Hospital-Treated Infections and Risk of Disability Worsening in Multiple Sclerosis

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Objective: To investigate the association between infections and disability worsening in people with multiple sclerosis (MS) treated with either B-cell depleting therapy (rituximab) or interferon-beta/glatiramer acetate (IFN/GA).
Methods: This cohort study spanned from 2000 to 2021, using data from the Swedish MS Registry linked to national health care registries, comprising 8,759 rituximab and 7,561 IFN/GA treatment episodes. The risk of hospital-treated infection was estimated using multivariable Cox models. The association between infections and increase in Expanded Disability Status Scale (EDSS) scores was assessed using a doubly robust generalized estimating equations model. Additionally, a piece-wise exponential model analyzed events of increased disability beyond defined cut-off values, controlling for relapses, and MRI activity.
Results: Compared with IFN/GA, rituximab displayed increased risk of both inpatient- and outpatient-treated infections (hazard ratio [HR], 2.08; 95% confidence interval [CI], 1.50–2.90 and HR, 1.37; 95% CI, 1.13–1.67, respectively). An inpatient-treated infection was associated with a 0.19-unit increase in EDSS (95% CI, 0.12–0.26). Degree of worsening was greatest for progressive MS, and under IFN/GA treatment, which unlike rituximab, was more commonly associated with MRI activity. After controlling for relapses and MRI activity, inpatient-treated infections were associated with disability worsening in people with relapsing–remitting MS treated with IFN/GA (HR, 2.01; 95% CI, 1.59–2.53), but not in those treated with rituximab.
Interpretation: Compared to IFN/GA, rituximab doubled the infection risk, but reduced the risk of subsequent disability worsening. Further, the risk of worsening after hospital-treated infection was greater with progressive MS than with relapsing–remitting MS. Infection risk should be considered to improve long term outcomes.

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Risk of disability accrual in multiple sclerosis (MS) increases from the fifth decade of life, which contrasts with a decreasing relapse rate with increasing age.[1–3] Recent studies, leveraging data from large clinical trials, suggest that disability worsening, as defined by increase in Expanded Disability Severity Status (EDSS) score, mostly occur independent of relapses even in the relapsing–remitting disease stage.[4–6] This phenomenon has been defined as progression independent of relapse activity (PIRA), as opposed to relapse-associated worsening (RAW).[4] It should be noted, however, that the ratio of PIRA against RAW is smaller in relapsing–remitting MS (RRMS) with shorter disease duration, especially when imaging-based measures of

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inflammatory disease activity are also considered.[7] Further, a proportion of events of disability worsening confirmed over some time, usually 3 or 6 months, are not sustained at longer follow up.[6]

Our understanding of mechanisms underlying progression remains incomplete. Neuropathological observations have linked progressive MS with focal and generalized low-grade inflammatory activation in the gray and white matter of the brain,[8] as well as faster loss of brain parenchymal volume.[9] Factors contributing to increased risk of accumulating disability include ageing processes decreasing the resilience of the central nervous system, as well as changes in immune functions.[10] Systemic infection has been hypothesized as 1 potential factor contributing to risk of disability progression.[11] However, this hypothesis has so far not been assessed in well-sized population-based clinical materials. Existing studies in RRMS cohorts support the notion that infections increase the risk of MS relapse.[12–15] Interestingly, albeit based on small materials, it has also been suggested that relapses subsequent to infection are more likely to be associated with a sustained EDSS increase, perhaps indicative of worsened neurological damage.[16] The question if and to what degree infections contribute to disability progression in MS has become more pertinent with increasing use of highly effective disease-modifying therapies (DMTs) that impair the immune system's physiological defenses against infection.[17,18] In particular B cell-depleting therapies (BCDT), but to some degree also other highly effective DMTs, have been associated with an increased risk of hospital-treated infections, compared with first-generation DMTs, such as interferons and glatiramer acetate (IFN/GA).[19]

To investigate a possible association between infections and accrual of disability in MS, we leveraged a Swedish nationwide cohort to: (1) determine incidence of hospital-treated infections in people with MS (PwMS) treated with rituximab or IFN/GA, (2) investigate the association between hospital-treated infections and increase in EDSS, and (3) explore to what degree a putative association between infections and disability progression remains after controlling for relapse and neuroimaging outcomes.

