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Transitioning From S1P Receptor Modulators to B Cell–Depleting Therapies in Multiple Sclerosis

Clinical, Radiographic, and Laboratory Data

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Abstract

Background and Objectives

Patients with multiple sclerosis (MS) transition from oral sphingosine-1-receptor (S1P) modulators to anti-CD20 therapies for several circumstances. Optimal timing of this transition is uncertain, given competing concerns of rebound disease activity and ensuring immune reconstitution. The objective of this study was to evaluate the relationship between inflammatory activity and the transition period from fingolimod to anti-CD20 therapies in a real-world MS cohort.

Methods

Medical records were reviewed for all patients at our center transitioning from fingolimod to rituximab or ocrelizumab between 2010 and October 2020. Time periods reviewed were the following: before fingolimod discontinuation, interval between fingolimod and anti-CD20 treatments, and after the first anti-CD20 infusion. The primary outcome was clinical relapses; MRI activity, time to absolute lymphocyte count (ALC) recovery, and infections were secondary. Clinical and demographic factors significant in univariable analyses were included in multivariable analyses.

Results

Transition data were available for 108 patients (68.5% women, 68.5% relapsing-remitting MS, mean age 44.6 years). The median (interquartile range) interval between fingolimod and anti-CD20 therapy was 28 (1–115.2) days. Six of 51 patients (11.8%) with intervals >1 month and 0/57 patients with shorter intervals experienced a relapse (MRI confirmed) within 6 months of fingolimod discontinuation. In the year following anti-CD20 initiation, 4/108 patients (3.7%) experienced a relapse (median 214.5 days after infusion). An additional 7% of those undergoing contrast-enhanced MRIs developed Gd⁺ lesions. ALC normalized following treatment switch in 89/92; the interval between treatments was unrelated to ALC recovery or infection.

Discussion

Delaying anti-CD20 start to monitor ALC after S1P modulator discontinuation may not be necessary and could increase rebound risk. ALC monitoring could instead occur after a rapid switch to anti-CD20 treatment.

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Glossary

ALC = absolute lymphocyte count; **DMT** = disease-modifying therapy; **EDSS** = Expanded Disability Status Scale; **EMR** = electronic medical record; **FDA** = Food and Drug Administration; **IgG** = immunoglobulin G; **IQR** = interquartile range; **MS** = multiple sclerosis; **NK** = natural killer; **S1P** = sphingosine-1-receptor; **SARS-CoV-2** = severe acute respiratory syndrome coronavirus 2; **UCSF** = University of California, San Francisco.

Fingolimod was the first oral disease-modifying therapy (DMT) approved for the treatment of relapsing forms of multiple sclerosis (MS).¹ Since then, 2 other sphingosine-1-receptor (S1P) modulators (ozanimod^{2,3} and siponimod⁴) have been approved, with a fourth (ponesimod) currently in phase III trials. Overall, S1P receptor modulators are significantly more effective than first-line self-injectables (glatiramer acetate and interferon beta-1a/b). There are, however, scenarios in which a patient might switch from an S1P modulator to an anti-CD20 therapy (e.g., ocrelizumab, rituximab, or ofatumumab),⁵ including patient preference, incomplete control of MS activity or disease progression, adverse effects, development of contraindications, or as bridge therapy before conception.⁶ In clinical practice, absolute lymphocyte counts (ALCs) are often checked as a safety measure in patients starting anti-CD20 therapies and to determine the optimal timing of vaccines—including for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)—to confer maximal protection against infection, but recent or active fingolimod treatment can confound interpretation. In fact, during the phase III trials for fingolimod,^{1,7} ALC decreased by approximately 75% because of sequestering of circulating lymphocytes in the lymph nodes.

Given case reports and cases series,⁸⁻¹⁰ including in pregnancy,^{11,12} of rebound MS inflammatory activity after fingolimod discontinuation, its US Food and Drug Administration (FDA) labeling was updated in 2018.¹³ Clinical approaches to minimize this rebound have been variable and variably effective.^{8,14} Unfortunately, clinical trials provide limited guidance because recent use of S1P modulators was exclusionary for both ocrelizumab¹⁵ and ofatumumab¹⁶ phase 3 trials (<2% participants with prior exposure). Therefore, real-world data sets are necessary.

Here, we characterized clinical and radiographic MS activity in the transition from fingolimod to an anti-CD20 therapy in our center. We evaluated possible protective factors (e.g., duration of interval between treatments, ALC levels) and risks of overimmunosuppression (e.g., infection).

Methods

Sample Selection

We performed a retrospective analysis of prospectively collected clinical data from patients with clinically isolated syndrome/MS cared for at the University of California, San Francisco (UCSF) Multiple Sclerosis and Neuroinflammation Center. We screened the electronic medical record (EMR) to identify patients who were treated with fingolimod at any time point between 2010 (when fingolimod was first FDA approved) and October 2020

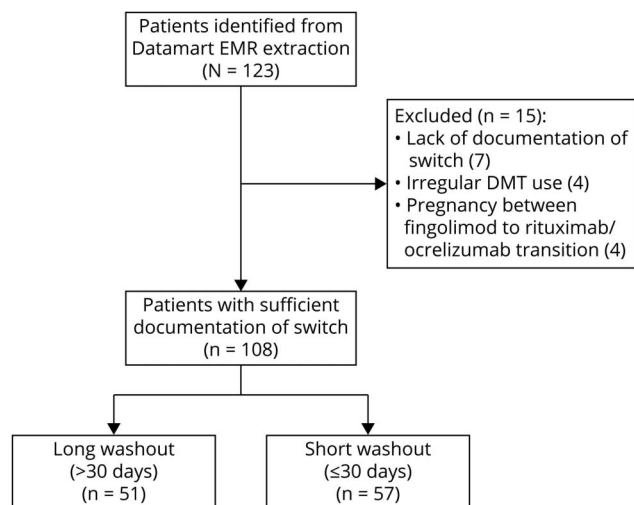
and then switched to an anti-CD20 monoclonal antibody. We identified 123 patients who made this transition, 108 of whom were included in analyses (Figure 1). The other 15 patients were excluded from analyses for the following reasons: unclear documentation/data missing in the EMR (n = 7), challenges adhering to daily oral DMT (n = 4), and pregnancy occurring during the fingolimod to ocrelizumab/rituximab transition (n = 4).

