Supplementary Online Content

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This supplementary material has been provided by the authors to give readers additional information about their work.

eTable 1: Definitions of study outcomes and baseline medical history

Outcome	Codes	Data source
Serious infections, hospitalized	ICD10: A00–B99, D73.3, E06.0, E32.1, G00–G02, G04.2, G05–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, N30.0, N30.8, N30.9, N34.0, , N34.1, N34.2, N39.0, N41.2, N43.1, N45.2, N45.3, N45.4, N48.2, N61, N70, N73, N75.1	Main diagnosis in the inpatient component of the Patient registry If main diagnosis was MS (G35), contributory diagnoses were also considered
Fatal infections	As above	Causes of Death registry, underlying cause of death
Any systemic antibacterial	ATC: J01	Prescribed drug registry
Hospitalized Herpetic infections	ICD10: B00, B02, B01	Main diagnosis in the inpatient component of the Patient registry If main diagnosis was MS (G35), contributory diagnoses were also considered
Herpes antivirals	ATC: D06BB03, D06BB53, J05AB01, S01AD03, J05AB09, J05AB11	Prescribed drug registry
PML	ICD10: A81.2	Main or contributory diagnosis in the inpatient component of the Patient registry
Baseline medical history	**Codes**	**Data source**
Malignancy	Any invasive malignancy	The Cancer Registry
Antidepressants use	ATC: N06AB03, N06AB04, N06AB05, N06AB06, N06AB08, N06AB10, N06AX03, N06AX06, N06AX11, N06AX12, N06AX16, N06AX18, N06AX22, N06AX26	Prescribed drug registry
Antipsychotics use	ATC: N05AD01, N05AE04, N05AE05, N05AF01, N05AF03, N05AF05, N05AG02, N05AH02, N05AH03, N05AH04, N05AX08, N05AX12, N05AX13	Prescribed drug registry
MACE	ICD10: I20.0, I21, I60, I61, I62, I63, I64	Main or contributory diagnosis in the Patient register (in- and outpatient care)
Arrhythmia	ICD10: I44, I45, I47, I48, I49	Main or contributory diagnosis in the Patient register (in- and outpatient care)
Diabetes mellitus	ATC: A10	Prescribed drug registry
COPD	ICD10: J44	Main or contributory diagnosis in the Patient register (in- and outpatient care)

Notes: ICD10 codes without a decimal place should be read as including all subdiagnoses.

eTable 2. Patients with RRMS and general population comparators excluded for having had the outcomes of interest in the last 6 months before treatment start.

	IFNβ/GA (n = 2217)	Fingolimod (n = 1535)	Natalizumab (n = 1588)	Rituximab (n = 3260)	General pop. (n = 42,645)
Excluded, N(%)					
Serious infections,	19 (0.9)	11 (0.7)	15 (0.9)	36 (1.1)	111 (0.3)
Any antibacterial use	345 (15.6)	273 (17.8)	253 (15.9)	542 (16.6)	4990 (11.7)
PML	1 (0.0)	0 (0.0)	0 (0.0)	3 (0.1)	1 (0.0)
Hospitalized herpes	1 (0.0)	0 (0.0)	0 (0.0)	4 (0.1)	0 (0.0)
Herpes antiviral use	33 (1.5)	30 (2.0)	24 (1.5)	83 (2.5)	529 (1.2)

eTable 3: Proportion with non-missing data before imputation, by cohort

	IFNβ/GA (n = 2217)	Fingolimod (n = 1535)	Natalizumab (n = 1588)	Rituximab (n = 3260)	General pop. (n = 42,645)
Treatment start, year	100%	100%	100%	100%	100%
Demographic characteristics					
Age	100%	100%	100%	100%	100%
Sex	100%	100%	100%	100%	100%
Country of Birth	100%	100% (1 subject had missing data)	100%	100% (1 subject had missing data)	100% (8 subjects had missing data)
Educational level	100% (17 subjects had missing data)	100% (11 subjects had missing data)	100% (27 subjects had missing data)	100% (39 subjects had missing data)	100% (907 subjects had missing data)
Any sick leave, last year	96%	95%	91%	72%	85%
Any disability pension, last year	96%	95%	91%	72%	85%
Medical history previous 5 years, all except recent cancer	100%	100%	100%	100%	100%
Cancer, last 5 years	96%	95%	92%	73%	86%
MS-associated characteristics					
Previous use of DMTs	100%	100%	100%	100%	-
MS duration	94%	94%	96%	94%	-
Any relapse last year	100%	100%	100%	100%	-
MSIS-29 physical	15%	84%	82%	55%	-
MSIS-29 psychological	15%	84%	82%	55%	-
EDSS	52%	62%	66%	65%	-
EQ-5D	14%	81%	42%	47%	-
SDMT score	13%	81%	82%	53%	-

