

Supplementary Online Content

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Impact of previous treatment history and B-cell depletion treatment duration on infection risk in relapsing-remitting multiple sclerosis: A nationwide cohort study

Contents

Table S1: Definition of outcomes	2
Table S2: Events, Incidence Rates, and Cox Proportional Hazard Models in the Full Cohort	3
Table S3: Baseline characteristics in the switch cohort	4
Figure S1: Drug survival – proportion of patients remaining on rituximab treatment over time	5
Table S4: Events, Incidence Rates, and Cox Proportional Hazard Models in the Full Cohort with follow up until February 29, 2020	6
Table S5: Events, Incidence Rates, and Cox Proportional Hazard Models in the Switch Cohort with follow up until February 29, 2020	7
Figure S2: Infection rate in rituximab by time on treatment, follow up until February 29, 2020	8
Table S6: Events, Incidence Rates, and Cox Proportional Hazard Models in the Switch Cohort where duration of previous treatment is ≥ 1 year	9

Table S1: Definition of outcomes

Outcome	Component	Source	Coding	Included codes
Severe infections	Hospitalization for infection	Main or contributory diagnosis in the inpatient component of Patient Register	ICD-10	A00-B99, D73.3, E06.0, E32.1, G00-G02, G04.2, G05-G07, H00.0, H44.0, H60.0-H60.3, H66-H67, 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, K57.0, 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, N390, N41.2, N43.1, N45.2, N45.3, N45.4, N48.2, N61, N70, N73, N75.1, U07.1, U07.2
	Fatal infections	Causes of Death registry, underlying cause of death	ICD-10	As above
Outpatient infections	Specialist care outpatient infections	Main or contributory diagnosis in the outpatient component of Patient Register	ICD-10	As above
Antibiotics	Any systemic antibacterial	Prescribed drug registry	ATC	J01

Note: ICD-10 codes without a decimal place include all subdiagnoses

Table S2: Events, Incidence Rates, and Cox Proportional Hazard Models in the Full Cohort

	N	Events	PYR	IR	Crude HR (95% CI)	HR (95% CI) ¹	HR (95% CI) ²	HR (95% CI) ³
Serious infection								
Rituximab first line	1458	98	4308.4	22.7 (18.5-27.5)	Ref.	Ref.	Ref.	Ref.
Rituximab later line	3236	255	11918.2	21.4 (18.9-24.1)	0.94 (0.74-1.18)	0.94 (0.75-1.19)	0.87 (0.69-1.11)	0.82 (0.63-1.07)
Other DMT first line	2774	69	6663.3	10.4 (8.1-12.9)	0.46 (0.34-0.62)	0.47 (0.35-0.65)	0.45 (0.32-0.62)	0.48 (0.34-0.68)
Other DMT later line	3275	121	10640.4	11.4 (9.4-13.5)	0.50 (0.38-0.65)	0.50 (0.38-0.66)	0.49 (0.37-0.64)	0.48 (0.35-0.67)
General population	20308	521	79018.3	6.6 (6.0-7.2)	0.29 (0.23-0.36)	0.29 (0.23-0.36)	0.29 (0.23-0.36)	
Outpatient infection								
Rituximab first line	1458	228	4002.7	57.0 (49.8-64.6)	Ref.	Ref.	Ref.	Ref.
Rituximab later line	3236	581	11032.6	52.7 (48.5-57.0)	0.94 (0.81-1.10)	0.94 (0.81-1.10)	0.90 (0.77-1.06)	0.90 (0.75-1.08)
Other DMT first line	2774	230	6353.7	36.2 (31.7-41.0)	0.63 (0.53-0.76)	0.61 (0.51-0.74)	0.64 (0.52-0.77)	0.63 (0.52-0.78)
Other DMT later line	3275	371	10020.4	37.0 (33.4-40.9)	0.66 (0.56-0.78)	0.66 (0.56-0.78)	0.69 (0.57-0.82)	0.70 (0.57-0.85)
General population	20308	1705	75678.3	22.5 (21.5-23.6)	0.41 (0.35-0.47)	0.41 (0.35-0.47)	0.41 (0.36-0.47)	
Systemic antibacterial								
Rituximab first line	1458	583	2991.0	194.9 (179.4-211.1)	Ref.	Ref.	Ref.	Ref.
Rituximab later line	3236	1659	7520.5	220.6 (210.1-231.3)	1.17 (1.06-1.28)	1.10 (1.00-1.21)	1.04 (0.94-1.14)	1.03 (0.92-1.14)
Other DMT first line	2774	863	4905.1	175.9 (164.4-187.9)	0.90 (0.81-1.00)	0.81 (0.73-0.90)	0.79 (0.70-0.88)	0.79 (0.70-0.89)
Other DMT later line	3275	1359	7062.7	192.4 (182.3-202.8)	1.03 (0.94-1.14)	0.90 (0.82-1.00)	0.85 (0.77-0.95)	0.84 (0.75-0.95)
General population	20308	7341	57583.7	127.5 (124.6-130.4)	0.70 (0.64-0.76)	0.67 (0.61-0.73)	0.67 (0.62-0.73)	