Data Collection

MS clinical history was extracted from the EMR, including the following: year of MS onset, MS subtype (based on clinician evaluation) at fingolimod discontinuation, Expanded Disability Status Scale (EDSS) score by the treating Neurostatus¹⁷-trained neurologist in over 90% of cases, reason for fingolimod discontinuation, timing of the first anti-CD20 infusion following fingolimod discontinuation, and clinical relapses from the 12 months prediscontinuation to the 12 months (or until the most recent visit, if within 12 months) after fingolimod discontinuation. DMT start and stop dates were reconciled between the medication prescriptions in the EMR and the clinical notes to account for scenarios where a clinician may have instructed a patient to discontinue the medication but omitted to discontinue it in the medication orders or a situation where a medication was discontinued in the orders and by the patient but remained erroneously included in the active medications in the notes. Clinical relapses were defined as new or worsening neurologic symptoms for at least 24 hours in the absence of fever or infection, as documented in clinical records by the treating neurologist. Annualized relapse rates for the 12 months before and after fingolimod discontinuation were calculated. When the EDSS score was not explicitly included in the treating neurologist's note, this was approximated using the documented neurologic examination, symptoms, and reported ambulatory abilities by a neurologist (R.M.B.), blinded to timing of the EDSS score with respect to fingolimod discontinuation. Any use of steroids given prophylactically by a treating clinician in an effort to prevent relapses during this time frame was also recorded. Infections following fingolimod discontinuation were collected through review of neurologist notes as well as other EMR entries, where available.

Neuroradiology reports for brain MRIs and spinal cord (cervical and thoracic) MRIs were collected when available for the entire time interval from 12 months pre-fingolimod discontinuation to 12 months after discontinuation. Neuroimaging reports were manually reviewed for the presence of T2-weighted hyperintense lesions that were new relative to a

Figure 1 CONSORT Diagram



A total of 123 patients were identified as having transitioned from fingolimod to ocrelizumab or rituximab between 2010 and October 2020 at the UCSF Multiple Sclerosis and Neuroinflammation center; 108 were included in analyses. DMT = disease-modifying therapy; EMR = electronic medical record; UCSF = University of California, San Francisco

prior MRI (per protocol at UCSF) and for gadolinium-enhancing (Gd⁺) lesions when contrast was administered.

Laboratory data were collected from the EMR and categorized into 3 primary phases: pre-fingolimod discontinuation, post-fingolimod discontinuation but pre-anti-CD20 initiation (i.e., during the interval between treatments), and following the first anti-CD20 infusion. Data included ALC, CD4⁺ helper T-cell count (CD4), CD8⁺ cytotoxic T-cell count (CD8), CD19⁺ B-cell count (CD19), CD56⁺ natural killer (NK) cell count, and immunoglobulin G (IgG) serum concentration. In accordance with existing literature,¹⁸ we defined lymphopenia as an ALC under $0.8 \times 10^9/L$. For patients with ALCs under this threshold at the post-anti-CD20 infusion follow-up, where possible, we collected additional laboratory data until normalization (ALC $>0.8 \times 10^9/L$) was observed or until most recent laboratory evaluation. In this subset of patients with sustained low ALC, we further extracted pre-fingolimod (or other immunosuppressive) laboratory values for comparison.

Standard Protocol Approvals, Registrations, and Patient Consents

The UCSF Committee of Human Research approved the study protocol for retrospective analysis of EMR-derived MS data with no patient contact (Ref #13-11686).

Statistical Analyses

Our primary outcome was clinical relapses after fingolimod discontinuation. Although it was not possible to truly distinguish rebound activity from recrudescence of baseline MS activity, relapses occurring <180 days following fingolimod discontinuation were considered to be due to rebound activity. We evaluated MRI activity (MRI demonstrating any

new T2 hyperintense and/or Gd⁺ lesions), time to ALC recovery, and infections as secondary outcomes. We considered interval between treatments in 2 ways, first as a continuous variable and second as a categorical variable. Here, patients were categorized into 2 groups based on the duration of the interval between treatments. The median interval duration in the cohort was 28 days. Given that this was approximately 1 month, for simplicity of interpretation in clinical practice, intervals greater than 30 days were considered long, whereas intervals under 30 days were considered short. Descriptive statistics were reported with mean and SD, median, interquartile range (IQR), range, or frequency, as appropriate.

In sensitivity analyses to evaluate the association between demographic (age, sex, and race) and clinical (MS duration, baseline EDSS, time on fingolimod, and laboratory measures) predictors and each outcome, we first performed univariable regressions. Any factors showing a significant association were included in a multivariable logistic regression when the duration of interval between treatments was a categorical variable (short/long interval) and a multivariable linear regression when the interval duration was measured continuously in days from fingolimod discontinuation.