eTable 4: Sequential adjustment for groups of potential confounders

	HR1 (95% CI)	HR2 (95% CI)	HR3 (95% CI)	HR4 (95% CI)	HR5 (95% CI)	HR5 (95% CI)	HR6 (95% CI)
Serious infections							
IFNβ/GA	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)		
Fingolimod	1.63 (1.09-2.43)	1.81 (1.21-2.71)	1.80 (1.20-2.70)	1.38 (0.91-2.10)	1.30 (0.84-2.03)	0.78 (0.54-1.13)	0.75 (0.52-1.09)
Natalizumab	1.29 (0.85-1.98)	1.53 (0.99-2.35)	1.56 (1.02-2.41)	1.35 (0.87-2.09)	1.12 (0.71-1.77)	0.67 (0.45-1.00)	0.65 (0.44-0.98)
Rituximab	2.22 (1.57-3.15)	2.34 (1.65-3.32)	2.39 (1.66-3.42)	1.92 (1.33-2.78)	1.70 (1.11-2.61)	1.0 (Ref)	1.0 (Ref)
General pop.	0.59 (0.43-0.82)	0.64 (0.47-0.89)	0.64 (0.46-0.88)	0.81 (0.58-1.12)			
Any antibacterial use							
IFNβ/GA	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)		
Fingolimod	1.07 (0.95-1.20)	1.11 (0.99-1.25)	1.14 (1.01-1.28)	1.06 (0.94-1.20)	1.06 (0.93-1.20)	0.88 (0.77-0.99)	0.89 (0.78-1.01)
Natalizumab	1.20 (1.07-1.35)	1.21 (1.08-1.36)	1.25 (1.11-1.41)	1.21 (1.08-1.37)	1.15 (1.01-1.31)	0.94 (0.82-1.06)	0.95 (0.83-1.08)
Rituximab	1.20 (1.08-1.32)	1.21 (1.10-1.34)	1.28 (1.16-1.42)	1.23 (1.10-1.37)	1.23 (1.08-1.40)	1.0 (Ref)	1.0 (Ref)
General pop.	0.77 (0.71-0.83)	0.77 (0.71-0.84)	0.80 (0.73-0.87)	0.90 (0.82-0.98)			
Herpes antiviral use							
IFNβ/GA	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)	1.0 (Ref)		
Fingolimod	2.02 (1.53-2.69)	2.09 (1.57-2.77)	1.98 (1.49-2.63)	1.82 (1.35-2.46)	1.82 (1.34-2.46)	1.65 (1.25-2.18)	1.73 (1.31-2.29)
Natalizumab	2.19 (1.66-2.90)	2.14 (1.62-2.84)	2.07 (1.56-2.74)	1.84 (1.36-2.48)	1.71 (1.27-2.32)	1.52 (1.14-2.03)	1.62 (1.21-2.17)
Rituximab	1.40 (1.06-1.85)	1.40 (1.06-1.85)	1.22 (0.92-1.63)	1.07 (0.79-1.45)	1.07 (0.76-1.49)	1.0 (Ref)	1.0 (Ref)
General pop.	0.61 (0.48-0.77)	0.60 (0.47-0.76)	0.57 (0.45-0.73)	0.61 (0.48-0.78)			