Methods

Data Sources

The Swedish MS Registry (SMSreg) is a publicly funded registry with high coverage of the prevalent MS population in Sweden, collecting data on MS treatments and a range of physician-rated (eg, EDSS) and patient-reported outcomes.[20] Data sourced from the SMSreg have been shown to have high validity.[21] In this study, we used data collected between January 1, 2000 and October 3, 2021 (the study period) that are linked to 3 Swedish national population and health registers with virtually complete coverage, which are the: Total Population Register with information on demographic variables; the Swedish Patient Register with information on inpatient (since 1964, with national coverage since 1987), and specialized outpatient (since 2001) care including diagnoses coded according to Swedish revisions of the International Classification of Diseases (ICD) codes, and the Causes of Death Register (since 1952).[22] Ethical approval for the study was obtained from the Swedish Ethical Review Authority (DNR: 2021–02384).

Study Design

This was a cohort study using prospectively collected data, where we identified all PwMS ever treated with rituximab (Mabthera, Rixathon, Ritemvia, or Truxima), IFN (Avonex, Rebif, Betaferon, or Extavia), or GA (Copaxone) with at least 1 visit recorded in the SMSreg during the study period. IFNs and GA were grouped together as IFN/GA. Because PwMS could receive multiple DMTs during the study period, we studied all treatment episodes of each patient, but combined continuous treatment episodes with different drug brands of the same class as 1 episode. We performed a total of 5 analyses using the study cohort (see Fig for specification of cohorts used in each step), to assess: (1) the incidence of infections among PwMS treated with rituximab or IFN/GA (analysis 1); (2) the association between rituximab and the risk of hospital-treated infections using IFN/GA as the reference (analysis 2); (3) the association between hospital-treated infections and change in EDSS scores (analysis 3); (4) events of disability progression with or without neuroimaging outcomes (analysis 4); and (5) the association between hospital-treated infections and increase in EDSS exceeding pre-defined cut-off values after controlling for relapses and magnetic resonance imaging (MRI) activity (analysis 5). Because rituximab was first used for MS in Sweden in 2009, only treatment episodes initiated after January 2009 were included in the analysis. In total, 7,561 and 8,759 treatment episodes were included in the analyses related to rituximab and IFN/GA, respectively.

Hospital-treated infections were defined by ICD codes from the Swedish Patient Register using both primary and secondary diagnoses recorded for an inpatient or specialized outpatient visit. Infections were classified as bacterial, viral, or other infections (Table S1). We analyzed hospital-treated infections as time-varying and repeated events (ie, allowing more than 1 event during the study period), but considered consecutive events within 30 days as a single event. EDSS was first studied as an ordinal scale to examine the impact of hospital-treated infections on EDSS. We then defined disability progression as a binary