We further performed analyses on laboratory variables, including ALC, as well as lymphocyte subsets: CD4, CD8, CD19, NK counts, and IgG concentrations. Specifically, to address the immune reactivation hypothesis for fingolimod discontinuation rebound, Kaplan-Meier analyses were performed. We evaluated the temporal relationship between ALC (and other lymphocyte subset) reconstitution and various clinically important end points.

To evaluate trends in ALC normalization after fingolimod discontinuation, we used survival analysis censored at ALC normalization or last available laboratory evaluation. For each patient in our full cohort, all available laboratory results following anti-CD20 initiation were reviewed. Analyses were performed in R version 3.6.0.

Data Availability

Anonymized data not published within this article will be made available by request from any qualified investigator.

Results

Demographic and Clinical Features

The final cohort analyzed included 108 patients, whose clinical and demographic characteristics broadly match those of the general MS patient population^{19,20} and more specifically patients on fingolimod²¹ (Table 1). As noted above, the median interval between treatments for the cohort as a whole was 28 days (IQR 1–115.2 days).

When we analyzed demographic and clinical factors associated with interval between treatments, first evaluated as a categorical variable (short vs long, as shown in Table 1), we observed longer interval between treatments in patients with a

Table 1 Clinical and Demographic Characteristics of 108 UCSF MS Center Patients Switching From Fingolimod to an Anti-CD20 Therapy Between 2010 and 2020

Variable	Total (N = 108)	>30 d (N = 51)	<30 d (N = 57)	p Value
Sex, female, n (%)	74 (68.5)	34 (66.7)	40 (70.2)	0.85
Age, y, mean (SD)	44.6 (11.4)	45.6 (11.6)	43.8 (11.1)	0.40
Race, n (%)				0.36
American Indian or Alaska Native	3 (2.8)	2 (3.9)	1 (1.8)	
Asian	4 (3.7)	3 (5.9)	1 (1.8)	
Black	8 (7.4)	2 (3.9)	6 (10.5)	
White	70 (65)	31 (60.8)	39 (68.4)	
Other/unknown/declined	23 (21.3)	13 (25.5)	10 (17.5)	
Ethnicity, n (%)				0.078 ^a
Hispanic or Latino	14 (13.0)	9 (17.6)	5 (8.8)	
Not Hispanic or Latino	86 (79.6)	36 (70.6)	50 (87.7)	
Unknown/declined	8 (7.4)	6 (11.8)	2 (3.5)	
EDSS score, median (IQR), within 1 y fingolimod d/c	3 (2.0, 5.4)	3.5 (2.0, 6.1)	2.5 (2.0, 4.0)	0.18
EDSS score, median (IQR), within 1 y following anti-CD20 start	3 (2.0, 4.8)	4 (2.0, 5.8)	2.5 (2.0, 4.0)	0.20
Disease duration, y, mean (SD) ^b	12.1 (7.2)	11.8 (6.6)	12.3 (7.8)	0.69
MS subtype, n (%)				<0.001 ^a
Relapsing-remitting	74 (68.5)	27 (52.9)	47 (82.5)	
Secondary progressive	19 (17.6)	10 (19.6)	9 (15.8)	
Primary progressive	15 (13.9)	14 (27.5)	1 (1.8)	
Continuous time on fingolimod, wk				0.13
Mean (SD)	145.9 (96.7)	131.1 (81.2)	159.2 (107.8)	
Median (IQR)	115.2 (70.1–210.0)	121.6 (65.3–189.3)	113.9 (76.6–257.4)	
Anti-CD20 initiated following fingolimod discontinuation, n (%)				0.31
Ocrelizumab	72 (66.7)	37 (72.5)	35 (61.4)	
Rituximab	36 (33.3)	14 (27.5)	22 (38.6)	

Table 1 Clinical and Demographic Characteristics of 108 UCSF MS Center Patients Switching From Fingolimod to an Anti-CD20 Therapy Between 2010 and 2020 (continued)

Variable	Total (N = 108)	>30 d (N = 51)	<30 d (N = 57)	p Value
Duration of fingolimod discontinuation interval, d, median (IQR)	28 (1.0, 115.2)	120 (46.5, 438.5)	3 (1, 16)	<0.001 ^a
Reason for fingolimod discontinuation, n (%)				<0.001 ^a
Disease breakthrough	55 (50.9)	17 (33.3)	38 (66.7)	
Adverse reaction	15 (13.9)	8 (15.7)	7 (12.3)	
Inefficacy for progressive MS	12 (11.1)	12 (23.5)	0 (0.0)	
Insurance	4 (3.7)	3 (5.9)	1 (1.8)	
Pregnancy	4 (3.7)	2 (3.9)	2 (3.5)	
Risk reduction	3 (2.8)	0 (0.0)	3 (5.3)	
Other	10 (9.3)	6 (11.8)	4 (7.0)	
Not reported	5 (4.6)	3 (5.9)	2 (3.5)	
ARR in the year before fingolimod discontinuation, mean (SD) (RRMS only, n = 74)	0.15 (0.36)	0.12 (0.32)	0.23 (0.43)	0.29

Abbreviations: ARR = annualized relapse rate; EDSS = Expanded Disability Status Scale; IQR = interquartile range; RRMS = relapsing-remitting multiple sclerosis; UCSF = University of California, San Francisco.

^a Statistically significant.

^b For patients with noncontinuous fingolimod use (e.g., patients discontinuing for pregnancy and restarting postpartum), time on medication was calculated from the most recent first dose observation to time of discontinuation before starting anti-CD20 therapy.

