Rituximab versus Fingolimod after Natalizumab in Multiple Sclerosis Patients

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Objective: Many JC virus antibody-positive relapsing–remitting multiple sclerosis (RRMS) patients who are stable on natalizumab switch to other therapies to avoid progressive multifocal leukoencephalopathy.
Methods: We compared outcomes for all RRMS patients switching from natalizumab due to JC virus antibody positivity at 3 Swedish multiple sclerosis centers with different preferential use of rituximab and fingolimod (Stockholm, n = 156, fingolimod 51%; Gothenburg, n = 64, fingolimod 88%; Umeå, n = 36, fingolimod 19%), yielding a total cohort of N = 256 (fingolimod 55%).
Results: Within 1.5 years of cessation of natalizumab, 1.8% (rituximab) and 17.6% (fingolimod) of patients experienced a clinical relapse (hazard ratio for rituximab = 0.10, 95% confidence interval [CI] = 0.02–0.43). The hazard ratio (favoring rituximab) for adverse events (5.3% vs 21.1%) and treatment discontinuation (1.8% vs 28.2%) were 0.25 (95% CI = 0.10–0.59) and 0.07 (95% CI = 0.02–0.30), respectively. Furthermore, contrast-enhancing lesions were found in 1.4% (rituximab) versus 24.2% (fingolimod) of magnetic resonance imaging examinations (odds ratio = 0.05, 95% CI = 0.00–0.22). Differences remained when adjusting for possible confounders (age, sex, disability status, time on natalizumab, washout time, follow-up time, and study center).
Interpretation: Our findings suggest an improved effectiveness and tolerability of rituximab compared with fingolimod in stable RRMS patients who switch from natalizumab due to JC virus antibody positivity. Although residual confounding factors cannot be ruled out, the shared reason for switching from natalizumab and the preferential use of either rituximab or fingolimod in 2 of the centers mitigates these concerns.

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The approval of natalizumab (NTZ; Tysabri) improved possibilities to treat highly active relapsing–remitting multiple sclerosis (RRMS). However, long-term treatment with NTZ increases the risk of progressive multifocal leukoencephalopathy (PML),[1,2] a serious and potentially lethal opportunistic brain infection with JC virus (JCV). To enable PML risk assessment for multiple sclerosis (MS) patients with NTZ therapy, serological testing for JCV is recommended.[3] Studies of large cohorts show that >50% of the population display positive JCV serology (JCV^+).[4] The benefit of continued treatment in these patients therefore has to be carefully weighed against the risk of PML, and discontinuation of NTZ treatment has to be managed carefully as disease activity will return upon cessation of drug dosing.[5] In a large cohort of patients who had participated in randomized clinical trials (RCTs), clinical and neuroradiological disease activity peaked between 4 and 7 months after last

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NTZ dosing.[6] In addition, smaller studies have reported rebound phenomena, with reoccurring disease activity over and beyond that of pretreatment levels,[7–9] perhaps explained by patients treated in clinical practice having more active disease than those included in RCTs. Currently there is no clear consensus on how to reduce the risk of a sometimes violent return of disease activity in the situation of NTZ discontinuation.[10,11]

A frequent choice of disease-modifying therapy (DMT) after NTZ is fingolimod (FGL; Gilenya). Results from a recent register-based study suggest that FGL is more effective than interferon beta/glatiramer acetate in reducing the risk of disease reactivation in this patient group.[12] Nonetheless, up to 20% of patients switching to FGL experience relapse during the first 6 months.[13] Data also show that limiting the washout period to no more than 3 months significantly reduces the relapse risk.[14] However, in most studies all reasons for interrupting NTZ have been included, making it difficult to draw firm conclusions about the long-term relapse risk for MS patients switching solely due to JCV^+.

An alternative DMT subsequent to NTZ is rituximab (RTX; MabThera/Rituxan). RTX is approved for the treatment of B-cell lymphoma, rheumatoid arthritis, and systemic vasculitis, but also has a history of off-label use in MS. To date only 1 placebo-controlled phase II study in RRMS has been conducted,[15] and currently there are no data supporting the use of RTX in the context of patients switching from NTZ.

The aim of the present study was to compare the effectiveness, tolerability, and safety of RTX and FGL using prospectively collected data entered into the Swedish MS register from 3 large MS centers with different treatment allocations to RTX and FGL.

