

Supplementary Online Content

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eMethods. Supplemental Methods

Power to detect difference in serious infection risk for fingolimod: Under the hypothesis that fingolimod would be associated with a similar increased risk of serious infections as rituximab compared to IFN/GLAT-treated patients and given our fingolimod-treated vs IFN/GLAT-treated event number and adjustment for the main confounder, advanced disability, based on type 1 error 0.05 and two tailed score test, the study is powered at 30.5% for expected hazard ratio of 1.4.

eTable 1. ICD Codes to Identify Infections*			
Serious Infections	ICD 10	ICD 9	Additional Criteria
Any serious infections	A00–B99, D73.3, E06.0, E32.1, G00–G07, H00.0, H44.0, H60.0–H60.3, H66–H77, H70, I30.1, I40.0, J00–J22, J32, J34.0, J36, J38.3, J39.0, J39.1, J44.0, J85, J86, K04.4, K04.6, K04.7, K10.2, K11.3, K12.2, K14.0, K57.2, K57.4, K57.8, K61, K63.0, K65.0, K65.1, K65.2, K65.9, L00–L08, L30.3, M00–M01, M46.2–M46.5, M60.0, M65.0, M71.0, M71.1, M72.6, M86, N10, N11, N12, N13.6, N15.1, N15.9, N30, N34, N39, N41.2, N43.1, N45.2, N45.3, N45.4, N48.2, N61, N70, N73, N75.1, R65.1, R65.1X, R65.2, R65.2X	001-139, 680-682, 245.0, 254.1, 320-324, 373.1, 360.0, 380.1, 382, 383, 422.92, 460-466, 470-478, 480-488, 491.22, 513, 510, 522.4, 522.7, 526.4, 527.3, 528.3, 529, 566, 569.5, 567.21, 567.22, 567.23, 567.9, 590, 595, 597, 599, 601.2, 603.1, 604.0, 607.2, 611.0, 614, 616.3, 680-686, 711, 730, 728.0, 727.4, 728.86, 785.52, 995.9, 995.9X	<ul style="list-style-type: none"> 1) Primary discharge diagnosis 2) Secondary discharge diagnosis if MS code (340, G35) in primary position 3) Hospitalizations for the same infection within 24 hours are counted as one hospitalization
PML	A81.2	46.3	<ul style="list-style-type: none"> 1) Primary and secondary discharge diagnoses 2) Chart reviewed
Herpes Zoster	B02 Exclude B02.22, B02.23, B02.29	053 Exclude 053.12, 053.13, 053.19	<ul style="list-style-type: none"> 1) Primary discharge diagnosis 2) Secondary discharge diagnosis if code is related to the eye (053.2X, B02.3X) 3) Chart reviewed
Other Herpetic Infections	B00, B01	052, 054	<ul style="list-style-type: none"> 1) Primary discharge diagnosis 2) Secondary discharge diagnosis if code is related to the eye (054.4X, B00.5X, B01.81) 3) Chart reviewed
Zoster Encephalitis/Zoster Meningitis	B02.0, B02.1	53.0	<ul style="list-style-type: none"> 1) Primary and secondary discharge diagnoses 2) Chart reviewed
Herpes Encephalitis/Herpes Meningitis	B00.3, B00.4	054.3, 054.72	<ul style="list-style-type: none"> 1) Primary and secondary discharge diagnoses 2) Chart reviewed
Meningitis	A39, A87, G00, G01, G02, G03	036, 047, 049, 320, 321, 322	<ul style="list-style-type: none"> 1) Primary discharge diagnosis 2) Chart reviewed
Encephalitis	A83, A84, A85, A86, G04, G05	062, 063, 064, 066.41, 323 Exclude 323.1, 323.52, 323.82, 323.9	<ul style="list-style-type: none"> 1) Primary and secondary discharge diagnoses