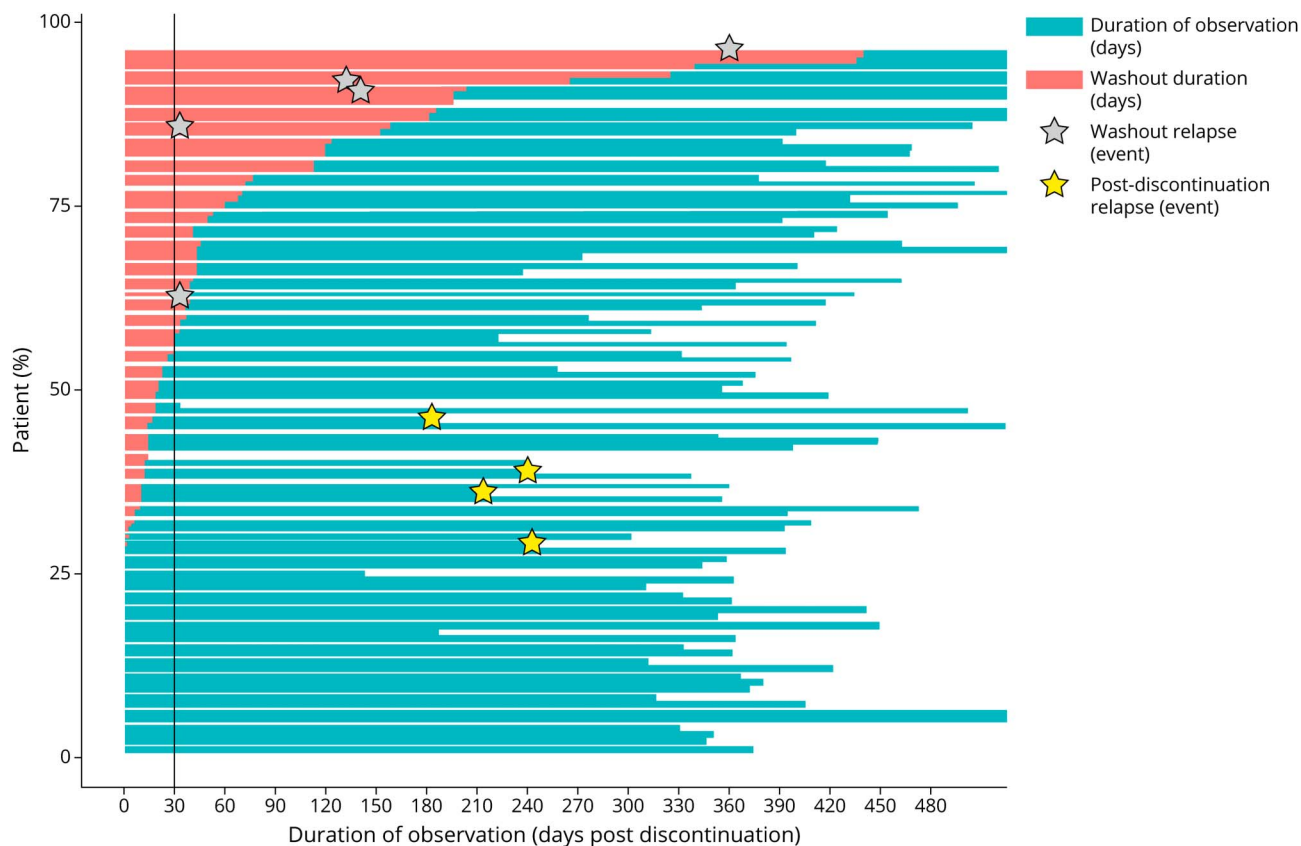
progressive MS phenotype ($p < 0.001$). In addition, while only reaching trend-level significance, there was a greater proportion of Hispanic/Latino patients in the longer interval (>30 days) category ($p = 0.078$; Table 1). Furthermore, reasons for discontinuation differed between longer and shorter intervals ($p < 0.001$), with long intervals associated with less breakthrough disease activity on fingolimod (33.3% vs 66.7%) and more perceived inefficacy of fingolimod against disability progression (23.5% vs 0.0%). Similar associations were seen when we evaluated interval between treatments as a continuous variable.

Clinical and MRI Activity After Fingolimod Discontinuation

Activity During the Interval Between Fingolimod Discontinuation and First Anti-CD20 Infusion

In the full cohort ($n = 108$), in the interval between treatments, 6 clinical relapses were recorded, all occurring in

Figure 2 Timing of the 10 (9 Shown) Clinical Relapses in the 12 Months Following Fingolimod Discontinuation



The vertical black line indicates the split between categorically long and short intervals between treatments (± 30 days); red and blue coloring indicate the treatment status: between treatments (red) or after the first anti-CD20 infusion (blue). Data truncated at 500 days after fingolimod discontinuation.

patients with an interval greater than 1 month (long interval), representing 6/51 patients (11.8%) in that group (demographics provided in eTable 1, links.lww.com/NXI/A719); the median time between fingolimod discontinuation and relapse was 136 days (min 32, max 460) (Figure 2). In only one of these cases was a protracted interval between treatments the result of clinical decision making, where breakthrough inflammatory activity occurred despite active SIP treatment. The other 5 relapses occurred in patients struggling with insurance approvals ($N = 2$), those who self-discontinued ($N = 2$) and 1 with an adverse response to fingolimod ($N = 1$) (eTable 1). No clinical relapses occurred in the 57 patients with an interval less than 1 month (0%). Two of the long interval patients received prophylactic steroids to prevent a relapse based on the decision of their treating clinician; neither of them relapsed during the year following fingolimod discontinuation.