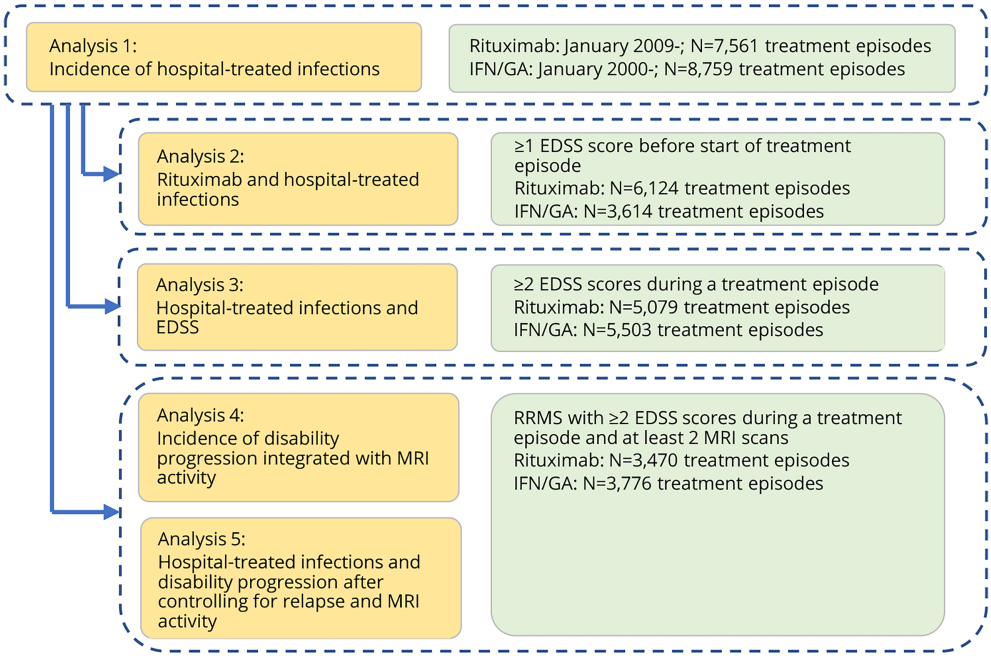

FIGURE: Study Design.

outcome (yes/no), where "yes" was defined as a ≥1.5-point increase in EDSS from a previous score of 0, a ≥1.0-point increase in EDSS from a previous score of 1.0 to 5.0, or a ≥0.5-point increase in EDSS from a previous score of ≥5.5, provided that such increase was sustained for at least 3 months.[23] Finally, to understand whether disability worsening occurred subsequent to a relapse, we also integrated information on relapses during each treatment episode, as time-varying, as well as repeated events.

Statistical Analyses

In analysis 1, we followed all PwMS from the start of a treatment episode of a DMT, until the end of the treatment episode, death, emigration, or end of study period (ie, October 3, 2021), whichever came first, to assess incidence of hospital-treated infections with rituximab or IFN/GA. The number of hospital-treated infections was divided by the accumulated person-time during follow-up to calculate the overall incidence rate (IR) of infection, as well as by age at start of DMT (<40 years, ≥40 years, or unknown), sex, type of MS (RRMS; secondary progressive MS [SPMS], primary progressive MS [PPMS], or unknown), region of care (Stockholm, western Sweden, southern Sweden, middle part of Sweden, northern Sweden, south-eastern Sweden, or unknown), and Charlson Comorbidity Index (0, 1, or ≥2). We calculated the adapted version for Charlson Comorbidity Index as described previously, using data from the Swedish Patient Register.[24]

In analysis 2, using the same cohort, we used Cox model to assess the relative risk of incurring a hospital-treated infections while exposed to rituximab as compared to IFN/GA. We used time since the start of each treatment episode as the underlying time scale and the first hospital-treated infection during the treatment episode as outcome. As individuals could have multiple treatment episodes, we applied a robust sandwich estimator to adjust for the relatedness between multiple records of the same individual. All analyses were adjusted for age and calendar year (as continuous variables), as well as sex, MS subtype, and region of care (as categorical variables). As disability status may influence both the choice of DMT and the risk of infection, we further included EDSS as a continuous variable at the start of the treatment episode. Accordingly, we restricted analysis 2 to PwMS with a recorded EDSS before the start of a treatment episode. In addition to any infection, we also analyzed severity of infection (inpatient- or outpatient-treated), and type of infection (bacterial, viral, or other infections). In a sensitivity analysis, instead of focusing on first event of hospital-treated infection, we studied all events of hospital-treated infections as the outcome, to examine whether associations differed for first infection and repeated infections.

In analysis 3, we used a doubly robust generalized estimating equations (drGEE) model conditioned on each PwMS,[25] to assess EDSS scores in relation to hospital-treated infections. This model generates an estimated mean difference in EDSS scores in relation to the exposure (ie, an infection), necessitating restriction of the study population to those with ≥2 EDSS scores within a treatment episode. The drGEE model inherently controls for

unmeasured time-invariant confounders within an individual, and we adjusted for time since start of a treatment episode to eliminate the influence of natural disease progression (ie, EDSS change) over time (model 1). To assess if the effect of infections was modified by other variables, we additionally modelled an interaction between infection and DMT (model 2), an interaction between infection and MS subtype (model 3), or both (model 4). To assess the robustness of the findings, we also performed several sensitivity analyses. First, to eliminate a potential short-term impact of severe infections on EDSS score, we excluded EDSS scores recorded within 3 months of an inpatient-treated infection. Second, to assess the validity of the drGEE model, we additionally performed subgroup analyses by MS subtype, using the between-within linear mixed model.[26] This analysis was adjusted for age, sex, region of care, calendar year, number of infections, Charlson Comorbidity Index, and DMT (model 1), as well as an interaction between infection and DMT (model 2).