HR1: Crude (unadjusted) hazard ratio.
HR2: Hazard ratio adjusted for age, and sex.
HR3: Hazard ratio adjusted for age, sex, education level, and country of birth.
HR4: Hazard ratio adjusted for age, sex, education level, country of birth, sick leave, disability pension, hospitalizations previous 5 years, history of infections, cancer, antidepressants and antipsychotics use, MACE, arrhythmia.
HR5: Hazard ratio adjusted for age, sex, educational level, country of birth, sick leave, disability pension, hospitalizations previous 5 years, history of infections, cancer, antidepressants and antipsychotics use, MACE, arrhythmia, year of treatment start, region of treating clinic, relapses last year, MS duration, EDSS, MSIS-29, EQ5D, SDMT
HR6: Hazard ratio adjusted as HR5, and also for number of previous DMTs

eTable 5: Observed serious infections ordered by assigned main diagnosis

ICD10	Description	IFNβ/GA (n = 2217)	Fingolimod (n = 1535)	Natalizumab (n = 1588)	Rituximab (n = 3260)
A04	Other bacterial intestinal infections	0	2	1	5
A08	Viral and other specified intestinal infections	0	0	0	1
A09	Infectious gastroenteritis and colitis, unspecified	4	2	4	4
A15	Respiratory tuberculosis	0	0	0	1
A41	Other sepsis	2	2	2	3
A46	Erysipelas	1	1	3	4
A48	Other bacterial diseases, not elsewhere classified	0	0	0	1
A49	Bacterial infection of unspecified site	0	0	0	2
A60	Anogenital herpesviral [herpes simplex] infections	0	0	0	1
A69	Other spirochetal infections	0	0	0	5
A78	Q fever	0	0	0	1
A81	Atypical virus infections of central nervous system	0	1	0	1
A87	Viral meningitis	0	0	0	2
A98	Other viral hemorrhagic fevers, not elsewhere classified	0	0	0	1
B00	Herpesviral [herpes simplex] infections	1	0	0	0
B01	Varicella [chickenpox]	0	0	2	1
B02	Zoster [herpes zoster]	0	2	0	0
B17	Other acute viral hepatitis	0	0	1	0
B34	Viral infection of unspecified site	1	4	3	5
B35	Dermatophytosis	0	0	0	1
B37	Candidiasis	0	0	0	1
B99	Other and unspecified infectious diseases	0	1	1	1
H66	Suppurative and unspecified otitis media	0	0	1	0
H67	Otitis media in diseases classified elsewhere	0	1	0	0
J01	Acute sinusitis	1	0	0	4
J03	Acute tonsillitis	1	0	1	3
J06	Acute upper resp infections of multiple and unsp sites	1	1	0	4
J09	Influenza due to certain identified influenza viruses	0	1	0	0
J10	Influenza due to other identified influenza virus	0	3	1	2
J11	Influenza due to unidentified influenza virus	0	1	0	1
J13	Pneumonia due to Streptococcus pneumoniae	0	0	0	3
J14	Pneumonia due to Hemophilus influenzae	0	0	0	3

Code	Diagnosis				
J15	Bacterial pneumonia, not elsewhere classified	4	2	2	5
J18	Pneumonia, unspecified organism	3	6	3	7
J20	Acute bronchitis	0	1	0	1
J32	Chronic sinusitis	1	0	0	1
J85	Abscess of lung and mediastinum	0	1	0	0
K10	Other diseases of jaws	0	0	0	1
K57	Diverticular disease of intestine	0	2	0	1
K61	Abscess of anal and rectal regions	0	2	1	1
K65	Peritonitis	1	0	0	2
L02	Cutaneous abscess, furuncle and carbuncle	4	0	2	3
L03	Cellulitis and acute lymphangitis	2	0	0	1
L04	Acute lymphadenitis	0	0	1	0
L08	Other local infections of skin and subcutaneous tissue	0	0	0	4
M46	Other inflammatory spondylopathies	0	0	0	1
M65	Synovitis and tenosynovitis	0	1	0	0
M72	Fibroblastic disorders	1	1	0	0
N10	Acute tubulo-interstitial nephritis	5	3	6	12
N30	Cystitis	0	2	1	1
N39	Other disorders of urinary system	7	8	1	8
N70	Salpingitis and oophoritis	0	1	2	4
N73	Other female pelvic inflammatory diseases	0	0	0	1
N75	Diseases of Bartholin's gland	0	0	0	1
G35*	Multiple sclerosis	1	5	6	9
A04	*Other bacterial intestinal infections*	0	0	0	1
A09	*Infectious gastroenteritis and colitis, unspecified*	0	0	0	1
A40	*Streptococcal sepsis*	0	0	1	2
A41	*Other sepsis*	0	0	1	2
B34	*Viral infection of unspecified site*	0	1	0	0
B37	*Candidiasis*	0	1	0	0
B96	*Oth bacterial agents as the cause of diseases classd elswhr*	0	0	0	1
H00	*Hordeolum and chalazion*	0	0	0	1
J01	*Acute sinusitis*	0	0	0	1
J06	*Acute upper resp infections of multiple and unsp sites*	0	0	0	1
J20	*Acute bronchitis*	0	0	1	1
N39	*Other disorders of urinary system*	1	3	3	2