The demographic and clinical characteristics of the 6 patients with relapses are summarized in eTable 1 (links.lww.com/NXI/A719). All 6 patients had MRIs performed during the interval between treatments: 6/6 confirmed new T2 lesions, with 5/6 showing contrast enhancement. Furthermore, 4 of these 6 patients had MRI data available in the year after beginning an anti-CD20 DMT: 1 patient had new

T2 lesions (compared with the MRI obtained between treatments) and 3 did not. None of these MRIs showed enhancement, and none of these patients experienced another relapse in the 12 months that followed anti-CD20 initiation.

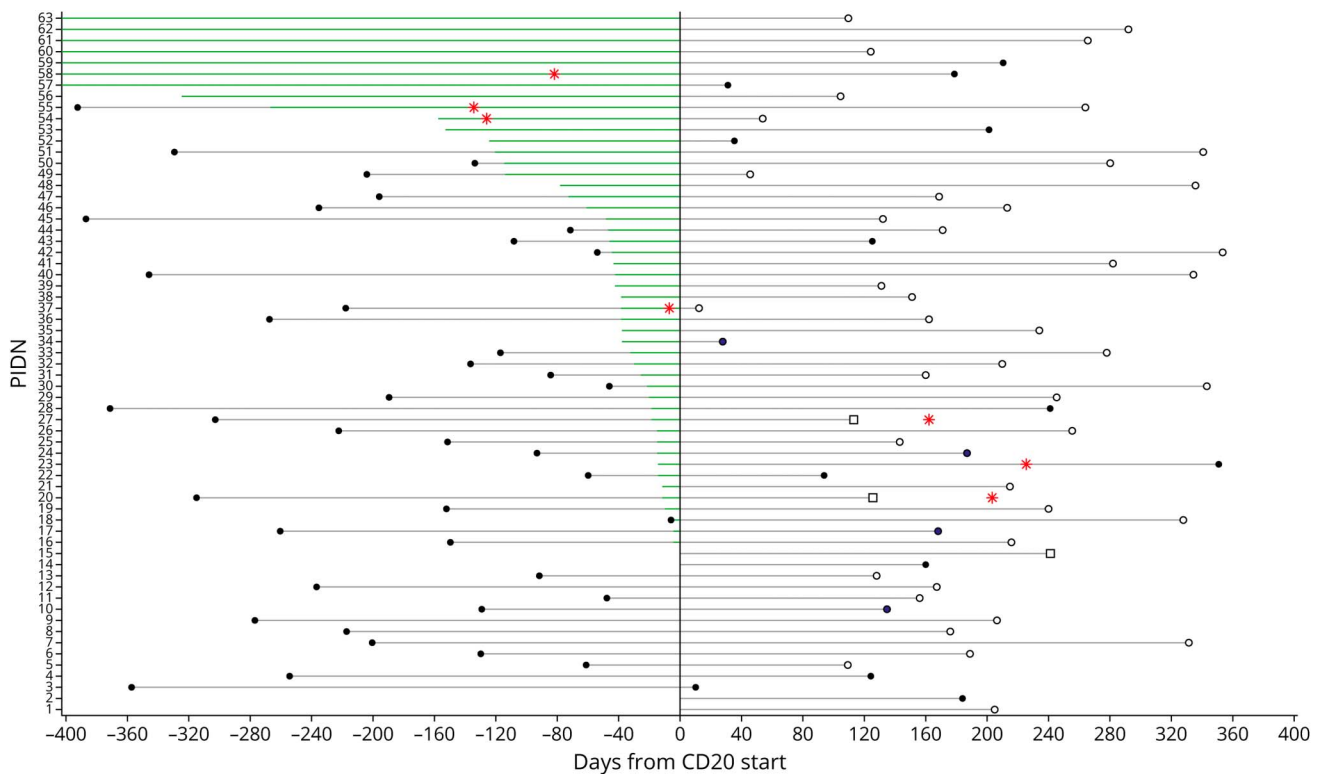
In our full cohort of 108 patients, 3 additional MRIs were obtained during this interval between treatments and available in the EMR for our review: 1 for a short-interval patient and 2 for long-interval patients; none were Gd+. Including all patients with MRIs during the interval between treatments, 5/9 patients showed gadolinium enhancement corresponding with a clinical relapse, all in the long-interval group.

Clinical and MRI Activity After Anti-CD20 Treatment Initiation

Clinical Activity

In the 12 months immediately following anti-CD20 initiation, 4 patients went on to experience a clinically documented relapse (Figure 2). All were in the short-interval group (4/57, i.e., 7.0%) compared with zero in the long-interval group (0/51, 0%, unadjusted, $p = 0.16$). These relapses occurred at a median 227 (min 181, max 242) days after discontinuing fingolimod, and median 214.5 (min 163,

Figure 3 Clinical Relapses and MRI Activity in the Subset of 63 Patients With MRIs Available



Data presented on a timeline relative to anti-CD20 initiation. Green lines denote time off active treatment (interval), and red asterisks indicate clinical relapse. The end points denote available MRIs: blue-filled segment end points indicate Gd+ MRI, black-filled segment end points indicate the presence of new T2 lesions from prior comparison, and open end points denote MRIs unchanged from pre fingolimod discontinuation reference image.

max 239) days following anti-CD20 treatment initiation. For one of these patients, an accompanying MRI was available for review (125 days after the relapse), confirming new T2 lesions. A description of the clinical and demographic characteristics for these 4 patients is provided in eTable 2 (links.lww.com/NXI/A719).