In analysis 4, we integrated neuroimaging data into our analysis by including RRMS patients with ≥2 brain MRI scans, at least 1 of which was conducted during a treatment episode. MRI activity was defined as newly appearing/enlarging T2 lesions as compared to a previous scan. Regular MRI monitoring with variable intervals has been part of clinical routine in Sweden since long. However, national guidelines implemented in 2016 stipulated annual scans for PwMS below 60 years, with total T2 lesion counts and numerical change of the MRI examination recorded in the SMSreg.[27] We did not consider contrast enhancing lesions as such sequences are not recommended for routine follow-up, leading to possible bias between time periods and treatment groups. Treatment episodes were segmented according to intervals between consecutive MRI scans, which were then categorized as MRI active/inactive, or of unknown MRI status (lack of data). Subsequently, we stratified disability progression (defined by a worsening in EDSS score steps as defined above) according to MRI activity. Further, we calculated the proportion of PwMS with or without a history of at least 1 inpatient-treated infection.

Finally, in analysis 5, we used piece-wise exponential regression to assess the association of hospital-treated infections with disability progression, after controlling for relapses and MRI activity as 2 time-varying covariates. We used time since start of DMT as the offset term and adjusted for age, sex, region of care, Charlson Comorbidity Index, and calendar year. To validate the robustness of this analysis, we prolonged the sustained time for defining disability progression from 3 to 6 months.

All analyses were conducted in Python (version 3.8) and R software (version 4.1). A 2-sided $p < 0.05$ was considered statistically significant.

Results

We found an overall IR of 35.5 and 94.6 per 1,000 person-years for inpatient- and outpatient-treated infections during treatment episodes with rituximab, respectively. The corresponding numbers for IFN/GA were 15.2 and 47.6 per 1,000 person-years, respectively (Table 1). We observed a comparable incidence rate of hospital-treated infections in RRMS during the study period to that in our previous study (Table S2).[28] A progressive disease type (PPMS or SPMS), older age at start of DMT (≥40 years), and male sex were independently associated with a higher IR of inpatient-treated infections in both DMT groups. Comparing the 2 DMTs using Cox model, rituximab was significantly associated with a more than doubled risk of inpatient-treated infections and a 26% (95% CI, −5% to 66%) higher risk of outpatient-treated infections, compared with IFN/GA (Table 2). The estimates were similar across different types of infection (Table S3), as well as in the sensitivity analysis considering repeated infections, instead of only the first event of infection (Table S4).

In the subsequent analysis using drGEE model, we observed that an event of inpatient-treated infection was associated with a 0.19-unit increase in EDSS, on average. Additionally, when comparing this association across MS subtypes and types of DMT, we identified statistically significant interactions (Table 3). Hence, the overall association for increase in EDSS with inpatient-treated infections was mainly driven by progressive MS and treatment episodes with IFN/GA, although a similar pattern was not seen for outpatient-treated infections. Censoring of EDSS scores recorded within 3 months of an inpatient-treated infection rendered similar findings (Table S5). The between-within linear mixed model applied to sub-groups corroborated the general findings of the drGEE model; however, it also indicated a significant association between EDSS increase and inpatient-treated infections across all MS subtypes (Table S6). Notably, a significant interaction between IFN/GA and inpatient-treated infections was observed exclusively in RRMS, but not in progressive MS-forms (see Table S6).

