INTRODUCTION

Several new disease-modifying therapies (DMTs) have emerged during the last decades for people with multiple sclerosis (MS), which brings both opportunities and challenges to daily praxis. There are multiple issues other than drug efficacy that must be addressed before deciding on treatment modality. Besides disease-related inflammatory aggressiveness and subjects’ susceptibility to drug-specific adverse events, subjects’ preferences, and cost-benefit aspects also have to be taken into consideration. As a consequence, a gap is developing between the national guidelines authorized by the Swedish Medical Products Agency and real-life treatment selection.

Sweden stands out with its high use of off-label rituximab (RTX), representing approximately 40% of all ongoing DMTs in MS care. Furthermore, a Swedish study that included subjects with MS from three tertiary academic hospitals showed that as many as 53.3% of all subjects were given RTX as the primary DMT for MS. The published data extracted from the Swedish MS registry show increased...
off-label use of RTX for both relapsing-remitting MS (RRMS) and progressive disease (PMS).

Rituximab is a chimeric anti-CD20 monoclonal antibody initially mainly used by oncologists and rheumatologists for blood malignancies and certain forms of vasculitis in rheumatoid arthritis.4,5 RTX has also shown effects in neurological conditions such as myasthenia gravis and chronic inflammatory demyelinating neuropathy.6,7 Favorable properties of RTX are the strong efficacy data shown by two randomized studies,8,9 its acceptable safety profile, and the 6- to 12-month treatment interval. Furthermore, a recent retrospective comparative study showed that RTX in RRMS was superior to all other DMTs in terms of drug discontinuation, and with better clinical efficacy compared with injectable first-line DMTs and oral dimethyl fumarate.10

Although highly effective in MS, RTX does have important safety aspects due to its immunogenicity and immunosuppressive potential. The most common adverse event relates to the cytokine outflow following CD20 B-cell lysis, which constitutes a risk of infusion-related adverse reactions. Moreover, RTX secondary immunosuppression due to B-cell depression implies susceptibility to severe infections.11,12 A recently published register-based study by Luna et al13 showed that rituximab for MS was associated with the highest rate of serious infections compared with natalizumab, fingolimod, interferon beta, and glatiramer acetate.

Several published university hospital-based observational studies have shown that rituximab is highly effective for treating MS with an acceptable safety profile.14-16 However, until now there have been no previous publications regarding RTX efficacy from neurological units at non-regional hospitals, with sparse experience from RTX treatment of other diagnoses with approved indications for RTX.

The aim of this observational registry-based study was to evaluate the effect and safety of off-label rituximab treatment for MS in a population-based cohort treated at a Swedish secondary hospital, Helsingborg General Hospital, with a catchment area of 250 000 inhabitants.

2 | MATERIALS AND METHODS

2.1 | Study design

This study is a retrospective, observational, registry-based, longitudinal study of RTX treatment for definite MS (ICD G35.9) and its subtypes RRMS and PMS at secondary hospital level.

2.2 | Ethics

Access to data in the Swedish National MS Registry for research purposes was in accordance with the registry regulations and was granted by the National Swedish Registry holder. Ethical permission for retrospective analysis of data extracted from subjects' records was given by the Swedish Ethical Review Authority.

2.3 | Data collection

The Swedish National MS Registry was searched to identify subjects eligible for inclusion. Only data from people with MS treated by the day-care clinic at Helsingborg General Hospital were available for the research group. Inclusion criteria were as follows: (a) a definite diagnosis of MS, (b) at least one infusion of RTX given up until March 2019, and (c) available data regarding efficacy and safety during treatment follow-up.

The data collected from hospital-based medical records were as follows: (a) demographics, (b) DMT before starting on RTX, (c) RTX treatment-related data including initiation, duration, and discontinuation, (d) long-term follow-up evidence of disease activity, (e) long-term follow-up of adverse events, and in selected cases (f) estimates of IgG antibodies and B-cell deprivation time-locked to RTX infusions.

