 27053635

30. Filippi M, Preziosa P, Rocca MA. Magnetic resonance outcome measures in multiple sclerosis trials: time to rethink? Curr Opin Neurol. 2014; 27:290–9. doi: 10.1097/WCO.0000000000000095 PMID: 24792339

31. Harris JO, Frank JA, Patronas N, McFarlin DE, McFarland HF. Serial gadolinium-enhanced magnetic resonance imaging scans in patients with early, relapsing-remitting multiple sclerosis: implications for clinical trials and natural history. Ann Neurol. 1991; 29:548–55. doi: 10.1002/ana.410290515 PMID: 1859184

32. Bermel RA, Naismith RT. Using MRI to make informed clinical decisions in multiple sclerosis care. Curr Opin Neurol. 2015; 28:244–9. doi: 10.1097/WCO.0000000000000204 PMID: 25987772

33. Losseff NA, Miller DH, Kidd D, Thompson AJ. The predictive value of gadolinium enhancement for long term disability in relapsing-remitting multiple sclerosis—preliminary results. Mult Scler, 2001; 7:23–5. doi: 10.1177/135245850100700105 PMID: 11321189

34. Alroughani RA, Akhtar S, Ahmed SF, Al-Hashel JY. Clinical predictors of disease progression in multiple sclerosis patients with relapsing onset in a nation-wide cohort. Int J Neurosci. 2015; 125:831–7. doi: 10.1080/00207454.2014.976641 PMID: 25329929

35. Stangel M, Penner IK, Kallmann BA, Lukas C, Kieseier BC. Towards the implementation of ‘no evidence of disease activity’ in multiple sclerosis treatment: the multiple sclerosis decision model. Ther Adv Neurol Disord. 2015; 8:3–13. doi: 10.1177/1756285614560733 PMID: 25584069

36. Frissell T, Forsberg L, Nordin N, Kiesel C, Alfredsson L, Askling J, et al. Comparative analysis of first-year fingolimod and natalizumab drug discontinuation among Swedish patients with multiple sclerosis. Mult Scler. 2016; 22:85–93. doi: 10.1177/1352458515579216 PMID: 25921036

37. O’Day K, Meyer K, Stafkey-Mailey D, Watson C. Cost-effectiveness of natalizumab vs fingolimod for the treatment of relapsing-remitting multiple sclerosis: analyses in Sweden. J Med Econ. 2015; 72:152–8. doi: 10.1001/jamaneurology.2014.3537 PMID: 25531931

38. Gani R, Giovannoni G, Bates D, Kemball B, Hughes S, Kerrigan J, et al. Cost-effectiveness analyses of natalizumab (Tysabri) compared with other disease-modifying therapies for people with highly active relapsing-remitting multiple sclerosis in the UK. Pharmacoeconomics. 2008; 26:617–27. doi: 10.2165/00019053-200826070-00005 PMID: 18963952

39. Tramacere I, Del Giovanne C, Salanti G, D’Amico R, Filippini G. Immunomodulators and immunosuppressants for relapsing-remitting multiple sclerosis: a network meta-analysis. Cochrane Database Syst Rev. 2015;9:CD011381. doi: 10.1002/14651858.CD011381.pub2 PMID: 26384035

40. Mavridis D, Giannatsi M, Cipriani A, Salanti G. A primer on network meta-analysis with emphasis on mental health. Evid Based Ment Health. 2015; 18:40–6. doi: 10.1136/eb-2015-102088 PMID: 25908686

41. Conway DS, Cohen JA. Natalizumab and fingolimod: insight into their relative efficacies in clinical practice. Mult Scler. 2014; 20:1280–1. doi: 10.1177/1352458514535283 PMID: 25160120

42. Hauser SL, Johnston SC. Balancing risk and reward: the question of natalizumab. Ann Neurol. 2009; 66:A7–8. doi: 10.1002/ana.21873 PMID: 19810091