Patients and Methods

Study Population

The source population was all MS patients ever recorded in the Swedish MS register, at the Karolinska (Stockholm, until February 24, 2015), Sahlgrenska (Gothenburg, until April 18, 2015), and Norrland's (Umeå, until April 12, 2015) University Hospitals with the following inclusion criteria: a diagnosis of RRMS, JCV^+, ending treatment with NTZ and subsequently switching to either RTX or FGL. Exclusion criteria were: NTZ treatment for <6 months, switch for reasons other than only JCV^+ status, a washout period exceeding 6 months, and patients who had registered a wish not to be included in studies. The study population was identified through the Swedish MS register (www.neuroreg.se) and cross-checked against the local clinical records systems. Patients eligible for inclusion were further examined by in-depth medical chart review (Fig 1). This study was part of the STOPMS (Stockholm Prospective Assessment of MS) project and approved by the regional ethical review boards of Stockholm (2009/2107-31/2) and Umeå (2013/445-31).

Outcomes

Outcomes were: magnetic resonance imaging (MRI) gadolinium-enhancing (Gd^+) T1 lesions and new cerebral T2 lesions as compared with a reference MRI scan performed after DMT switch as judged from the original neuroradiology report, clinical relapses, adverse events (AEs), and drug survival, all within the first 1.5 years of RTX or FGL treatment. MRI scans were performed according to standard follow-up guidelines and MRI protocols, using 1.5 or 3T MRI scanners. MRI scans for Gd^+ lesions were included in the analyses if performed at least 3 months into RTX or FGL treatment and before the treatment had ended. MRI scans for new T2 lesions were included if the examination had been done before the treatment had ended and there was an available reference MRI scan performed after the start of RTX or FGL. Registered AEs were: severe infections requiring medication, except for uncomplicated lower urinary tract infections; AEs causing discontinuation of therapy; and AEs related to the first infusion of RTX or the first dosing of FGL (both reported separately). The date for discontinuation of therapy was calculated as the date for the last administration of the drug plus 6 months for RTX and 1 month for FGL, to adjust for the time the drug was still effective after administration.

Data Collection

Data on treatments, JCV^+ status, relapses, and Expanded Disability Status Scale (EDSS) were abstracted from the Swedish MS register and complemented with additional data from clinical records, primarily regarding detailed descriptions of MRI results, clinical relapse symptoms, and AEs (scored according to Common Terminology Criteria for Adverse Events[16]). Data collection was done manually at the respective centers using a common data collection form. Suspected/registered relapses were adjudicated by 2 evaluators, blinded to treatment allocation and patient identity, based on clinical record data. All patients with ongoing treatment with RTX or FGL were followed until the date of data censure given above, whereas patients who had discontinued their treatment with RTX or FGL were followed until the time of data censure or 1 year after the last administration of the discontinued treatment, whichever came first.

Statistical Analyses

Baseline patient characteristics are presented in Table 1. Differences in baseline characteristics were tested using the Wilcoxon rank sum test for continuous variables and Fisher exact test for categorical variables. For the outcomes Gd^+ and T2 MRI lesions, the number of patients with positive scans per patient with valid scans was calculated, and the differences in these proportions were tested in logistic regression models. For the outcomes clinical relapses, AEs, and drug survival, person-years and yearly incidence were calculated, and Kaplan–Meier curves and Cox proportional hazards models were used, with time from the first administration of RTX or FGL as timescale.