2.4 | Follow-up parameters

Clinical worsening of disease (CWD) was defined as a functional decline affecting subjects’ everyday life activities. Parameters considered were as follows: (a) increased weakness of lower extremities affecting walking distance or requiring a change in aids for locomotion (crutches, walker, or wheelchair), (b) impaired coordination or development of paralysis in upper extremities, or (c) loss of bladder and/or bowel control requiring medication and/or intermittent catheterization. MS fatigue and Expanded Disability Status Scale (EDSS) scores were considered uncertain information for evaluating CWD due to the lack of systematic data in medical records at outpatient visits.

A relapse was defined as new neurological symptoms, or worsening of previously existing symptoms, lasting for a minimum of 24 hours and without the presence of fever or infection. The symptoms had to be confirmed and documented in medical records as a relapse indicating EDA. The annual relapse rate 2 years before RTX initiation and up until the last follow-up before March 1, 2019, was registered in the study database.

Magnetic Resonance Imaging (MRI) evidence of disease activity was gathered from radiologists’ interpretations from written reports for estimating new MS lesions. Follow-up scans were compared to the most recent previous MRI evaluation. New lesions, and whether or not the new lesions were gadolinium-enhancing, were registered in the study database. Gadolinium enhancement was considered as ongoing inflammatory activity, and T2-weighted circumscribed increased signal intensities were considered as inflammatory lesions of an earlier date.

Adverse events were recorded in the database when documentation was found in subjects’ records, that is, ongoing symptoms witnessed by caregivers or in connection with an outpatient visit or hospitalization. Amnestic events were not included as they were considered to be uncertain information.

I) Infusion-related adverse events that occurred during the intravenous RTX treatment or within 1 week were classified as follows:
• Minor—when no action besides lowering the infusion pace was taken, or
• Major—when infusion was interrupted and action was taken to treat or diagnose.

II) Non-infusion-related adverse events that occurred later than 1 week after the latest RTX infusion were classified as follows:

• Mild—no treatment or treatment was given without the need for inpatient care, or
• Moderate—with hospitalization but without persistent disability, or
• Severe—potentially life-threatening.

2.5 | Statistics

Statistical Package for the Social Sciences (IBM SPSS Statistics: Windows, version 25.0.: IBM Corp.) was used for analyses. Statistical significance was defined as a two-tailed P-value below .05. Kaplan-Meier survival plots were used to estimate and visualize the proportion of subjects free of CWD.

Since ARR and the number of contrast-enhancing lesions per MRI were not normally distributed, differences between groups were calculated using Wilcoxon signed-rank test.

A comparison between the number of subjects with new lesions on baseline MRI, and with new lesions on MRI during treatment, was carried out using McNemar’s test.

3 | RESULTS

3.1 | Study population and treatment

Three hundred and thirty-three potentially eligible subjects with a MS diagnosis were listed at Helsingborg General Hospital at the time of study inclusion (March 1, 2019). Four of the 333 subjects treated with the biosimilar Ritemvia® were excluded from the analysis due to possible differences in side effect profile compared with RTX (MabThera®). Eighty-six of the 333 subjects had been exposed to RTX (n = 74 on RTX treatment at inclusion; n = 1000 mg every 6-12 months. The most common RTX dosage during the follow-up period was 500 mg (n = 79 or 95%), and the most common RTX treatment interval was 6 months (n = 72 or 87%). Routine clinical follow-up was carried out at 6- to 12-month intervals (mean: 8.9 months ± 3.3 SD, range: 2-31 months). In the event of worsening of disease, subjects were asked to contact the clinic for an extra visit.

3.2 | Follow-up parameters

Figure 1 shows the proportion of subjects on RTX that were without CWD during a 3-year follow-up after treatment initiation. The Kaplan-Meier plot illustrates the higher magnitude of the RTX-induced decrease in clinical disease activity in the RRMS group compared with PMS. Fifteen of the 83 subjects had CWD on RTX treatment with a cumulative survival of 86% in RRMS and 30% in PMS of subjects without CWD.