Legend: N, number of patients; Events, number of patients with infection; PYR, person-years of follow-up; IR, incidence rate per 1000 PYR; HR, hazard ratio with 95% confidence interval from Cox proportional hazards model adjusting for:

- 1) Age, sex and start year
- 2) 1+ comorbidities and demographics
- 3) 2+ MS-specific

Table S3: Baseline characteristics in the switch cohort

	RTX with switch from NTZ	RTX with switch from INJ	RTX with switch from DMF	RTX with switch from FGL
Number of observations	886	786	626	346
Start year, median (IQR)	2017 (2015-2018)	2016 (2014-2018)	2018 (2016-2019)	2016 (2015-2018)
Age in years, mean (SD)	38.5 (10.4)	43.0 (9.8)	38.9 (10.5)	38.5 (9.7)
Female, n (%)	598 (67.5)	552 (70.2)	445 (71.1)	228 (65.9)
Born in Sweden, n (%)	765 (86.3)	666 (84.7)	541 (86.4)	295 (85.5)
Education, 12+ yrs, n (%)	393 (44.7)	376 (48.3)	299 (48.0)	155 (45.3)
Years since MS diagnosis, mean (SD)	7.7 (5.8)	7.7 (6.1)	5.6 (5.6)	8.0 (5.4)
Hospitalized infection 5 yrs before DMT, n (%)	35 (4.0)	22 (2.8)	25 (4.0)	14 (4.0)
Infection outpatient care 5 yrs before DMT, n (%)	120 (13.5)	93 (11.8)	103 (16.5)	61 (17.6)
Antibiotics 5 yrs before DMT, n (%)	511 (57.7)	420 (53.4)	368 (58.8)	221 (63.9)
Charlson comorbidity index, mean (SD)	0.1 (0.6)	0.1 (0.5)	0.1 (0.4)	0.1 (0.5)
Any relapse year before DMT, n (%)	95 (10.7)	183 (23.3)	143 (22.8)	88 (25.4)
EDSS, mean (SD)	2.0 (1.5)	1.7 (1.3)	1.6 (1.4)	1.9 (1.4)
MSIS29 physical, mean (SD)	1.8 (0.8)	1.7 (0.8)	1.7 (0.7)	1.9 (0.9)
MSIS29 psychological, mean (SD)	2.2 (0.9)	2.1 (0.9)	2.2 (0.9)	2.2 (1.0)
Duration of previous DMT, years, mean (SD)	3.5 (2.9)	5.5 (4.6)	1.9 (1.5)	2.5 (1.8)
History of natalizumab, n (%)	886 (100.0)	15 (1.9)	39 (6.2)	134 (38.7)
History of fingolimod, n (%)	99 (11.2)	5 (0.6)	28 (4.5)	346 (100.0)
History of dimethyl fumarate, n (%)	49 (5.5)	38 (4.8)	626 (100.0)	29 (8.4)
1 previous treatment, n (%)	266 (30.0%)	658 (83.7%)	312 (49.8%)	50 (14.5%)
2 previous treatments, n (%)	429 (48.4%)	72 (9.2%)	225 (35.9%)	158 (45.7%)
3+ previous treatments, n (%)	191 (21.6%)	56 (7.1%)	89 (14.2%)	138 (39.9%)
Reason for previous treatment stop: Adverse events, n (%)	45 (5.1%)	175 (22.3%)	245 (39.1%)	79 (22.8%)
Reason for previous treatment stop: Lost of effect, n (%)	76 (8.6%)	423 (53.8%)	294 (47.0%)	196 (56.6%)
Reason for previous treatment stop: Other, n (%)	765 (86.3%)	188 (23.9%)	87 (13.9%)	71 (20.5%)