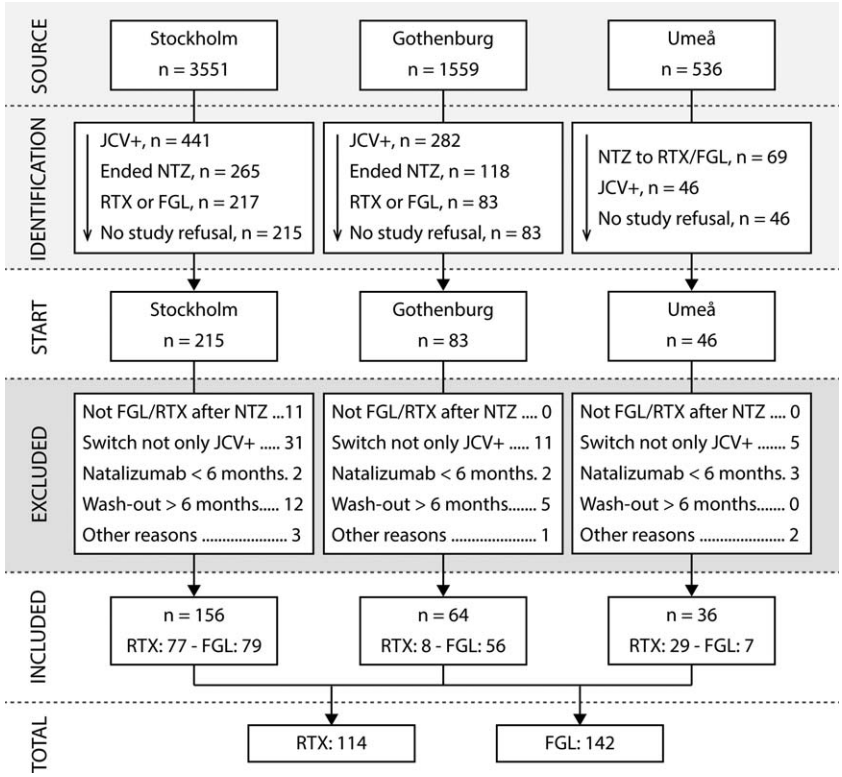


FIGURE 1: Flow chart depicting patient disposition for the different centers, resulting in the studied fingolimod (FGL) and rituximab (RTX) groups. The source population was all multiple sclerosis (MS) patients recorded in the Swedish MS register. Study subjects in Stockholm and Gothenburg were identified as JC virus serology positive (JCV^+) patients who had ended natalizumab (NTZ) treatment, had been treated with RTX or fingolimod FGL, and had not registered a will to be excluded from studies. Identification of suitable patients in the center in Umeå was done by identifying patients switching from NTZ directly to RTX or FGL, who were JCV^+ and had not registered a will to be excluded from studies. Patients were then excluded if they had switched to any treatment other than RTX or FGL directly after NTZ, if the decision for a switch in therapy was not solely based on JCV^+ status, if NTZ treatment had been <6 months, if the washout period between NTZ and RTX or FGL had been >6 months, or if the patient for any other reason did not satisfy the inclusion and exclusion criteria (eg, patients with insufficient follow-up or compliance).

Cumulative incidence for registered reason of discontinuation of therapy was estimated without censoring of competing reasons (eg, for discontinuation due to AEs, all other reasons for discontinuation were considered competing events) using the cmprsk package in R. To explore potential confounding factors, the continuous variables age, time on NTZ, washout time, and follow-up time (only in logistic models), and the categorical variables sex, baseline EDSS, and study center were included in sequential regression models. Hazard ratios (HRs) and odds ratios (ORs) were first calculated with none of the factors, with age and sex, and by sequentially adding baseline EDSS, time on NTZ, washout time, follow-up time (for OR only), and study center. This was done using a complete-case strategy, discarding patients not having complete data for any of these parameters.

Statistical analyses were performed in R v.3.2.1 and Access 2013 (Microsoft, Redmond, WA).

Results

Study Population

In total, we identified 256 patients who had switched from NTZ to either RTX or FGL solely due to JCV^+ status at the 3 centers, 114 and 142 in the RTX and FGL groups, respectively (see Fig 1). Notably, the relative allocation to either of the 2 DMTs differed considerably by center. There were also certain differences in the baseline characteristics between the 2 treatment groups (see Table 1). In particular, RTX patients had a shorter washout period (median = 1.45 vs 2.12 months for FGL), a higher proportion of patients with a washout period of <3 months (93.0% vs 74.6% for FGL), and a shorter follow-up time (median = 1.24 vs 1.82 years for FGL). In contrast, differences in sex, age, disease duration, baseline EDSS, and time on NTZ were relatively small between the groups. Only a few patients, and only from the Stockholm study center, had some missing baseline data. Missing data in the Stockholm RTX group were: time since MS debut, 1 patient; time since MS diagnosis, 3 patients. Missing data in the Stockholm FGL group were: time since MS diagnosis, 1 patient; baseline EDSS, 1 patient. These patients are too few to make any statement on whether they differed from the patients having complete data. NTZ and FGL had in all but a few cases

TABLE 1. Baseline Characteristics and Comparison between the Rituximab and Fingolimod Groups