Figure 2 shows the highly significant change in annual relapse rate (ARR) before and after RTX initiation. Subjects free from clinical relapses and with <1 year of follow-up were excluded from this first analysis group (n = 19). In the remaining cohort of 64 subjects (RRMS n = 50; PMS n = 14), ARR dropped from mean 0.38 ± 0.5 SD before rituximab initiation to mean 0.05 ± 0.19 SD at follow-up (P < .00001). Thirty-three subjects suffered relapses during the 2 years prior to RTX initiation (RRMS n = 26, PMS n = 7) compared with eight subjects, all in the RRMS cohort, during the entire follow-up period after RTX initiation (median: 23.5, range: 1-76 months). The majority of relapses (n = 6; 75%) occurred within a year of RTX initiation.

Figure 3 shows subjects with MRI visualized disease activity 1 year before RTX initiation compared with follow-up. Follow-up MRIs were routinely scheduled at 6- to 12-month intervals or when clinically indicated (mean: 11.6 ± 5.4 SD, range: 3-34 months), only the scans that detected new lesions were visualized in the graph. New enhancing lesions were mainly seen during the first year after RTX initiation.

Among the 76 subjects (n = 60 RRMS; 13 primary PMS; three secondary PMS), baseline MRIs showed new inflammatory lesions in 44 (58%) compared with 20 (26%) during the long-term follow-up. Subjects with no available MRI at baseline or during the first year of follow-up were excluded (n = 7). In the RRMS branch (n = 60), the number of new lesions dropped from 36 to 18 (P < .0001), and in PMS (n = 16) from eight to two (P = .07).

For comparison with other studies, we carried out a second analysis including only contrast-enhancing lesions (CELs), with a homogenous baseline and follow-up period of 1 year before and 1 year after RTX initiation. One or more CELs were seen in 39/83 (47%) subjects at baseline (145 CELs/154 MRIs) compared with 5/83 (6%) subjects (18 CELs/74 MRI scans) during the first year after RTX initiation. Enhancing lesions per MRI investigation yielded a ratio of CELs/MRI that dropped from 0.94 to 0.24 (P < .00001). In the RRMS cohort, 1.05 CELs/MRI (136 CELs/129 MRI scans) dropped to 0.31 (P = .00003). No CELs were seen in the PMS subtypes after RTX initiation.
TABLE 1 Baseline characteristics of 83 subjects that had received at least one rituximab infusion for multiple sclerosis (MS), managed at a general hospital in Helsingborg, Sweden

|                          | RRMS (pts n = 66) | SPMS (pts n = 13) | PPMS (pts n = 4) | Total (pts n = 83) |
|---------------------------|-------------------|-------------------|------------------|-------------------|
| Age in years, mean (range)| 41.5 (17-69)      | 51 (40-69)        | 48.5 (45-58)     | 44 (17-69)        |
| Female, n (%)             | 42 (63.6)         | 11 (84.6)         | 2 (50)           | 55 (66.3)         |
| Disease duration in years, mean (range) | 5.8 (0.0-25.7) | 17.1 (4.6-26.3) | 1.7 (0.3-2.1) | 6.4 (0.0-26.3) |
| Treatment time in months, mean (range) | 23 (2-76) | 20 (1-75) | 17.5 (6-60) | 23.5 (1-76) |
| Patients with new lesions at baseline, n (%) | 35 (53) | 7 (53.8) | 1 (25) | 43 (51.8) |
| ARR the year before RTX initiation, median (SD) | 0.46 ± 0.6 | 0.38 ± 0.5 | 0.75 ± 0.74 | 0.46 ± 0.6 |
| Indication for RTX, n (%) |                    |                    |                  |                   |
| Inefficacy                | 20 (30.3)         | 3 (23.1)          | 1 (25)           | 24 (28.9)         |
| JCV positivity            | 16 (24.2)         | 3 (23.1)          | –                | 19 (22.9)         |
| Adverse events            | 16 (24.2)         | 2 (15.4)          | –                | 18 (21.7)         |
| Naïve                     | 10 (15.2)         | 4 (30.9)          | 3 (75)           | 17 (20.5)         |
| Patients request          | 3 (4.5)           | 1 (7.7)           | –                | 4 (5.8)           |
| ADA                       | 1 (1.5)           | –                 | –                | 1 (1.2)           |
| Previous DMT, n (%)       |                    |                    |                  |                   |
| NTZ                       | 27 (40.9)         | 4 (30.8)          | –                | 31 (37.3)         |
| No previous               | 10 (15.2)         | 4 (30.8)          | 3 (75)           | 17 (20.5)         |
| IFN                       | 11 (16.7)         | 2 (15.4)          | 1 (25)           | 14 (16.9)         |
| DMF                       | 10 (15.2)         | –                 | –                | 10 (12.0)         |
| GA                        | 4 (6.1)           | 1 (7.7)           | –                | 5 (6.0)           |
| FGM                       | 2 (3.0)           | 1 (7.7)           | –                | 3 (3.6)           |
| TFM                       | 2 (3.0)           | –                 | –                | 2 (2.4)           |
| IVIG                      | –                 | 1 (7.7)           | –                | 1 (1.2)           |