Radiologic Activity

Overall, a total of 63 patients underwent brain MRIs during the 12 months after anti-CD20 initiation: 59 had prior MRI available for comparison, and 57 received gadolinium. Of the 57 MRIs with contrast, 4 (7.0%) were Gd+; 3 were from the short-interval group (none of which overlapped with the patients who experienced clinical relapses; mean 163 days after first anti-CD20 infusion, range: 135–187), and 1 was from the long-interval group (28 days after anti-CD20 treatment initiation).

In the 59 MRIs with prior comparison available, 15 (25.4%) indicated 1 or more new T2 lesions: 14 of these were relative to an MRI obtained during fingolimod treatment (N = 9 from the short-interval group; N = 5 from the long-interval group), and 1 occurred at a second time point, in the patient who relapsed during the long interval between treatments. A breakdown of MRI findings, categorized into 3-month periods, is provided in eTable 3 (links.lww.com/NXI/A719).

In total then, over the 12 months after anti-CD20 initiation, 4/108 patients experienced a clinical relapse, and a further 7% of those undergoing contrast-enhanced MRIs developed Gd+ lesions. When evaluated as a composite end point (Gd+ MRI and/or clinical relapse), 7 notes of nonrebound activity occurred in patients with a short (<30 days) interval between DMTs, whereas just 1 occurred in the long-interval group (Figure 3). In a multivariable logistic regression adjusting for age, sex, MS type, relapses in the year before discontinuation, race and ethnicity, a categorically short interval between treatments was associated with greater disease-related activity ($p = 0.034$).

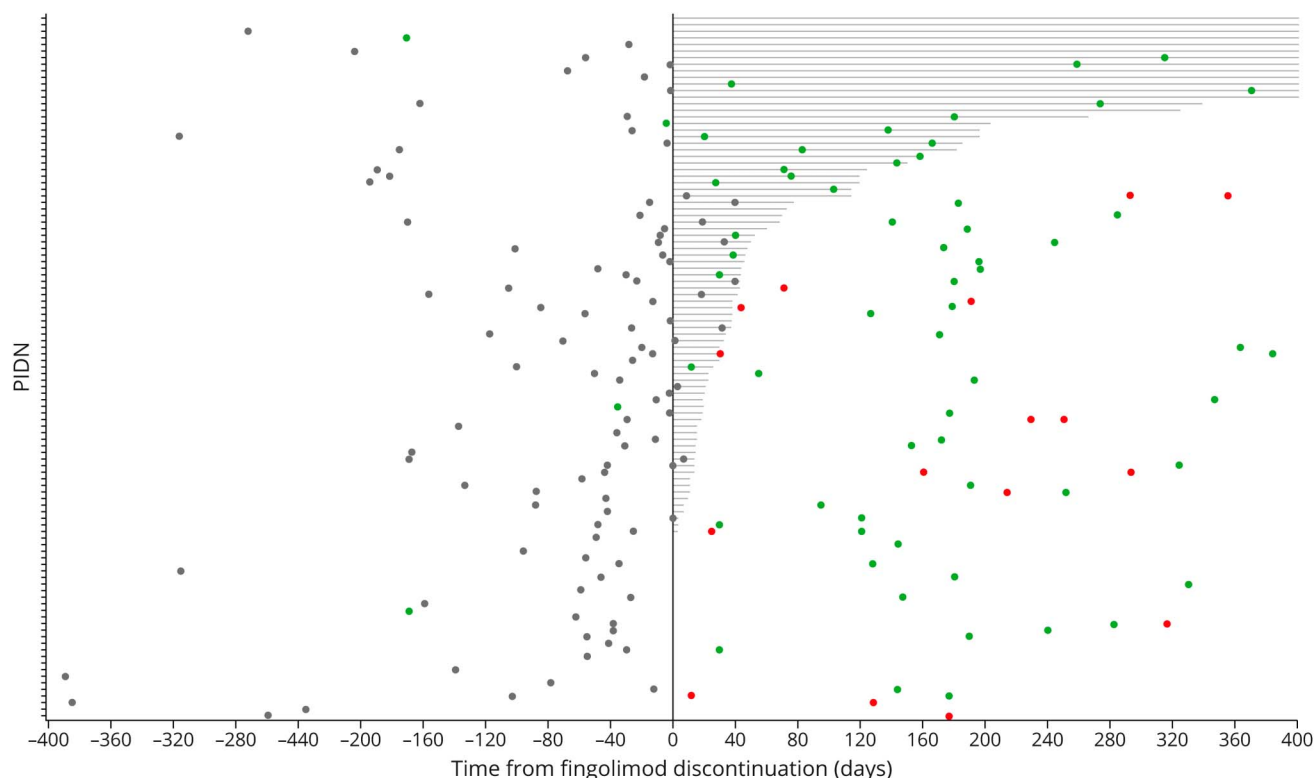
Disease Activity in Patients Experiencing Breakthrough Relapses on Fingolimod

In total, 55 patients switched from fingolimod to anti-CD20 monoclonals due to disease breakthrough on fingolimod; 3 (5.5%) experienced a relapse in the year following anti-CD20 therapy at a mean 201.7 days (SD 38.0) from the first anti-CD20 infusion (with no accompanying MRIs performed during this period).