Characteristic	Study Group		*p*
	Rituximab, n = 114	Fingolimod, n = 142	
Age, yr, median (IQR)	40.17 (33.74–50.44)	40.79 (33.73–47.73)	0.601[a]
Male sex, No. [%]	41 [36.0]	56 [39.4]	0.605[b]
MS duration, yr, median (IQR)			
Since MS debut	9.79 (5.81–16.61)	10.40 (7.19–14.88)	0.874[a]
Since MS diagnosis	8.00 (4.53–11.84)	7.88 (5.20–11.22)	0.908[a]
Baseline EDSS, median (IQR)	2.00 (1.00–3.50)	2.50 (1.50–3.50)	0.803[a]
Time on NTZ, yr, median (IQR)	3.49 (2.07–5.37)	3.16 (1.79–4.58)	0.149[a]
Washout period, mo, median (IQR)	1.45 (1.13–2.03)	2.12 (1.88–3.01)	<0.001[a]
Washout < 3 months, No. patients [%]	106 [93.0]	106 [74.6]	<0.001[b]
Follow-up time, yr, median (IQR)	1.24 (0.75–2.02)	1.82 (1.40–2.36)	<0.001[a]
Center, No. patients [%]			<0.001[b]
Stockholm	77 [67.5]	79 [55.6]	
Gothenburg	8 [7.0]	56 [39.4]	
Umeå	29 [25.4]	7 [4.9]	

Missing data in rituximab group: since MS debut, 1 patient; since MS diagnosis, 3 patients. Missing data in fingolimod group: since MS diagnosis, 1 patient; baseline EDSS, 1 patient.
[a]Probability value calculated with the Wilcoxon rank sum test.
[b]Probability value calculated with Fisher exact test.
EDSS = Expanded Disability Status Scale; IQR = interquartile range; MS = multiple sclerosis; NTZ = natalizumab.

(<5%) been administered according to clinical routine with intravenous (IV) infusions of 300mg every 4 weeks and oral administration once daily of 0.5mg, respectively. RTX had in all but a few cases (<5%) been administered as a single IV infusion of 500 or 1,000mg every 6 months; however, in some cases the first infusion had been repeated after 2 weeks. All 3 centers strive to follow the guidelines of the Swedish MS Society (http://www.mssallskapet.se/Checklistor.html), which states that MRI/EDSS rating should be performed at cessation of NTZ and on a yearly basis with ongoing treatment with RTX and FGL, respectively. However, the number of MRIs per patient showed some differences among the centers. In Stockholm, there were 0.54 scans per patient compared with 0.72 and 0.94 in Gothenburg and Umeå, respectively. For the entire RTX cohort, 0.61 scans/patient were available for the analysis compared with 0.67 for FGL. Although these differences may affect the detection of several outcomes, the effect at an aggregate level is likely to be small.

Effectiveness of RTX as Compared with FGL

MRI scans performed at least 3 months into the treatment demonstrated 24 patients with Gd^+ lesions within the first 1.5 years of treatment, 1 (1%) in the RTX group and 23 (16%) in the FGL group (Table 2). The proportions of patients with positive scans among patients with valid scans were 0.01 and 0.24 for RTX and FGL, respectively. Logistic regression for patients with a Gd^+ lesion, comparing RTX to FGL, resulted in a crude OR of 0.05 (95% confidence interval [CI] = 0.00–0.22), and was not significantly affected by adjustments for differences in age, sex, EDSS, time on NTZ, washout time, follow-up time, and study center, yielding an adjusted OR of 0.01 (95% CI = 0.00–0.08; Supplementary Table 1).

Twenty-seven patients had a clinical relapse within the first 1.5 years of treatment, 2 (2%) in the RTX group and 25 (18%) in the FGL group (see Table 2), corresponding to yearly relapse incidence rates of 0.02 and 0.16, respectively. The decrease over time in proportion of patients without clinical relapse is shown in Figure 2A. The Cox proportional hazards model for time to first relapse, comparing RTX to FGL, resulted in a crude HR of 0.10 (95% CI = 0.02–0.43), and an HR of 0.09 (95% CI = 0.02–0.40) when adjusting for age, sex, EDSS, time on NTZ, washout time, and study center (see Supplementary Table 1).