In an additional analysis, we also incorporated MRI data for 3,470 and 3,776 treatment episodes with rituximab and IFN/GA, respectively. We recorded 350 (10.1%) and 714 (18.9%) events of disability progression under treatment episodes with rituximab and IFN/GA, respectively (Table 4). The distribution by MRI status differed between rituximab and IFN/GA. Specifically, disability worsening with MRI activity following infection was very uncommon for rituximab (1 case with MRI activity vs 17 cases without MRI activity); the corresponding numbers were 12 and 18 for IFN/GA, respectively. Furthermore, the relation between episodes with previous infections leading or not leading

TABLE 1. Incidence rate of hospital-treated infections during treatment episodes with rituximab or IFN/GA

Characteristics	Rituximab			IFN/GA		
	No. (incidence rate, per 1,000 person-years) of hospital-treated infections					
	No. of treatment episodes	Inpatient-treated infection	Outpatient-treated infection	No. of treatment episodes	Inpatient-treated infection	Outpatient-treated infection
Overall	7,561	1,058 (35.5)	2,817 (94.6)	8,759	728 (15.2)	2,282 (47.6)
Age at start of DMT						
<40 years	3,038	377 (31.0)	1,396 (114.8)	4,661	310 (13.0)	1,260 (52.8)
≥40 years	4,038	626 (39.1)	1,284 (80.2)	3,712	386 (17.6)	936 (42.7)
Unknown	485	55 (34.2)	137 (85.1)	386	32 (14.7)	86 (39.6)
Sex						
F	5,227	664 (32.5)	2,198 (107.7)	6,327	480 (13.8)	1811 (52.2)
M	2,334	394 (42.1)	619 (66.1)	2,432	248 (18.7)	471 (35.5)
Type of MS						
PPMS	420	77 (47.8)	103 (64.0)	254	43 (38.3)	77 (68.6)
RRMS	5,724	561 (25.3)	2,125 (95.8)	6,235	346 (10.3)	1,546 (45.9)
SPMS	1,365	393 (67.7)	562 (96.8)	2,131	311 (25.6)	581 (47.8)
Unknown	52	27 (140.0)	27 (140.0)	139	28 (27.4)	78 (76.2)
Region of care						
Stockholm	2,204	321 (36.3)	1,170 (132.3)	1985	159 (15.7)	688 (68.1)
Western Sweden	1,082	140 (35.9)	243 (62.4)	1,566	122 (13.4)	417 (45.8)
Southern Sweden	1,020	139 (39.2)	281 (79.2)	1,633	113 (12.0)	469 (50.0)
Middle Sweden	1,152	114 (25.9)	403 (91.6)	1,235	122 (18.7)	268 (41.1)
Northern Sweden	1,266	186 (31.0)	420 (70.0)	1,201	114 (19.2)	204 (34.3)
South-eastern Sweden	837	158 (51.1)	300 (97.0)	1,126	96 (14.1)	229 (33.7)
Unknown				13	2 (19.1)	7 (66.8)
Charlson Comorbidity Index						
0	7,304	968 (33.9)	2,638 (92.3)	8,513	718 (15.3)	2,228 (47.6)
1	118	59 (97.1)	123 (202.5)	138	6 (9.2)	27 (41.6)
≥2	139	31 (51.3)	56 (92.7)	108	4 (8.2)	27 (55.3)

DMT = disease-modifying therapy; F = female; M = male; MS = multiple sclerosis; PPMS = primary progressive MS; RRMS = relapsing–remitting MS; SPMS = secondary progressive MS.

to disability worsening differed between the 2 DMTs. Namely, only 20 of 212 events (9.4%) of hospital-treated infection were associated with worsening disability under treatment episodes with rituximab, whereas the corresponding number for IFN/GA was 43 of 161 (26.7%).