ALC Normalization and Other Laboratory Characteristics

Of the 108 patients in our cohort, 92 had ALC counts available following fingolimod discontinuation (Figure 4). Using

Figure 4 ALCs in the Subset of 92 Patients With ALC Labs Checked, Relative to Fingolimod Discontinuation



Dots indicate ALC values available. Green dots indicate ALC in the normal range, defined as $>0.8 \times 10^9/L$. Dots indicating ALC values below the normal range are gray before fingolimod discontinuation and red after fingolimod discontinuation. The vertical line indicates fingolimod discontinuation, and the horizontal gray lines represent the interval between fingolimod and anti-CD20 treatments. ALC = absolute lymphocyte count.

survival analysis censored at last follow-up, the median (95% CI) time to blood draw showing ALC normalization (ALC = 0.8×10^9 or above) following fingolimod discontinuation was 245 (200–349) days. When we evaluated predictors of time to ALC normalization, age, sex, MS phenotype, MS disease duration, interval between treatments, and anti-CD20 type (rituximab or ocrelizumab) were not associated with time to normalization ($p > 0.05$ for each analysis). Furthermore, time to ALC normalization was also similar between patients with and without a relapse in the 12 months following anti-CD20 initiation ($p = 0.22$, $N = 92$ whole cohort; $p = 0.35$, $N = 46$ short interval between treatments only).

At 12 months, 57/92 patients had documented normalization of ALC counts. When we evaluated predictors of ALC normalization within 12 months of fingolimod discontinuation, age, sex, MS phenotype, MS disease duration, interval between treatments, and anti-CD20 type (rituximab or ocrelizumab) were associated with ALC normalization within 12 months ($p > 0.05$ for each analysis). Overall, when using uncensored data (all time points) for all patients with ALC levels available following fingolimod discontinuation ($N = 92$), only 3 (3.3%) patients had sustained low ALC (ALC $<0.8 \times 10^9/L$) after anti-CD20 initiation, the longest being recorded 40 months after fingolimod discontinuation.

ALC Normalization After Short Interval Between Treatments

We then sought to understand the patterns of ALC normalization in the systemic circulation in the 57 patients whose interval between treatments was under 1 month (consort diagram; Figure 1). The reason for this was to inform clinical practice; specifically, for a scenario where a <1 month interval between treatments may be recommended based on our observation of minimal relapses but where there was a concern for ensuring ALC normalization in the circulation following fingolimod discontinuation. Using Kaplan-Meier analyses, the median time to ALC normalization in this cohort (defined as ALC $>0.8 \times 10^9/L$) was 245 days (SD 353.8). When split by sex, time to ALC normalization was nearly 1.5× faster in women than was observed in men (median days [95% CI]: women, 238 [179–284]; men, 349 [288–657]; $p = 0.12$).

Laboratory Values in Patients With Relapses During Interval Between Treatments

The apparent greater increase in ALC counts in the 4 patients experiencing a relapse during the interval between treatments (mean 1.12, median 0.92, SD 0.96) relative to the 27 patients who did not relapse and had laboratory values available (mean = 0.47, median = 0.50, SD = 0.34) was not significant ($p = 0.18$), nor were differences in CD4 counts, CD8 counts,

or CD19 counts between the groups ($p > 0.10$ for each comparison, N range 21–25).

Relationship Between ALC and Infection Risk

Infections were collected from manual review of the clinical notes between fingolimod cessation and ALC normalization (where post-anti-CD20 laboratory values were available). Of the full cohort ($n = 108$), 7 patients were excluded from analyses because of uncertainty around the presence and timing of infection; 101 were included. Of these, 30 (29.7%) had a documented infection following fingolimod cessation, 23 of whom had an interval between treatments >30 days and 7 who did not. The duration of interval (number of days) was not significantly different between patients with and without infection ($p = 0.15$). Other possible predictors of infection included in univariable analyses included sex, age, race, MS duration, MS subtype, and number of infections in the year before fingolimod discontinuation. Infections were more common in progressive subtypes ($p = 0.040$) and in patients with a greater number of documented infections on fingolimod in the year leading up to treatment switch ($p = 0.0045$).

Discussion

A rebound in disease activity following fingolimod discontinuation has previously been described for up to 7 months after cessation.^{8,22–24} To date, variably effective approaches to reduce this risk⁸ have included short intervals to new treatment, bridge therapies to anti-CD20 medications in patients planning to discontinue DMTs,⁶ and possibly high-dose steroids. In our real-world cohort of 108 patients who transitioned from fingolimod to an anti-CD20 therapy at various intervals between treatments, we noted 10 relapses in the year following fingolimod cessation. Notably, none were recorded in the 57 patients with an interval shorter than 30 days; in this group, the median treatment interval duration was 3 days. Although 4 of these patients (7.0%) did subsequently experience a relapse, these relapses started at least 6 months after fingolimod discontinuation (mean 219.3 [SD 28.5] days), and the 3 patients with Gd+ MRIs had these at mean 163.3 (SD 26.3) days after anti-CD20 initiation, suggesting that clinical activity could have been due to underlying disease activity rather than discontinuation rebound activity per se. Follow-up MRIs and clinical examinations indicated clinical stability after the transition; of the 4 patients with relapses in the 12 months following anti-CD20 initiation, none went on to experience continued exacerbations. Although 0/57 patients in our short-interval group experienced a relapse within 6 months, in a recent review of 128 patients discontinuing fingolimod followed for up to 6 months, overall 12.5% (16/128) experienced a relapse.¹⁴