Legend: RTX, rituximab; NTZ, natalizumab, INJ, injectables; DMF, dimethyl fumarate; FGL, fingolimod

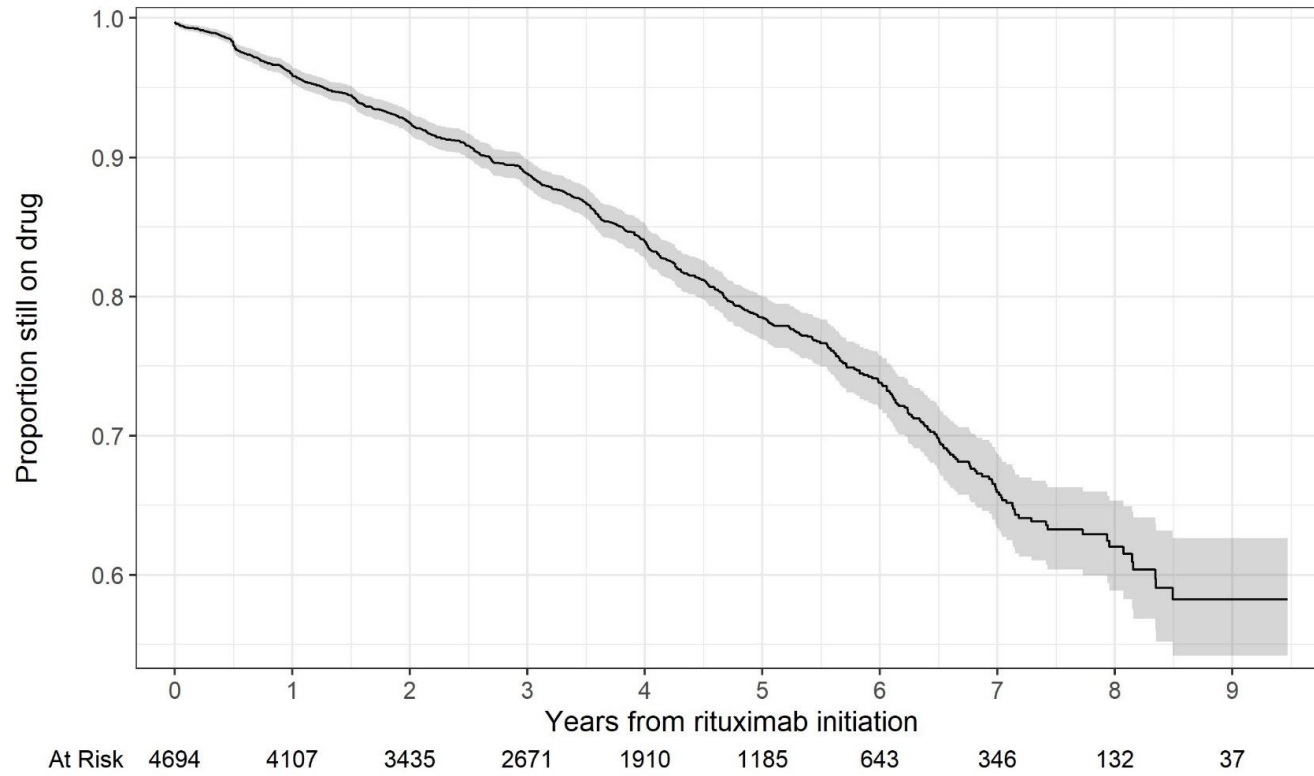


Figure S1: Drug survival – proportion of patients remaining on rituximab treatment over time