Notes: *) Main diagnosis assigned was MS, listed are all infections noted as secondary diagnoses. Patients may have several secondary diagnoses.

eTable 6: All observed inpatient serious infection diagnoses during the follow-up (including secondary diagnoses and multiple diagnoses per patient)

ICD10	Description	IFNβ/GA (n = 2217)	Fingolimod (n = 1535)	Natalizumab (n = 1588)	Rituximab (n = 3260)
A04	Other bacterial intestinal infections	0	4	1	10
A08	Viral and other specified intestinal infections	0	0	1	2
A09	Infectious gastroenteritis and colitis, unspecified	4	3	4	8
A15	Respiratory tuberculosis	0	0	0	1
A26	Erysipeloid	1	0	0	0
A28	Other zoonotic bacterial diseases, not elsewhere classified	1	0	0	0
A40	Streptococcal sepsis	0	0	2	2
A41	Other sepsis	4	4	7	8
A46	Erysipelas	2	2	3	5
A48	Other bacterial diseases, not elsewhere classified	0	0	0	1
A49	Bacterial infection of unspecified site	0	0	1	2
A60	Anogenital herpesviral [herpes simplex] infections	0	0	0	1
A69	Other spirochetal infections	0	0	0	5
A78	Q fever	0	0	0	2
A81	Atypical virus infections of central nervous system	0	1	0	6
A85	Other viral encephalitis, not elsewhere classified	0	0	0	2
A87	Viral meningitis	0	0	0	2
A98	Other viral hemorrhagic fevers, not elsewhere classified	0	0	0	1
B00	Herpesviral [herpes simplex] infections	1	0	0	2
B01	Varicella [chickenpox]	0	0	3	1
B02	Zoster [herpes zoster]	0	4	0	1
B17	Other acute viral hepatitis	0	0	1	0
B18	Chronic viral hepatitis	2	0	1	0
B25	Cytomegaloviral disease	0	0	0	2
B34	Viral infection of unspecified site	2	6	3	5
B35	Dermatophytosis	0	0	0	1
B37	Candidiasis	0	2	0	1
B59	Pneumocystosis	0	0	0	1
B95	Strep as the cause of diseases classified elsewhere	2	0	2	8
B96	Oth bacterial agents as the cause of diseases classd elswhr	6	3	3	16
B97	Viral agents as the cause of diseases classified elsewhere	1	0	0	0
B99	Other and unspecified infectious diseases	1	1	1	2
G02	Meningitis in oth infec/parastc diseases classd elswhr	0	0	2	0

G05	Encphlts, myelitis & encephalomyelitis in dis classd elswhr	0	0	0	2
G06	Intracranial and intraspinal abscess and granuloma	0	0	3	0
H00	Hordeolum and chalazion	0	0	0	1
H66	Suppurative and unspecified otitis media	0	0	1	0
H67	Otitis media in diseases classified elsewhere	0	1	0	0
J00	Acute nasopharyngitis [common cold]	0	0	1	0
J01	Acute sinusitis	1	0	0	7
J02	Acute pharyngitis	0	1	0	0
J03	Acute tonsillitis	1	0	1	3
J05	Acute obstructive laryngitis [croup] and epiglottitis	0	0	0	1
J06	Acute upper resp infections of multiple and unsp sites	2	1	1	11
J09	Influenza due to certain identified influenza viruses	0	1	0	1
J10	Influenza due to other identified influenza virus	0	4	2	2
J11	Influenza due to unidentified influenza virus	0	1	0	1
J13	Pneumonia due to Streptococcus pneumoniae	0	0	0	5
J14	Pneumonia due to Hemophilus influenzae	0	0	0	3
J15	Bacterial pneumonia, not elsewhere classified	7	3	4	10
J17	Pneumonia in diseases classified elsewhere	0	0	0	1
J18	Pneumonia, unspecified organism	4	6	3	14
J20	Acute bronchitis	0	1	1	2
J32	Chronic sinusitis	1	0	0	3
J85	Abscess of lung and mediastinum	0	1	0	0
J86	Pyothorax	0	0	0	3
K10	Other diseases of jaws	0	0	0	1
K57	Diverticular disease of intestine	0	2	0	1
K61	Abscess of anal and rectal regions	0	2	1	4
K63	Other diseases of intestine	1	0	0	0
K65	Peritonitis	2	0	2	6
L02	Cutaneous abscess, furuncle and carbuncle	7	1	4	4
L03	Cellulitis and acute lymphangitis	2	1	0	1
L04	Acute lymphadenitis	0	0	1	0
L08	Other local infections of skin and subcutaneous tissue	1	0	0	6
M46	Other inflammatory spondylopathies	0	0	2	1
M65	Synovitis and tenosynovitis	0	2	0	0
M72	Fibroblastic disorders	1	1	0	0
N10	Acute tubulo-interstitial nephritis	7	5	6	19
N30	Cystitis	1	3	2	4
N39	Other disorders of urinary system	14	21	8	17