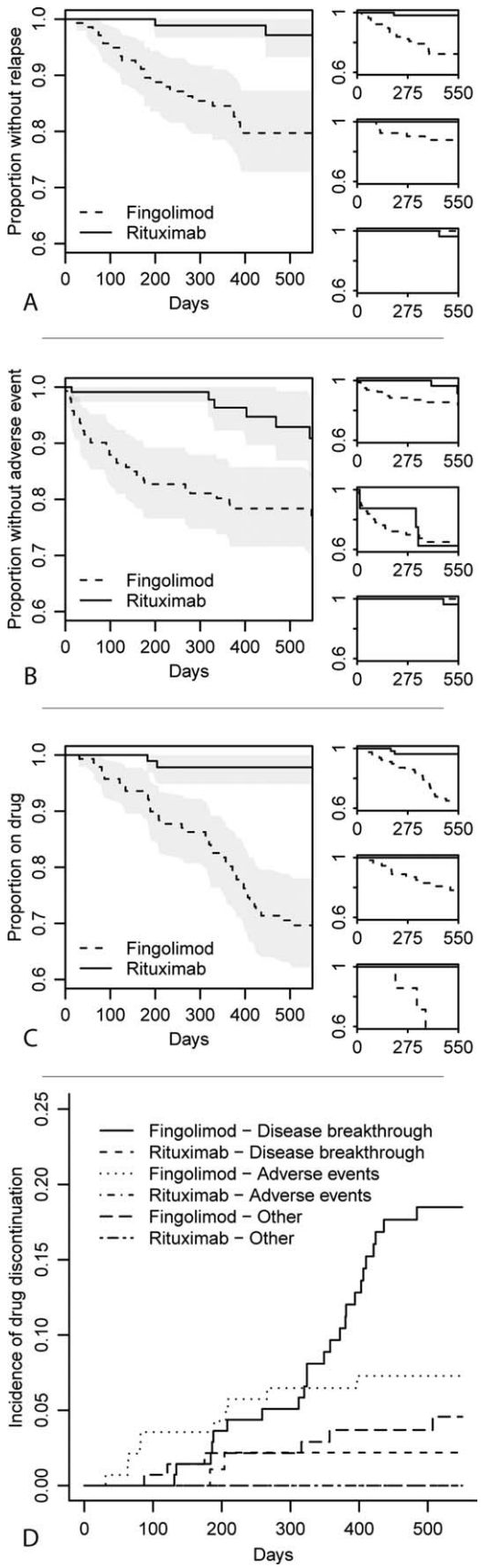
TABLE 2. Distribution of Outcomes for the RTX and FGL Groups

Result	Stockholm		Gothenburg		Umeå		Total	
	RTX, n = 77	FGL, n = 79	RTX, n = 8	FGL, n = 56	RTX, n = 29	FGL, n = 7	RTX, n = 114	FGL, n = 142
Gd^+ lesions, within 1.5 years								
Patients with positive scan	1	10	0	9	0	4	1	23
Patients with valid scan[a]	36	48	6	40	27	7	69	95
Patients with positive scan/ patients with valid scan	0.03	0.21	0.00	0.23	0.00	0.57	0.01	0.24
Gd^+/new T2 lesions, within 1.5 years								
Patients with positive scan	1	15	0	11	0	5	1	31
Patients with valid scan[b]	42	60	6	40	27	7	75	107
Patients with positive scan/ patients with valid scan	0.02	0.25	0.00	0.28	0.00	0.71	0.01	0.29
Clinical relapse, within 1.5 years								
Patients with clinical relapse	1	19	0	6	1	0	2	25
Person-years	67.85	83.63	11.56	62.17	42.03	8.50	121.44	154.30
Incidence of clinical relapse per year	0.01	0.23	0.00	0.10	0.02	0.00	0.02	0.16
AE, within 1.5 years								
Patients with AE	2	12	3	18	1	0	6	30
Person-years	67.45	91.22	9.17	48.32	42.09	8.50	118.71	148.04
Incidence of AE per year	0.03	0.16	0.33	0.37	0.02	0.00	0.05	0.20
First-dosing AEs								
Patients with first-dosing AE	22	5	3	5	5	0	30	10
First-dosing AEs/patient	0.29	0.06	0.38	0.09	0.17	0.00	0.26	0.07
Drug survival, within 1.5 years								
Patients who discontinued therapy	2	26	0	11	0	3	2	40
Person-years	67.87	94.82	11.56	66.15	42.31	8.50	121.74	169.47
Incidence of therapy discontinuation per year	0.03	0.27	0.00	0.17	0.00	0.35	0.02	0.24

[a]A scan done at least 3 months after treatment start and before treatment ended.
[b]A scan done at least 3 months after treatment start and before treatment ended, or a scan done after treatment start and before treatment ended, compared to a scan done after treatment start.
AE = adverse event; FGL = fingolimod; Gd^+ = gadolinium enhancing; RTX = rituximab.