Table S4: Events, Incidence Rates, and Cox Proportional Hazard Models in the Full Cohort with follow up until February 29, 2020

	N	Events	PYR	IR	Crude HR (95% CI)	HR (95% CI) ¹	HR (95% CI) ²	HR (95% CI) ³
Serious infection								
Rituximab first line	1230	54	2795.3	19.3 (14.5-24.8)	Ref.	Ref.	Ref.	Ref.
Rituximab later line	2970	162	8670.1	18.7 (15.9-21.7)	0.97 (0.71-1.32)	0.96 (0.71-1.31)	0.89 (0.65-1.21)	0.85 (0.60-1.20)
Other DMT first line	2410	51	5526.7	9.2 (6.9-11.9)	0.48 (0.33-0.70)	0.44 (0.30-0.65)	0.42 (0.28-0.62)	0.44 (0.29-0.67)
Other DMT later line	3120	103	9088.3	11.3 (9.3-13.6)	0.59 (0.42-0.83)	0.55 (0.39-0.76)	0.53 (0.37-0.75)	0.51 (0.34-0.76)
General population	18100	344	54363.9	6.3 (5.7-7.0)	0.33 (0.25-0.44)	0.33 (0.24-0.44)	0.33 (0.25-0.44)	
Outpatient infection								
Rituximab first line	1230	152	2622.5	58.0 (49.1-67.5)	Ref.	Ref.	Ref.	Ref.
Rituximab later line	2970	428	8128.3	52.7 (47.8-57.8)	0.92 (0.77-1.11)	0.93 (0.77-1.12)	0.89 (0.74-1.08)	0.91 (0.74-1.13)
Other DMT first line	2410	195	5286.5	36.9 (31.9-42.2)	0.64 (0.52-0.79)	0.61 (0.49-0.76)	0.63 (0.51-0.79)	0.62 (0.49-0.79)
Other DMT later line	3120	329	8619.2	38.2 (34.2-42.4)	0.67 (0.55-0.81)	0.66 (0.54-0.81)	0.69 (0.56-0.85)	0.69 (0.54-0.87)
General population	18100	1195	52399.1	22.8 (21.5-24.1)	0.40 (0.34-0.48)	0.40 (0.34-0.48)	0.42 (0.35-0.49)	
Systemic antibacterial								
Rituximab first line	1230	449	1999.7	224.5 (204.2-245.8)	Ref.	Ref.	Ref.	Ref.
Rituximab later line	2970	1384	5739.3	241.1 (228.6-254.0)	1.10 (0.99-1.23)	1.06 (0.96-1.18)	1.00 (0.90-1.12)	0.97 (0.86-1.09)
Other DMT first line	2410	770	4152.3	185.4 (172.6-198.8)	0.84 (0.75-0.94)	0.79 (0.70-0.89)	0.77 (0.68-0.87)	0.75 (0.66-0.86)
Other DMT later line	3120	1270	6259.2	202.9 (191.9-214.2)	0.95 (0.85-1.06)	0.89 (0.80-0.99)	0.84 (0.75-0.94)	0.80 (0.70-0.91)
General population	18100	5798	41095.6	141.1 (137.5-144.7)	0.66 (0.60-0.73)	0.64 (0.58-0.71)	0.65 (0.59-0.71)	

Legend: N, number of patients; Events, number of patients with infection; PYR, person-years of follow-up; IR, incidence rate per 1000 PYR; HR, hazard ratio with 95% confidence interval from Cox proportional hazards model adjusting for:

- 1) Age, sex and start year
- 2) 1+ comorbidities and demographics
- 3) 2+ MS-specific

Table S5: Events, Incidence Rates, and Cox Proportional Hazard Models in the Switch Cohort with follow up until February 29, 2020

	N	Events	PYR	IR	Crude HR (95% CI)	HR (95% CI) ¹	HR (95% CI) ²	HR (95% CI) ³	HR (95% CI) ⁴
Serious infection									
RTX with switch from NTZ	774	54	2387.4	22.6 (17.0-29.0)	Ref.	Ref.	Ref.	Ref.	Ref.
RTX with switch from INJ	755	38	2613.0	14.5 (10.3-19.5)	0.64 (0.42-0.97)	0.60 (0.39-0.93)	0.63 (0.41-0.98)	0.67 (0.42-1.07)	0.71 (0.42-1.19)
RTX with switch from DMF	564	21	1211.6	17.3 (10.7-25.5)	0.78 (0.47-1.30)	0.85 (0.50-1.44)	0.80 (0.48-1.36)	0.82 (0.47-1.42)	0.82 (0.47-1.42)
RTX with switch from FGL	336	20	1062.7	18.8 (11.5-27.9)	0.82 (0.49-1.37)	0.86 (0.51-1.44)	0.80 (0.48-1.34)	0.84 (0.49-1.44)	0.82 (0.48-1.40)
Outpatient infection									
RTX with switch from NTZ	774	131	2214.4	59.2 (49.5-69.7)	Ref.	Ref.	Ref.	Ref.	Ref.
RTX with switch from INJ	755	107	2482.2	43.1 (35.3-51.6)	0.73 (0.57-0.95)	0.75 (0.57-0.98)	0.76 (0.58-1.00)	0.80 (0.60-1.07)	0.85 (0.63-1.17)
RTX with switch from DMF	564	60	1142.5	52.5 (40.1-66.6)	0.89 (0.65-1.20)	0.83 (0.61-1.15)	0.79 (0.58-1.09)	0.77 (0.55-1.08)	0.78 (0.55-1.09)
RTX with switch from FGL	336	58	986.3	58.8 (44.7-74.9)	0.99 (0.73-1.34)	1.01 (0.74-1.37)	0.92 (0.67-1.26)	0.99 (0.71-1.36)	0.96 (0.69-1.33)
Systemic antibacterial									
RTX with switch from NTZ	774	385	1544.1	249.3 (225.1-274.9)	Ref.	Ref.	Ref.	Ref.	Ref.
RTX with switch from INJ	755	383	1714.6	223.4 (201.6-246.3)	0.91 (0.79-1.05)	0.87 (0.76-1.01)	0.91 (0.79-1.05)	0.91 (0.78-1.06)	0.95 (0.80-1.12)
RTX with switch from DMF	564	215	855.0	251.4 (219.0-286.2)	0.97 (0.82-1.14)	0.97 (0.81-1.15)	0.95 (0.80-1.14)	0.94 (0.78-1.14)	0.95 (0.79-1.14)
RTX with switch from FGL	336	162	670.6	241.6 (205.8-280.2)	0.97 (0.80-1.16)	0.98 (0.82-1.19)	0.94 (0.78-1.14)	0.96 (0.78-1.17)	0.94 (0.77-1.14)

Legend: RTX, rituximab; NTZ, natalizumab; INJ, injectables; DMF, dimethyl fumarate; FGL, fingolimod. N, number of patients; Events, number of patients with infection; PYR, person-years of follow-up; IR, incidence rate per 1000 PYR; HR, hazard ratio with 95% confidence interval from Cox proportional hazards model adjusting for:

- 1) Age, sex and start year
- 2) 1+ comorbidities and demographics
- 3) 2+ MS-specific
- 4) 3+ treatment history