	Exclude G04.89, G04.91, G05.3, G05.4		2) Chart reviewed
Urinary Tract Infection/Pyelonephritis	N10, N30, N34, N39	590, 595, 597, 599	1) Primary discharge diagnosis 2) Secondary discharge diagnosis and MS code (340, G35) in the primary position 3) Primary discharge diagnosis for 996.64 and T83.51 (infection and inflammatory reaction due to indwelling urinary catheter) and MS code in secondary position, but no sepsis codes
Any Sepsis	A02.1, A20.7, A22.7, A32.7, A40, A41, B37.7, R65.1, R65.1X, R65.2, R65.2X,	003.1, 020.2, 022.3, 038, 112.5, 785.52, 995.9, 995.9X	1) Primary and secondary discharge diagnoses
Urosepsis	UTI/pyelonephritis + any sepsis codes in same hospitalization	UTI/pyelonephritis + any sepsis codes in same hospitalization	1) Primary and secondary discharge diagnoses 2) Primary discharge diagnosis for 996.64 and T83.51 (infection and inflammatory reaction due to indwelling urinary catheter) and sepsis codes in secondary position
Pneumonia	B59, J09.X1, J10.0, J11.0, J12-J18, J85.1	136.3, 480-486, 487.0, 488.01, 488.11, 488.81	1) Primary or secondary discharge diagnosis
Outpatient Infections			
Any outpatient infection	A00-A79, A90-A99, B00-B19, B25-B89, B95-B99, H65-H67, H70, N10, N30, N34, N39, J00-J06, J09.X1, J10.0, J10.83, J11.0, J11.83, J12-J18, J20-J22, J31-J32, J36-J37, J39, J40, J47, J85.1, L01-L03, L08, N76.0, N76.2	001-041, 050-136, 381-383, 460-465, 466, 490, 494, 472-473, 475-476, 478, 480-486, 487.0, 488.01, 488.11, 488.81, 590, 595, 597, 599, 616.1, 680-682, 684, 686	1) 3-month interval for recurrent infections
Herpes Zoster	B02 Excluding B02.22, B02.23, B02.29	053 Excluding 053.12, 053.13, 053.19	1) 9-month interval for recurrent infections 2) Antiviral dispensed within 7 days of a diagnostic code, excluding consecutively

			dispensed antivirals indicating prophylaxis 3) Inpatient diagnostic code in the secondary position, not related to the eye (053.2X, B02.3X) and an antiviral treatment during hospitalization
Other Herpetic Infections	B00, B01	052, 054	1) 6-month interval for recurrent infections 2) Antiviral dispensed within 7 days of a diagnostic code, excluding consecutively dispensed antivirals indicating prophylaxis 3) Inpatient diagnostic code in the secondary position, not related to the eye (054.4X, B00.5X, B01.81) and an antiviral treatment during hospitalization
Urinary Tract Infection/Pyelonephritis	N10, N30, N34, N39	590, 595, 597, 599	1) 1-month interval for recurrent infections 2) Antibiotic dispensed within 7 days of a diagnostic code 3) Abnormal lab test (urinalysis, urine culture, dipstick) within 3 days before or after a diagnostic code
Pneumonia	B59, J09.X1, J10.0, J11.0, J12-J18, J85.1	136.3, 480-486, 487.0, 488.01, 488.11, 488.81	1) 3-month interval for recurrent infections 2) Abnormal chest x-ray or CT scan within 5 days before or after a diagnostic code
Acute or chronic URI	J00-J06, J31-J32, J36-J37, J39	460-465, 472-473, 475-476, 478	1) 2-month interval for recurrent infections
Lower Respiratory Infections	J20-J22, J40, J47	466, 490, 494	1) 2-month interval for recurrent infections
Otitis Media or Mastoiditis	A18.6, A38.0, B05.3, H65-H67, H70, J10.83, J11.83	017.4, 055.2, 381-383	1) 2-month interval for recurrent infections
Cellulitis	L01-L03, L08	680-682, 684, 686	1) 3-month interval for recurrent infections