There have been 2 mechanisms suggested for the fingolimod discontinuation rebound activity. The first mechanism has to do with dramatic postdiscontinuation increase in circulating peripheral lymphocyte counts. Similar to natalizumab, another DMT with a documented postdiscontinuation rebound,²⁵

fingolimod's protective effect is thought to be derived from its effect on lymphocyte trafficking—and in both instances, the availability of encephalitogenic lymphocytes to access the CNS compartment is reduced with treatment. Downregulation of the S1P receptor likely prevents the egress of some autoreactive T-cell populations sequestered in the lymph nodes and that are hypothesized to play an important role in MS pathogenesis.²⁶ However, rebounds have also been reported to occur independently of return of normal circulating lymphocyte levels, indicating that there may be other inflammatory factors in play.^{8,27} Some studies have suggested that the dramatic change in peripheral lymphocyte expression occurring 1–2 months after discontinuation¹³ may mediate the rebound phenomenon.²⁷ An alternative hypothesis proposes that a differential lymphocyte subset repopulation could play a role in determining the risk of postcessation rebound.^{8,22} Unfortunately, in our study, only 57/108 patients included had lymphocyte subset panels drawn in the year before discontinuation, and with the low rate of observed relapses, it was not possible to draw any conclusions. The apparent decreased relapse risk in patients with shorter intervals between treatments alleviates the concern that anti-CD20 effectiveness would be diminished because of persistent lymphocyte sequestration in the lymph nodes, if given soon after fingolimod discontinuation.

In addition to lymphocyte reconstitution, we aimed to address a major reason for favoring longer intervals between DMTs—concern that potential dual immunosuppression could leave patients at risk for developing infection. Here, we found no association between infection risk and shorter vs longer intervals between treatments. Planning the timing and sequencing of other DMTs that share similar mechanisms of action could be informed by the lack of significant difference in infection risk and near complete ALC reconstitution between the shorter- and longer-interval between treatment groups.

Despite being retrospective, this real-world study has many strengths. We reviewed every transition from fingolimod to an infusible anti-CD20 DMT at the UCSF MS Center since fingolimod's FDA approval in 2010 until 2020. Our data are generalizable to an ethnically diverse group of patients with MS representing a typical age range and sex composition of prevalent MS. Furthermore, data to address sustained lymphopenia, a principal concern in weighing the risk-to-benefit ratio of a longer interval after fingolimod discontinuation, were robust. Of the 108 patients in our data set, 87 had ALC both before discontinuation and after starting an anti-CD20 DMT. One important limitation is that our planned laboratory analyses were limited by the availability and timing of data collected prospectively and therefore left important questions about immune markers of discontinuation risk yet unanswered. For example, as part of routine anti-CD20 infusion monitoring, many of our post-DMT-switch laboratory values were drawn 6 months after first infusion and may have influenced our ALC recovery estimates. Reliance on clinical reports could have led to underascertainment of relapses both before and after anti-CD20 treatment initiation. In addition,

there was substantial heterogeneity in the timing of MRI and blood sample acquisition. These were not systematically collected at prespecified time points; rather, timing varied by patient, clinician, and insurance. As a consequence, we could have underestimated the true extent of new lesions after fingolimod discontinuation and also missed earlier ALC normalization. Over the observation period, the field and clinical practice moved toward rebaselining patients with an MRI approximately 6 months after initiation of B cell-depleting therapy. Finally, clinician—and patient—related factors likely played a role in the duration of the fingolimod discontinuation interval, potentially influencing the relative rebound risks observed. For example, patients deemed to be at a higher risk for relapse may have had a shorter discontinuation interval, which could obscure the risks associated with a longer time between medications in relapsing patients.

To summarize the clinical implications of our findings, in patients treated with anti-CD20 infusibles following fingolimod discontinuation, we observed a low overall rate of clinical activity (10/108). No relapses occurred in the 54 patients infused within 1 month of fingolimod discontinuation, many of whom had intervals between treatments that were only a few days. Furthermore, the 4 relapses that they experienced in the subsequent year could reasonably be attributed to MS, rather than rebound activity. Unfortunately, not all patients may be treated using a short-interval protocol, because of a possible need to receive vaccines (such as hepatitis B, varicella zoster, or SARS-CoV-2) before anti-CD20 depletion. Reassuringly, ALC normalized in most patients after fingolimod discontinuation, suggesting that monitoring ALCs for normalization before anti-CD20 initiation may not be clinically indicated. One reasonable suggestion could be to evaluate these at 8 months (cohort's median time to ALC normalization) after anti-CD20 initiation for evidence of persistent depletion. Future studies could focus on patterns of the ALC (including T-cell subset) repopulation using predefined laboratory assessments.

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movements for MS pendings and has worked on testing off label compounds for remyelination. J.M. Gelfand receives research support to UCSF from Genentech/Roche for a clinical trial and has received consulting fees from Biogen and Alexion. R.M. Bove has received consulting and advisory board fees from Alexion, Biogen, EMD Serono, Genzyme-Sanofi, Momenta, Novartis, and Roche-Genentech. She has received research support from CIAPM, Hilton Foundation, Sherak Foundation, National Multiple Sclerosis Society, Akili Therapeutics, Biogen, and Roche-Genentech. Go to Neurology.org/NN for full disclosures.

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Chu-Yueh Guo, MD	UCSF Weill Institute for Neurosciences, Division of Neuroimmunology and Glial Biology, Department of Neurology, University of California, San Francisco	Drafting/revision of the manuscript for content, including medical writing for content, and major role in the acquisition of data
Ari J. Green, MD	UCSF Weill Institute for Neurosciences, Division of Neuroimmunology and Glial Biology, Department of Neurology, and UCSF Department of Ophthalmology, University of California, San Francisco	Drafting/revision of the manuscript for content, including medical writing for content; study concept or design; and analysis or interpretation of data

Continued

Appendix (continued)

Name	Location	Contribution
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