Note: Demographics, disease and treatment characteristics, rituximab indications, and previous disease-modifying treatments are displayed. Abbreviations: ADAs, antidrug antibodies; ARR, annual relapse rate; DMF, dimethyl fumarate; DMT, disease-modifying therapy; FGM, fingolimod; GA, glatiramer acetate; IFN, interferon; IVIG, intravenous immunoglobulin; JCV, John Cunningham virus; NTZ, natalizumab; PPMS, primary progressive multiple sclerosis; pts, patients; RRMS, relapsing-remitting multiple sclerosis; RTX, rituximab; SPMS, secondary progressive multiple sclerosis; TFN, teriflunomide.

FIGURE 1 Proportion of subjects without clinical worsening of disease after initiation of rituximab for multiple sclerosis (MS), managed at a general hospital in Sweden. Survival is displayed as a Kaplan-Meier plot over 36 mo for relapsing-remitting and progressive MS. The number of subjects at each estimate is given at the bottom of the graph.
Forty-eight infusion-related adverse events were documented in patient records. At least one infusion reaction was seen in 40 subjects (48%) with no clear decline in incidence over cycle time. Reactions were mostly mild (68% or 94.4%), and were thus classified as minor, even though intervention by lowering the infusion pace was considered necessary in many cases. The most common complaint was an itch in the throat during the infusion (n = 32). Four subjects experienced major infusion reactions requiring an intervention, and three out of four developed a chest rash during the first cycle of treatment. The fourth patient experienced a temporary shortness of breath during the 11th cycle, leading to a chest X-ray with no pathological findings. Treatment was temporarily stopped in all four subjects but was tolerated well when recommenced. New treatment was scheduled with 2-3 weeks' delay (mean: 18 days ± 3). Then, an increased dosage of corticosteroids and antihistamines was given as premedication and the infusion rate was set at a slower pace.

Table 2 shows the characteristics of 26 subjects who experienced non-infusion–related adverse events with a probable or possible link to RTX treatment. One or more events were seen in 26 of 83 subjects. Infection was the most frequent adverse event (n = 19 subjects or 34%) that required medical attention including antibiotics for 22 events. All infectious adverse events were judged as being possibly related to RTX immunosuppression, although IgG levels were consistently above 6 g/L. In one subject with 10 infections, the association of RTX was questioned due to a previous history of frequent urinary tract and respiratory infections requiring antibiotics. Four cases with RTX-related infectious adverse events were classified as moderate as they required hospitalization.

Two malignancies were registered after three and four cycles of treatment, a bladder tumor and a breast cancer. However, none of the malignancies were considered to be associated with RTX, as they were diagnosed only 18 months after first cycle of RTX treatment.