Mouth/Oral Thrush	B37.0	112.0	1) 1-month interval for recurrent infections
Onychomycosis/Tinea Pedis	B35.1, B35.3	110.1, 110.4	1) Incidence, no recurrence
Yeast Vaginitis	B37.3	112.1	1) 1-month interval for recurrent infections 2) Antifungal dispensed within 7 days of a diagnostic code
Other fungal infections	B35-B49 Excluding those listed in the above 3 rows	110-118 Excluding those listed in the above 3 rows	1) 1-month interval for recurrent infections
Bacterial Vaginitis	N76.0, N76.2	616.1	1) 1-month interval for recurrent infections 2) Antibiotic dispensed within 7 days of a diagnostic code
Trichomonas Vaginitis	A59.01	131.01	1) 1-month interval for recurrent infections

*ICD codes without a decimal place should be read as including all subdiagnoses

eTable 2. ICD Codes to Identify Diabetes and COPD

	ICD 10	ICD 9	Additional Criteria
Diabetes	E08.36, E08.42, E09.36, E09.42, E10.10, E10.11, E10.21, E10.29, E10.311, E10.319, E10.36, E10.39, E10.40, E10.42, E10.51, E10.618, E10.620, E10.621, E10.622, E10.628, E10.630, E10.638, E10.641, E10.649, E10.65, E10.69, E10.8, E10.9, E11.00, E11.01, E11.21, E11.29, E11.311, E11.319, E11.329, E11.339, E11.349, E11.359, E11.42, E11.51, E11.618, E11.620, E11.621, E11.622, E11.628, E11.630, E11.638, E11.641, E11.649, E11.65, E11.69, E11.8, E11.9, E13.10, E11.36, E11.39, E11.40, E13.42, E13.36, O24.319, O24.32, O24.911, O24.912, O24.913, O24.92, O24.93,	250.XX, 357.2, 362.0, 366.41, 648.0	Hemoglobin A1c >7.5% or Fructosamine >319 OR A dispensing record for an oral hypoglycemic or insulin (not including metformin): ACARBOSE, ALBIGLUTIDE, ALOGLIPTIN, CANAGLIFLOZIN, CHLORPROPAMIDE, DAPAGLIFLOZIN, DIAZOXIDE, DULAGLUTIDE, EMPAGLIFLOZIN, ERTUGLIFLOZIN, EXENATIDE, GLIMEPIRIDE, GLIPIZIDE, GLUCAGON, GLUCOSE, GLYBURIDE, INSULIN, LINAGLIPTIN, LIRAGLUTIDE, MIGLITOL, NATEGLINIDE, PIOGLITAZONE, PRAMLINTIDE, REPAGLINIDE, ROSIGLITAZONE, SAXAGLIPTIN, SEMAGLUTIDE, SITAGLIPTIN, TOLAZAMIDE, TOLBUTAMIDE
Chronic Obstructive Pulmonary Disease	I278, I279, J40, J41, J42, J43, J44, J45, J46, J47, J60, J61, J62, J63, J64, J65, J66, J67, J68.4, J70.1, J70.3	416.8, 416.9, 490, 491, 492, 493, 494, 495, 496, 497, 498, 499, 500, 501, 502, 503, 504, 505, 506.4, 508.1, 508.8	

eTable 3. Outpatient Infections Rates and Risks of Lower Respiratory Tract Infections, Pneumonia, Otitis Media, and Fungal Nailbed Infections