Safety of RTX as Compared with FGL

Thirty-six patients reported an AE within the first 1.5 years of treatment, 6 (5%) in the RTX group and 30 (21%) in the FGL group (see Table 2), corresponding to yearly AE incidence rates of 0.05 and 0.20, respectively. The decrease over time in proportion of patients without AE is shown in Figure 2B. Cox proportional hazards model for time to first AE, comparing RTX to FGL, resulted in a crude HR of 0.25 (95% CI = 0.10–0.59), and an adjusted HR of 0.25 (95% CI = 0.10–0.62) when adjusting for age, sex, EDSS, time on NTZ, and washout time (see Supplementary Table 1). However, the significance was lost when also adjusting for study center (HR = 0.50, 95% CI = 0.19–1.35). The type and grade of the AEs are described in Supplementary Table 2. In the RTX cohort, 1 grade 3, 1 grade 2, and 4 grade



1 events were recorded. In the FGL cohort, 1 severe, potentially life-threatening grade 4 event was recorded, a laryngeal edema occurring in the setting of a bacterial infection, which necessitated invasive ventilation in intensive care. The patient subsequently made a full recovery. In addition, 2 grade 3, 8 grade 2, and 28 grade 1 events occurred in the FGL cohort. AEs related to the administration of either drug were analyzed separately, showing that reactions related to the first infusion of RTX, all grade 1, were recorded in 26% of patients in the RTX group, as compared with a 7% incidence of AEs at first dosing of FGL (see Table 2).

Drug Survival of RTX as Compared with FGL

Forty-two patients discontinued their therapy within the first 1.5 years of treatment, 2 (2%) in the RTX group and 40 (28%) in the FGL group (see Table 2), corresponding to yearly treatment discontinuation incidence rates of 0.02 and 0.24, respectively. The decrease over time in proportion of patients remaining on treatment is shown in Figure 2C. Cox proportional hazards model for time to discontinuation of treatment, comparing RTX to FGL, resulted in a crude HR of 0.07 (95% CI = 0.02–0.30), and an HR of 0.07 (95% CI = 0.01–0.30) when adjusting for age, sex, EDSS, time on NTZ, washout time, and study center (see Supplementary Table 1). The most common reason for discontinuation of treatment was disease breakthrough, followed by AEs. Cumulative incidence for reason of discontinuation is shown in Figure 2D.

Outcomes at the 3 Centers

For baseline characteristics for patients at the 3 centers, see Table 3 and Supplementary Tables 3 to 5. The proportion and change over time of patients experiencing a clinical relapse, AE, and evidence of disease activity on MRI in the 2 smaller cohorts (Gothenburg and Umeå) were largely in agreement with those of the larger Stockholm cohort and the respective treatment (see Table 2, Fig 2). There was a nonsignificant trend of higher rates of drug discontinuations (HR = 1.39, 95% CI = 0.63–3.07) and relapses (HR = 2.85, 95% CI = 1.00–8.12)

FIGURE 2: Plots depicting the different outcomes for the entire cohort (A–D, large plot) and individually for each center (A–C, smaller plots for Stockholm [top], Gothenburg [middle], and Umeå [bottom]). (A) Kaplan–Meier curve for time until first clinical relapse within the first 1.5 years of treatment. (B) Kaplan–Meier curve for time until first adverse event within the first 1.5 years of treatment. (C) Kaplan–Meier curve for drug survival within the first 1.5 years of treatment. (D) Cumulative incidence curves of reasons for rituximab and fingolimod therapy discontinuation. "Rituximab - Adverse events" and "Rituximab - other" were both zero and therefore are overlaid.

TABLE 3. Baseline Characteristics for the Different Centers: Stockholm, Gothenburg, and Umeå

Characteristic	Center		
	Stockholm, n = 156	Gothenburg, n = 64	Umeå, n = 36
Age, yr, median (IQR)	39.19 (33.22–46.19)	45.00 (38.75–50.25)	40.00 (28.75–49.25)
Male sex, No. [%]	60 [38.5]	28 [43.8]	9 [25.0]
RTX, No. [%]	77 [49.4]	8 [12.5]	29 [80.6]
MS duration, yr, median (IQR)			
Since MS debut	10.67 (7.09–16.25)	11.70 (8.06–15.51)	7.30 (3.35–9.08)
Since MS diagnosis	7.95 (5.16–11.62)	8.67 (6.22–13.28)	4.81 (2.45–7.89)
Baseline EDSS, median (IQR)	2.50 (1.50–4.00)	2.75 (1.50–4.00)	1.00 (0.00–2.00)
Time on NTZ, yr, median (IQR)	3.15 (1.91–4.63)	4.27 (2.22–5.46)	3.04 (1.08–3.72)
Washout period, mo, median (IQR)	2.03 (1.43–2.68)	2.10 (1.63–2.73)	1.37 (0.99–2.02)
Washout < 3 months, No. patients [%]	125 [80.1]	51 [79.7]	36 [100.0]
Follow-up time, yr, median (IQR)	1.72 (0.82–2.11)	1.45 (1.28–1.82)	2.56 (1.98–2.83)