In the final analysis, using piece-wise exponential model, we found that inpatient-treated infections were significantly associated with an increased risk of disability progression after controlling for relapses and MRI activity among patients treated with IFN/GA, but not among those treated with rituximab (Table 5). The sensitivity

TABLE 2. HR and 95% CI for experiencing at least 1 hospital-treated infection during treatment with rituximab, compared to treatment with IFN/GA

Severity of infection	Incidence rate per 1,000 person-yr (no./person-yr)		
	IFN/GA	Rituximab	HR (95% CI)
Inpatient-treated infection	12.38 (191/15,430)	25.74 (605/23,505)	2.27 (1.39–3.69)
Outpatient-treated infection	38.24 (536/14,016)	61.82 (1,321/21,369)	1.26 (0.95–1.66)

Estimated using Cox models adjusted for age, sex, type of MS, region of care, calendar year, and EDSS at start of treatment episode.
CI = confidence intervals; EDSS = Expanded Disability Status Scale; HR = hazard ratio; IFN/GA = interferons and glatiramer acetate; MS = multiple sclerosis.

TABLE 3. Hospital-treated infections and EDSS scores

Model		Inpatient-treated infections			Outpatient-treated infections		
		Mean difference (β)	Robust standard error	*p* Value	Mean difference (β)	Robust standard error	*p* Value
Model 1	Infection	0.189	0.036	<0.001***	0.015	0.012	0.219
Model 2	Infection	0.089	0.040	0.028*	−0.046	0.021	0.033*
	Infection*DMT (IFN/GA vs rituximab)	0.267	0.096	0.005**	0.095	0.034	0.006**
Model 3	Infection	0.104	0.04	0.010*	0.008	0.017	0.635
	Infection* (PPMS vs RRMS)	0.202	0.124	0.102	0.036	0.125	0.775
	Infection* (SPMS vs RRMS)	0.236	0.096	0.014*	0.017	0.029	0.567
Model 4	Infection	−0.031	0.059	0.597	−0.032	0.018	0.078
	Infection* (PPMS vs RRMS)	0.260	0.124	0.035*	0.037	0.125	0.767
	Infection* (SPMS vs RRMS)	0.306	0.119	0.010*	−0.029	0.029	0.316
	Infection*DMT (IFN/GA vs rituximab)	0.317	0.112	0.005**	0.092	0.032	0.004**

Model 1 was derived from doubly robust GEE model conditioned on individuals, adjusted for time since start of treatment episode; model 2 was additionally modelled for an interaction term between infection and DMT (ie, IFN/GA vs rituximab) based on model 1; model 3 was additionally modelled for an interaction term between infections and subtype of MS based on model 1; model 4 was additionally modelled for both interaction terms based on model 1.
DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; GEE = generalized estimating equations; IFN/GA = interferons and glatiramer acetate; MS = multiple sclerosis; PPMS = primary progressive MS; RRMS = relapsing–remitting MS; SPMS = secondary progressive MS.
*$p < 0.05$, **$p < 0.01$, ***$p < 0.001$.

analysis extending the time of validating a sustained EDSS increase to 6 months, including 330 events of disability progression with rituximab in RRMS and 676 with IFN/GA, yielded findings consistent with the main analysis (Table S7).

Discussion

Leveraging a large population-based real-world cohort of PwMS treated with BCDT (rituximab) or IFN/GA, we identified an association between infectious events and worsening of MS disability status. The magnitude of worsening was greatest for inpatient-treated infections, in individuals with a progressive disease course, and with treatment with IFN/GA. Given the possibility that infections impact mechanisms related to both RAW- and PIRA-related disability worsening, we also conducted analyses adjusted for relapses and neuroimaging outcomes.

TABLE 4. Disability progression and inpatient-treated infections during treatment episodes with rituximab or IFN/GA in RRMS

			Preceding infections in subpopulations with		
	Disability progression	No disability progression	Disability progression	Disability progression without MRI activity	Disability progression with MRI activity
Rituximab (n = 3,470)	350/3470 (10.1%)	192/3120 (6.1%)	20/350 (5.7%)	17/309 (5.5%)	1/9 (11.1%)
IFN/GA (n = 3,776)	714/3776 (18.9%)	118/3062 (3.9%)	43/714 (6.0%)	18/326 (5.5%)	12/170 (7.1%)

IFN/GA = interferons and glatiramer acetate; MRI, magnetic resonance imaging; RRMS = relapsing–remitting multiple sclerosis.