	No. Events	Person-Years	IR per 1000 Person-Years (95% CI)	aRR (95%CI) ^a	aRR (95%CI) ^b
Lower Respiratory Tract Infection					
Rituximab	337	6913.5	48.7 (43.5, 53.9)	1.15 (1.01, 1.31)	0.92 (0.80, 1.05)
Natalizumab	65	1575.4	41.3 (31.2, 51.3)	1.15 (0.88, 1.50)	0.88 (0.67, 1.16)
Fingolimod	40	867.6	46.1 (31.8, 60.4)	1.44 (1.05, 1.96)	1.14 (0.83, 1.57)
IFN/GLAT	1047	19,644.6	53.3 (50.1, 56.5)	1.26 (1.17, 1.35)	[reference]
Untreated	856	17,937.5	47.7 (44.5, 50.9)	0.96 (0.88, 1.04)	NA
General Population Controls	10,351	238,329.3	43.4 (42.6, 44.3)	[reference]	NA
Pneumonia					
Rituximab	45	6913.5	6.5 (4.6, 8.4)	1.29 (0.94, 1.77)	1.06 (0.73, 1.55)
Natalizumab	4	1575.4	2.5 (0.1, 5.0)	0.67 (0.25, 1.77)	0.51 (0.19, 1.38)
Fingolimod	3	867.6	3.5 (-0.5, 7.4)	0.90 (0.30, 2.68)	0.67 (0.22, 2.03)
IFN/GLAT	132	19,644.6	6.7 (5.6, 7.9)	1.18 (0.97, 1.43)	[reference]
Untreated	139	17,937.5	7.7 (6.5, 9.0)	1.02 (0.84, 1.24)	NA
General Population Controls	1194	238,329.3	5.0 (4.7, 5.3)	[reference]	NA
Otitis Media					
Rituximab	152	6913.5	22.0 (18.5, 25.5)	1.10 (0.93, 1.31)	1.02 (0.84, 1.25)
Natalizumab	44	1575.4	27.9 (19.7, 36.2)	1.29 (0.94, 1.77)	1.16 (0.83, 1.62)
Fingolimod	12	867.6	13.8 (6.0, 21.7)	0.70 (0.38, 1.28)	0.61 (0.33, 1.13)
IFN/GLAT	393	19,644.6	20.0 (18.0, 22.0)	1.09 (0.98, 1.22)	[reference]
Untreated	298	17,937.5	16.6 (14.7, 18.5)	0.91 (0.8, 1.03)	NA
General Population Controls	4816	238,329.3	20.2 (19.6, 20.8)	[reference]	NA
Fungal Nailbed Infection					
Rituximab	117	6913.5	16.9 (13.9, 20.0)	1.05 (0.88, 1.26)	0.77 (0.64, 0.95)
Natalizumab	24	1575.4	15.2 (9.1, 21.3)	1.09 (0.74, 1.61)	0.85 (0.57, 1.27)
Fingolimod	4	867.6	4.6 (0.1, 9.1)	0.33 (0.12, 0.90)	0.26 (0.09, 0.70)
IFN/GLAT	436	19,644.6	22.2 (20.1, 24.3)	1.37 (1.25, 1.50)	[reference]
Untreated	320	17,937.5	17.8 (15.9, 19.8)	0.98 (0.88, 1.09)	NA
General Population Controls	3561	238,329.3	14.9 (14.5, 15.4)	[reference]	NA

Abbreviations: LRI=lower respiratory infection; IR=incidence rate; aRR=adjusted risk ratio; 95% CI=95% confidence intervals; IFN=interferon-beta; GLAT=glatiramer acetate; NA=not applicable

^aAdjusted for age, sex, race/ethnicity, Charlson comorbidity index, chronic obstructive pulmonary disease, diabetes, obesity, hospitalization for infection in the previous 5 years

^bAdjusted for age, sex, race/ethnicity, Charlson comorbidity index, chronic obstructive pulmonary disease, diabetes, obesity, hospitalization for infection in the previous 5 years, advanced disability (defined as requiring a walker, wheelchair, Hoyer lift, and/or hospital bed), and previous use of disease-modifying therapies

eTable 4. Crude and mutually adjusted associations of disease-modifying therapies, clinical and demographic characteristics among multiple sclerosis patients serious infections: Sensitivity Analyses excluding hospitalization for UTI-related pseudorelapse