Missing data in Stockholm group: since MS debut, 1 patient; since MS diagnosis, 4 patients; baseline EDSS, 1 patient. No missing data in Gothenburg group or Umeå group.
EDSS = Expanded Disability Status Scale; IQR = interquartile range; MS = multiple sclerosis; NTZ = natalizumab; RTX = rituximab.

in the FGL cohort of Stockholm compared with Gothenburg. The mean age of FGL patients in the Stockholm cohort was 37.3 years compared with 46.0 years in the Gothenburg cohort, whereas MS disease duration was similar, suggesting that the FGL cohort in Stockholm to a higher degree was composed of younger patients with more inflammatory active disease. This was not due to channeling of more active patients to FGL, because the RTX cohort in Stockholm also had a lower mean age (39.7 years) than the FGL cohort in Gothenburg. The comparison between the RTX cohorts in Stockholm and Umeå was uninformative due to the low number of events in both groups.

Outcomes in Patients with Short Washout

In a separate analysis, the 212 patients, equally distributed between RTX and FGL, who had had a <3-month washout period between NTZ and subsequent therapy were studied. The proportion of patients experiencing a clinical relapse, AE, evidence of disease activity on MRI, or discontinued treatment closely mirrored that of the whole cohort (Supplementary Table 6).

Discussion

In this observational study, the effectiveness, tolerability, and safety of RTX and FGL for patients switching from NTZ solely due to JCV^+ status were compared. The patients who switched to RTX displayed significantly fewer MRI lesions, clinical relapses, and AEs, and had a better overall drug survival compared with FGL. The better drug survival of RTX seemed to be mainly a result of its greater effectiveness, as most discontinuations on FGL were due to disease breakthrough. Another contributing reason was that RTX was better tolerated than FGL in this patient population, despite a higher rate of first-time infusion AEs compared with first-dosing AEs for FGL.

Over the past decade, the treatment landscape for MS has undergone drastic changes.[17] However, some newer and more effective therapies are associated with risks of potentially serious side effects. Long-term treatment with NTZ is associated with an increased risk of virus infections, including PML. As of September 2013, 399 cases of PML in MS patients treated with NTZ had been confirmed worldwide, with a 26% mortality rate in symptomatic patients and a high degree of permanent neurological disability among the survivors.[18] A risk management plan with regular testing of JCV serology to assess the risk of PML has been introduced. As a consequence, a proportion of JCV^+ patients stable on NTZ switch to other therapies; however, they then incur the risk of disease reactivation. Because most NTZ-treated patients have documented high disease activity on previous first-line DMTs, they should switch to other highly effective DMTs. Among currently approved DMTs, FGL has been among the main options to switch to, as supported by recent evidence of superiority compared with interferon beta/glatiramer acetate regarding the risk of

reappearance of disease activation.[12] However, in a previous study, 20% of patients switching to FGL from NTZ experienced relapses during the first 6 months,[13] indicating insufficient effectiveness of FGL in a proportion of patients. In Sweden, off-label RTX has become an alternative switch DMT for patients stopping NTZ. Along with the absence of phase III RCT data, the existing studies examining RTX in the MS setting have been relatively small prospective studies[19–21] with limited follow-up or did not investigate RRMS patients.[22] Importantly, to date no RCT comparing effectiveness between different DMTs has been performed in the context of switching from NTZ solely due to JCV^+. This is an important issue underscored by the findings of a much higher rate of disease reactivation and drug discontinuations with FGL here and in other observational studies than in the pivotal RCTs with mainly drug-naive patients.[12,13,23–25]