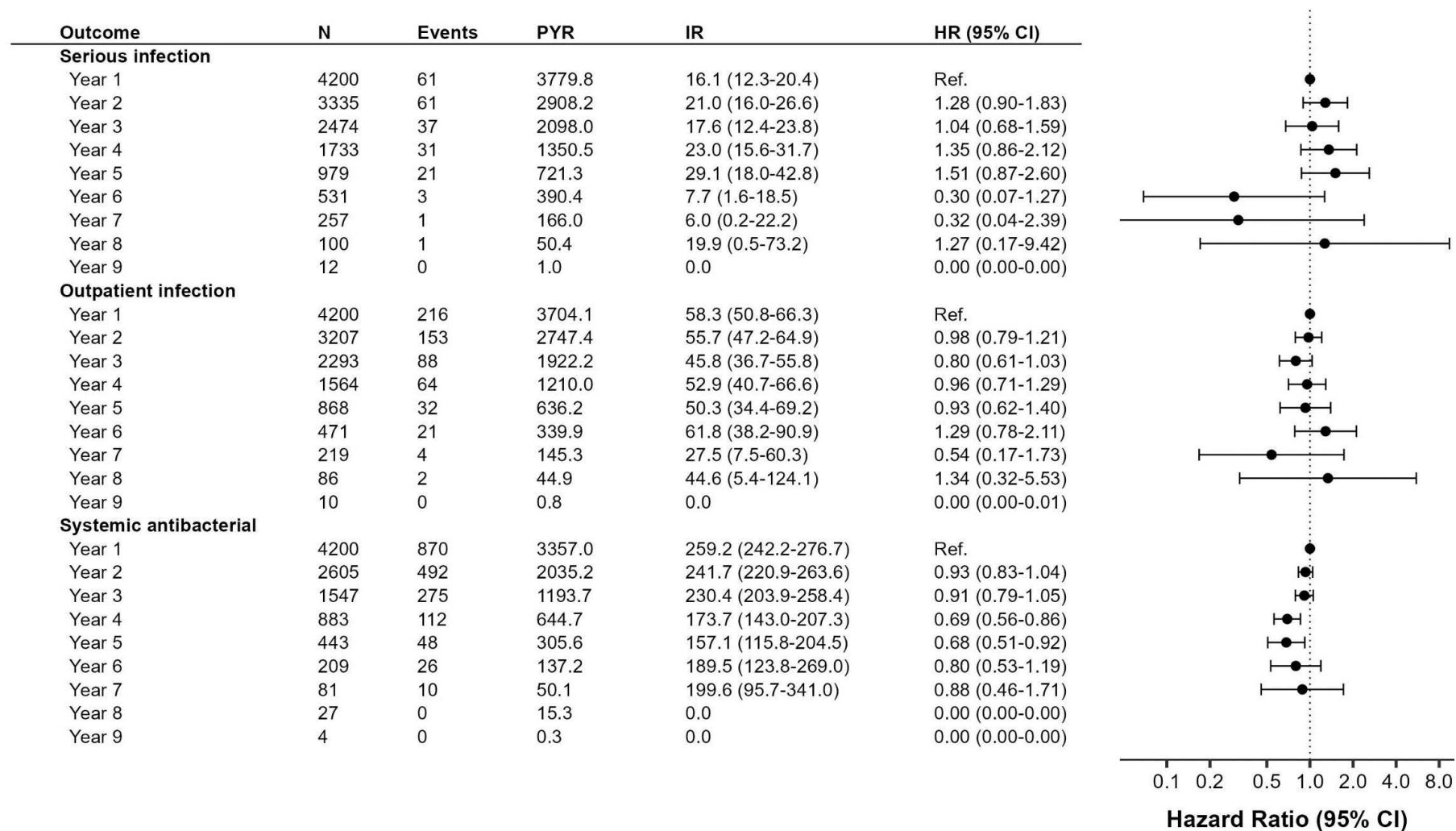


Figure S2: Infection rate in rituximab by time on treatment, follow up until February 29, 2020

Legend: N, number of patients; Events, number of patients with infection; PYR, person-years of follow-up; IR, incidence rate per 1000 PYR; HR, hazard ratio with 95% confidence interval from Cox proportional hazards model adjusting for age, sex, start year, comorbidities, demographics and MS clinical characteristics.