We could detect an association between inpatient-treated infection and disability progression independent of relapses during treatment episodes with IFN/GA for RRMS. Further, these patients also displayed greater risk of MRI lesion accrual associated with such events. However, there was also an increased proportion with history of infection in the IFN/GA cohort suffering disability progression without MRI activity as compared with rituximab.

The finding of an increased risk of infections in relation to BCDT compared with older IFN/GA platform drugs is in line with our previous study with partly overlapping study participants.[28] We observed similar incidence rates of infection for both DMTs during the time periods examined in the earlier study.[28] However, some important differences should be underscored. In the present study, we had access to longer follow-up time, and included all MS subtypes and a wider range of infections identified through the Swedish Patient Register.

TABLE 5. HR and 95% CI for disability progression in relation to hospital-treated infections in RRMS

	HR (95% CI)
Rituximab	
Inpatient-treated infection	1.13 (0.78–1.63)
Outpatient-treated infection	1.04 (0.90–1.20)
IFN/GA	
Inpatient-treated infection	2.01 (1.59–2.53)
Outpatient-treated infection	1.06 (0.94–1.20)

Model was derived from piecewise exponential regression, using time since start of treatment episode as the offset term, and adjusted for age, sex, region of care, Charlson Comorbidity Index, calendar year as well as MRI activity and relapses time-varying covariables.
CI = confidence interval; HR = hazard ratio; IFN/GA = interferons and glatiramer acetate; MRI, magnetic resonance imaging; RRMS = relapsing–remitting multiple sclerosis.

Treatment-related infections represent one of the primary concerns when assessing the benefit–risk balance of MS DMTs.[29] BCDT, such as ocrelizumab, ofatumumab, and rituximab, display superior efficacy, compared with active comparators, in preventing relapses in RRMS populations.[30–32] Ocrelizumab has also been shown to have superior efficacy in preventing disability worsening, compared with placebo, in PPMS patients.[19] Safety data obtained in randomized controlled trials, including open label extensions, do not suggest an increased risk of infections with BCDT compared with injectable or oral platform therapies.[30,31,33–36] This notion, however, contrasts with emerging data from real-world populations, including the present study, indicating that exposure to BCDT over longer time periods and in more heterogeneous populations increase the risk of infections compared with platform DMTs.[28]

We find that the association between infections and EDSS was greater for inpatient- compared to outpatient-treated infections, suggesting a relationship between severity of systemic inflammation and the risk of disability worsening. Existing evidence suggests that infections increase the risk of relapses and potentially also sustained EDSS worsening.[12–15] However, it is not known how this relates to the RAW/PIRA paradigm, or to what degree this is impacted by type of DMT. A main finding of this study is that risk of disability worsening is greater with progressive disease compared with RRMS. It may be speculated if this is indicative of systemic immune activation acting on underlying neurodegenerative processes being more prominent in those with a progressive disease course.[11] This notion is supported by both experimental studies and clinical observations.[37] For example, a more rapid cognitive decline is noted among patients with Alzheimer's disease with ongoing urinary tract infections, whereas inflammatory and neurodegenerative biomarkers measured in cerebrospinal fluid or via imaging have been shown to correlate with cognitive decline after major surgery.[38–41] Taken together, this calls for careful

evaluation of benefit–risk with BCDTs in PwMS in higher age groups and/or with a progressive disease course, especially with history of infections or co-existing risk factors such as diabetes. This also provides a rationale to further explore risk mitigation strategies such as extension of dosing intervals with BCDT.[42,43]

Another main finding is that the risk of suffering an increase in disability status was greater among RRMS patients treated with IFN/GA compared to rituximab when controlling for relapses. A separate analysis was conducted using MRI data, which revealed that individuals treated with IFN/GA suffering hospital-treated infections were more likely to display accrual of brain lesions. In turn suggesting that BCDT offers more effective suppression of adaptive immune activation potentially triggered by such events, compared with IFN/GA. However, it was also evident that RRMS patients who experienced disability progression without MRI activity had higher incidence of previous infections compared to those who did not experience disability progression, a pattern not observed in treatment episodes with rituximab. Admittedly, the distinction between RAW and PIRA-associated worsening is not possible to identify exactly, without access to both brain and spinal cord imaging. Further, a broader definition of relapses and longer follow up reduces the proportion with sustained disability worsening in RRMS.[6] Collectively, however, taking also into account our results on progressive MS and rituximab, our findings suggest that severe infections may impact both adaptive immune and neurodegenerative processes, thereby increasing the risk of worsening of MS disability.