Limitations of this study include its nonrandomized design, possibly leading to confounding by indication, because certain differences in the baseline characteristics between the 2 treatment groups were noted. Most notably, RTX patients had shorter median washout time and a longer time on NTZ (significant only in the Stockholm cohort). Nonetheless, the main conclusions remained after adjusting for these differences, and results were highly similar when the analyses were restricted to patients with <3 months of washout time. In addition, differences between RTX and FGL were similar in the 2 smaller cohorts with preferential use of either of the 2 drugs. There were also certain differences in the baseline characteristics between the centers, where the mean age of the FGL cohorts of Stockholm and Gothenburg differed. A younger and more inflammatory active case mix and a lower threshold for switching therapy could explain why there were nonsignificant trends for higher rates of relapses and drug discontinuations for FGL patients in Stockholm compared with Gothenburg. However, the RTX patients in Stockholm were also younger than the FGL patients in Gothenburg, suggesting that the threshold for switching JCV^+ NTZ patients to alternative treatments was lower in Stockholm than in Gothenburg. The seemingly large difference in person-years between the FGL and the RTX groups in Table 2 was due to more patients in the RTX group having started treatment with RTX within 1.5 years before the time of the study. This is illustrated by the difference in median follow-up time between the 2 groups: 1.24 and 1.82 years for RTX and FGL, respectively (see Table 1). This potential confounding factor was corrected for by calculating the yearly incidence of the outcomes, as well as through the Cox proportional hazards models. Furthermore, no account was taken for differences in dose and interval of therapy. The vast majority of FGL patients received the standard therapy of 0.5mg per day, but a few had a reduced weekly dosage, usually due to low lymphocyte counts. Patients on RTX received a maintenance dose of 500 or 1,000mg every 6 months, but with longer intervals in a small proportion of patients. Thus, patients with a lower than normal dose, in either group, might have been undertreated and thereby incurred an increased risk of breakthrough disease, but this should not affect the main outcomes, as these groups were small. Notably, the choice of a significantly lower dose of RTX compared with previous studies[15,19,20,22] seemingly did not affect effectiveness, but could possibly be a reason for the relatively low rate of AEs. The recording of AEs may be affected by differences in frequency of clinic visits, but for both FGL and RTX, 2 yearly visits (1 of which can be with a nurse) are recommended in national guidelines. Data extracted from the Swedish MS register are not complete for all patients and only include limited information on MRI and AEs. Given the cross-checking with clinical records, the risk of differences in completeness and accuracy of data sets is reasonably small for the 2 treatments and not biased for either therapy group, thus not influencing the final results significantly. We did not specifically analyze the characteristics of JCV^+ patients remaining on NTZ as compared to those switching therapy. It is likely, however, that the most important distinguishing feature between the groups is the JCV titers, where patients with high titers to a higher degree terminate NTZ. We do not expect this to affect the extent to which results can be generalizable for the JCV^+ patient population, but further studies are needed to address this issue.

In conclusion, this observational study of RRMS patients switching from NTZ due to JCV^+ status strongly indicates a superior effectiveness and tolerability of RTX compared with FGL. Both treatments appeared to be generally safe; however, 1 serious AE occurred in the FGL group. The results provide a strong motive for a formal RCT with RTX or another anti-CD20 monoclonal antibody in the context of patients switching from NTZ. In the absence of such data, RTX appears to be the superior choice, compared with FGL, in this patient population.

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Author Contributions

All authors participated in study concept and design. P.A., T.F., L.N., P.I.-J., J.S., A.B., M.A., C.M., and K.F. participated in the primary data acquisition. P.A. and T.F. did the statistical analysis. P.A., T.F., and F.P. drafted the report. All authors participated in the critical revision of the final version. J.L., A.S., and F.P. obtained funding. T.F., J.L., A.S., and F.P. supervised the study. P.A. and T.F. contributed equally and share first authorship.

Potential Conflicts of Interest

Biogen is the manufacturer of NTZ. Novartis is the manufacturer of FGL. C.M. has received honoraria for lectures and advisory boards from Biogen and Novartis. J.S. has received travel support and honoraria for lectures and advisory boards from Biogen. K.F. has received an unrestricted academic research grant from Biogen and compensation for lectures from Biogen and Novartis, which have been exclusively used to support research activities. J.L. has received travel support, honoraria for lectures and advisory boards, and unconditional research grants from Biogen and Novartis. A.S. has received honoraria for lectures and advisory boards from Biogen and Novartis. F.P. has received unrestricted academic research grants from Biogen and Novartis, and compensation for lectures and advisory boards from Biogen and Novartis, which have been exclusively used for the support of research activities.

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