N70	Salpingitis and oophoritis	1	1	2	5
N73	Other female pelvic inflammatory diseases	0	0	2	1
N75	Diseases of Bartholin's gland	0	0	0	1

eTable 7: Sensitivity analysis, 90 days lag time

Serious infections	Events	IR/1000 person-years (95% CI)	HR4 (95% CI)
IFNβ/GA	33	8.1 (5.6-11.4)	0.47 (0.31-0.70)
Fingolimod	49	13.5 (10-17.9)	0.68 (0.48-0.97)
Natalizumab	37	10.6 (7.5-14.7)	0.66 (0.44-0.97)
Rituximab	109	19.7 (16.2-23.8)	1.0 (Ref)
General pop.	657	5 (4.6-5.4)	0.40 (0.32-0.51)
Any antibacterial use			
IFNβ/GA	482	195.1 (178.1-213.3)	0.84 (0.74-0.94)
Fingolimod	424	207 (187.8-227.7)	0.88 (0.78-0.99)
Natalizumab	460	238.6 (217.3-261.4)	1.01 (0.89-1.14)
Rituximab	785	244.2 (227.5-261.9)	1.0 (Ref)
General pop.	11837	143.7 (141.2-146.4)	0.74 (0.68-0.80)
Herpes antiviral use			
IFNβ/GA	62	15.6 (12-20)	0.94 (0.68-1.30)
Fingolimod	101	29 (23.6-35.2)	1.62 (1.21-2.16)
Natalizumab	108	31.9 (26.2-38.5)	1.64 (1.23-2.19)
Rituximab	110	20.3 (16.7-24.5)	1.0 (Ref)
General pop.	1158	9 (8.4-9.5)	0.57 (0.46-0.71)

Abbreviations: IR, incidence rate; HR, hazard ratio. UTI, urinary tract infection
HR4: Hazard ratio adjusted for age, sex, education level, country of birth, sick leave, disability pension, hospitalizations previous 5 years, history of infections, cancer, antidepressants and antipsychotics use, MACE, arrhythmia.

The 90 days lag time means that patients with events in the first 90 days were excluded from analysis (and that the first 90 days were excluded from the time-at-risk).The primary intention of this sensitivity analysis was to assess the possible impact of planned prophylactic use of herpes antivirals, which we assumed would be started early in the DMT treatment course.

eTable 8: Distribution of herpes antiviral use in first 18 months of DMT treatment, among those with any herpes antivirals use and at least 18 months' follow-up

	IFNβ/GA	Fingolimod	Natalizumab	Rituximab
N obs	27	52	42	79
Total DDDs				
Min-Max	1.25-15.0	1.25-50.0	1.25-47.0	1.25-269.0
Median (IQR)	6.68 (3.75 - 7.0)	7.0 (7.0 -10.0)	7.0 (2.5 - 10.02)	7.0 (5.0 -15.0)
Mean (STD)	6.5 (3.6)	9.8 (8.6)	8.5 (8.9)	14.3 (31.3)
Filled prescriptions, No(%)				
1	17 (63%)	31 (60%)	28 (67%)	43 (54%)
2-3	7 (26%)	12 (23%)	7 (17%)	23 (29%)
4-5	3 (11%)	5 (10%)	6 (14%)	6 (8%)
6+	0 (0%)	4 (8%)	1 (2%)	7 (9%)