Although our findings are based on data from a high-quality MS registry[21] and national registries with virtually complete coverage, our study has several limitations. First, treatment patterns for MS have changed greatly in Sweden with IFN/GA dominating in the first and rituximab in the second half of the study period. As a result, residual confounding because of unmeasured factors such as differences in the infectious panorama is possible, although we controlled for calendar period in all analyses to mitigate this risk. Second, the data density in SMSreg increased during the study period, meaning that frequency of EDSS assessments and MRI data was higher in treatment episodes with rituximab compared with IFN/GA. Therefore, unlike studies leveraging data from clinical trials with frequent and structured EDSS assessments and MRI scans, the more infrequent EDSS scores in our cohort might have delayed the identification of disability worsening or possible later improvement. Further, the longer interval between some MRI scans may misclassify the disability progression as MRI active when new lesions are observed. These factors also made it infeasible to apply the broader definition of relapse or stricter definitions of PIRA or progression independent of any inflammatory activity (PIA), as recently proposed.[6,44] To address this, we applied MRI activity and relapses as time-varying covariables in the piece-wise exponential model to avoid directly identifying PIA, thereby mitigating the risk of potential misclassification. However, despite applying a criterion of 6-month sustained disability worsening in the sensitivity analysis, a significant proportion of such worsening (either defined as PIRA or PIA) may improve in the long run.[6] Additionally, as shown in a large scale validation of the SMSreg data, proportions of relapses not registered in SMSreg were higher with IFN/GA than rituximab, although this mostly affected relapses occurring before treatment start.[21] Third, although inclusion of MRI data provides indications of underlying mechanisms, access to additional biomarkers such as brain atrophy rate or soluble protein markers,[9,45] would be needed to probe in greater detail the underlying disease pathology. Fourth, inpatient hospitalization may be linked to disability independently of chronic brain inflammation.[46] However, the minimal association observed in RRMS patients receiving rituximab indicates that the identified association with IFN/GA treatment cannot be solely ascribed to inpatient infection. Fifth, choice of DMTs and organization of health care differ between geographic areas, which may explain the higher incidence of reported infections for PwMS residing in the region of Stockholm, which has easier access to outpatient specialized care compared to other parts of the country. This potential confounding, however, is less likely to affect inpatient-treated infections. Finally, it is unclear to what degree our data on rituximab can be extrapolated to other BCDT.

In conclusion, we corroborate earlier findings of an increased risk of infections with rituximab, compared with traditional self-injected platform therapies, and further demonstrate an association between infections and worsening of disability status. The latter was mainly driven by inpatient-treated infections, progressive MS, and treatment episodes with IFN/GA. Notably, inpatient-treated infections were associated with an increased risk of disability progression among RRMS patients treated with IFN/GA, independent of relapses, whereas these individuals also displayed increased tendency to display neuroimaging disease activity. Collectively, these observations are important for evaluating the benefit–risk balance of MS DMTs and highlight the importance of risk mitigation and de-escalation strategies to optimize long term outcomes in MS.[47]

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Potential Conflicts of Interest

F.P. has received fees for serving on Data Monitoring Committees in clinical trials with Roche. The other authors have no conflicts of interest to report.

Authors Contributions

F.P., F.F., T.F., and Y.H. contributed to the conception and design of the study. T.F., F.P., Y.P., and Y.H. contributed to acquisition and analysis of data. T.F., H.S., P.A., Y.H., F.P., and F.F. contributed to drafting the text or preparing the figures.

Data Availability

The data from the SMSreg are not publicly available due to privacy or ethical restrictions. Researchers who meet the criteria for accessing this type of sensitive data can request them from the registry holders subject to a legal review and approval of a project-specific data sharing agreement.

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