Table S6: Events, Incidence Rates, and Cox Proportional Hazard Models in the Switch Cohort where duration of previous treatment is ≥ 1 year

	N	Events	PYR	IR	Crude HR (95% CI)	HR (95% CI) ¹	HR (95% CI) ²	HR (95% CI) ³	HR (95% CI) ⁴
Serious infection									
RTX with switch from NTZ	665	59	2646.1	22.3 (17.0-28.3)	Ref.	Ref.	Ref.	Ref.	Ref.
RTX with switch from INJ	665	41	2900.2	14.1 (10.1-18.8)	0.63 (0.42-0.94)	0.58 (0.39-0.88)	0.61 (0.40-0.93)	0.71 (0.46-1.10)	0.68 (0.42-1.09)
RTX with switch from DMF	398	25	1110.0	22.5 (14.6-32.2)	1.01 (0.63-1.61)	0.90 (0.56-1.45)	0.93 (0.58-1.49)	1.15 (0.70-1.89)	1.15 (0.70-1.90)
RTX with switch from FGL	258	22	1013.8	21.7 (13.6-31.7)	0.97 (0.59-1.58)	1.00 (0.61-1.63)	0.97 (0.59-1.60)	1.15 (0.69-1.93)	1.19 (0.70-1.99)
Outpatient infection									
RTX with switch from NTZ	665	135	2407.3	56.1 (47.0-65.9)	Ref.	Ref.	Ref.	Ref.	Ref.
RTX with switch from INJ	665	111	2712.7	40.9 (33.7-48.9)	0.74 (0.57-0.95)	0.76 (0.58-0.99)	0.78 (0.60-1.02)	0.86 (0.65-1.14)	0.88 (0.64-1.21)
RTX with switch from DMF	398	58	1052.7	55.1 (41.8-70.2)	0.94 (0.69-1.28)	0.90 (0.65-1.23)	0.94 (0.68-1.30)	0.97 (0.69-1.38)	0.97 (0.69-1.38)
RTX with switch from FGL	258	53	904.2	58.6 (43.9-75.4)	1.03 (0.75-1.41)	1.02 (0.74-1.40)	0.96 (0.69-1.34)	1.01 (0.71-1.43)	1.00 (0.70-1.41)
Systemic antibacterial									
RTX with switch from NTZ	665	354	1630.5	217.1 (195.1-240.3)	Ref.	Ref.	Ref.	Ref.	Ref.
RTX with switch from INJ	665	377	1788.2	210.8 (190.1-232.6)	0.97 (0.84-1.13)	0.92 (0.79-1.06)	0.96 (0.83-1.12)	0.98 (0.84-1.15)	1.01 (0.85-1.21)
RTX with switch from DMF	398	162	814.1	199.0 (169.5-230.8)	0.85 (0.71-1.03)	0.90 (0.74-1.09)	0.92 (0.75-1.12)	0.90 (0.73-1.12)	0.91 (0.73-1.12)
RTX with switch from FGL	258	124	637.0	194.6 (161.9-230.4)	0.88 (0.72-1.09)	0.90 (0.73-1.11)	0.87 (0.70-1.08)	0.93 (0.75-1.16)	0.92 (0.73-1.15)

Legend: RTX, rituximab; NTZ, natalizumab; INJ, injectables; DMF, dimethyl fumarate; FGL, fingolimod. N, number of patients; Events, number of patients with infection; PYR, person-years of follow-up; IR, incidence rate per 1000 PYR; HR, hazard ratio with 95% confidence interval from Cox proportional hazards model adjusting for:

- 1) Age, sex and start year
- 2) 1+ comorbidities and demographics
- 3) 2+ MS-specific
- 4) 3+ treatment history