	Serious Infections without UTI			
	Crude HR (95%CI)	p-value	Adjusted HR (95%CI)	p-value
Age by 10 years	1.36 (1.23, 1.50)	<.0001	1.12 (1.02, 1.23)	0.0203
Sex (ref=male)	0.69 (0.56, 0.86)	0.0007	0.73 (0.58, 0.90)	0.0041
Race and Ethnicity (ref=White)	1.07 (0.88, 1.31)	0.4958		
Charlson Comorbidity Index (ref=0)				
1	1.47 (1.09, 1.99)	0.0128	1.37 (0.96, 1.95)	0.0867
2+	3.74 (2.96, 4.71)	<.0001	2.17 (1.62, 2.91)	<.0001
COPD	1.39 (1.01, 1.90)	0.0422	0.94 (0.65, 1.36)	0.7365
Diabetes	1.95 (1.45, 2.62)	<.0001	0.97 (0.70, 1.35)	0.8627
Obesity	1.09 (0.89, 1.34)	0.4131	--	--
Prior hospitalization for infection^a	4.59 (3.58, 5.88)	<.0001	2.41 (1.84, 3.17)	<.0001
Advanced disability^b	5.33 (4.37, 6.50)	<.0001	3.33 (2.64, 4.21)	<.0001
Any prior DMT use	1.84 (1.44, 2.34)	<.0001	1.41 (1.09, 1.83)	0.0086
DMT treatment				
Rituximab	2.33 (1.75, 3.09)	<.0001	1.31 (1.00, 1.73)	0.0504
Natalizumab	1.35 (0.87, 2.08)	0.1774	1.19 (0.77, 1.86)	0.4351
Fingolimod	NA		NA	
IFN/GLAT	[reference]		[reference]	

Abbreviations: HR=hazard ratio; 95% CI=95% confidence intervals; COPD=chronic obstructive pulmonary disease; IFN=interferon-beta; GLAT=glatiramer acetate; NA=not applicable; ref=reference category; DMT=disease modifying therapy

^aIn the previous 5 years

^bDefined as requiring a walker, wheelchair, Hoyer lift, and/or hospital bed

eTable 5. Number of events, incidence rates and 95% confidence intervals of Serious Infections due PML, Herpes, other causes of Meningitis or Encephalitis among DMT-treated MS Patients

	No. Events	Person-Years	IR per 1000 Person-Years (95% CI)
Progressive Multifocal Leukoencephalopathy			
Rituximab	0	6913.5	0 (0, 0)
Natalizumab	0	1575.4	0 (0, 0)
Fingolimod	0	867.6	0 (0, 0)
IFN/GLAT	0	19,644.6	0 (0, 0)
Varicella Zoster Virus			
Rituximab	0	6913.5	0 (0, 0)
Natalizumab	0	1575.4	0 (0, 0)
Fingolimod	0	867.6	0 (0, 0)
IFN/GLAT	0	19,644.6	0 (0, 0)
Herpes Simplex Virus*			
Rituximab	0	6913.5	0 (0, 0)
Natalizumab	1	1575.4	0.6 (-0.6, 1.9)
Fingolimod	0	867.6	0 (0, 0)
IFN/GLAT	1	19,644.6	0.05 (-0.05, 0.2)
Meningitis			
Rituximab	2	6913.5	0.3 (-0.1, 0.7)
Natalizumab	0	1575.4	0 (0, 0)
Fingolimod	0	867.6	0 (0, 0)
IFN/GLAT	5	19,644.6	0.3 (0.03, 0.5)
Encephalitis			
Rituximab	0	6913.5	0 (0, 0)
Natalizumab	0	1575.4	0 (0, 0)
Fingolimod	0	867.6	0 (0, 0)
IFN/GLAT	1	19,644.6	0.05 (-0.05, 0.2)

Abbreviations: PML=progressive multifocal leukoencephalopathy; no.=number; IR=incidence rate; 95% CI=95% confidence intervals; IFN=interferon-beta; GLAT=glatiramer acetate

*Both cases were HSV encephalitis.