One subject experienced a severe adverse event: a 36-year-old woman with pneumonia and concomitant neutropenia. The event was classified as potentially life-threatening. The patient was hospitalized for 4 days with an initial neutrophilic count of 0.1 × 10^9/L and was given both piperacillin/tazobactam (Tazocin®) and granulocyte-colony stimulating factor (G-CSF, Zarzo®). As the fourth RTX cycle had occurred within 6 months prior to the neutropenia, the event was considered a late-onset neutropenia, probably related to the RTX treatment. The patient had a recurrence of neutropenia (neutrophilic 0.6 × 10^9/L) 2 weeks after leaving the hospital and was then put on a twice-weekly G-CSF regimen for 10 months. The RTX regimen was resumed, and interval was changed to once year instead of every 6 months. The further treatment was well-tolerated during 6 months of follow-up, and MRI at 4 months did not reveal new lesions.

### 3.3 | Discontinuation

Twelve subjects discontinued RTX treatment during the follow-up period (RRMS 9, secondary PMS 3).

The reasons for discontinuation in the RRMS group were as follows: infections (n = 5, RRMS 3; PMS 3), pregnancy (n = 2), conversion to secondary progression (n = 2), RTX antibodies (n = 1), infusion-related rash (n = 1), and infusion-related tachycardia (n = 1).

The one subject that discontinued due to antibodies against RTX had incomplete B-cell depletion, and thus, immunological efficacy was questioned although no relapses or new lesions on MRI were seen while on RTX. The only available ADA test in the cohort was from this case. The treatment was stopped after discussion at the regular scheduled management round because of a potential risk of RTX inefficacy.

### 4 | DISCUSSION

This retrospective observational study of off-label RTX treatment for MS was performed at a single center in northern Europe, Helsingborg General Hospital in southern Sweden, serving a catchment area of 250 000 inhabitants. RTX dramatically reduced the annual clinical relapse rate as well as new lesions on MRI, most prominently seen in the RRMS group. RTX-related immunogenicity may have been the pathophysiological mechanism behind a late-onset neutropenia, a severe adverse event that has not previously been reported for RTX treatment of MS in Sweden.\(^{17}\) The importance of our study was to evaluate the effectiveness and safety of RTX for MS in a general hospital outpatient environment, which has previously not been investigated.

The RTX effectiveness in this study is similar to that previously reported in university hospital-based studies for MS treatment.\(^{14,16,18}\) Disease activity, both clinical and radiological, was significantly reduced by RTX. The annual relapse rate was reduced by 87%. For comparison, two university hospital-based studies
in Spain and Lebanon showed ARR reductions of 88% and 89%, respectively.¹⁴,¹⁶

In our full cohort, CELs were seen in 47% at baseline vs 6% at follow-up, and CELs/MRI investigation was 0.90 vs 0.06. Notably is that most scans showing contrast enhancement were done within 6 months after starting therapy. Therefore, the most interesting finding is the total absence of new lesions in 64/76 patients during the remaining follow-up period. As comparison between early follow-up scans and previous scans before starting therapy cannot deduce therapeutic efficacy, the previously published university hospital-based studies showed comparable results for MRI activity. Salzer et al¹⁸ found CELs in 26.2% at baseline vs 4.6% at follow-up, and CELs/MRI was 0.8 vs 0.054. New enhancing lesions were seen in 81.4% vs 7.4% in the Lebanese, and 2.56 CELs/MRI vs 0.06 in the Spanish, cohorts.¹⁴,¹⁶

The results for new lesions differ between studies, as different measurements for comparison have been chosen. Gadolinium enhancement is a temporary biological marker signaling active inflammation in the central nervous system that will be converted to T2 signal intensities within days to weeks. Accordingly, when only CELs are reported, a difference in numbers between studies is expected as radiological sampling is carried out at predetermined intervals. Consequently, our primary choice, in contrast to Alcalá et al and Saltzer et al, was to report all new lesions, not only those with enhancement. The common nominator, despite the choice of MRI measurement for monitoring efficacy, is a significant and impressive drop in new lesions after RTX initiation as reported by us as well as others.¹⁴,¹⁸

There is some difference between results in this and previous studies concerning secondary infectious adverse events. In this study, 19/83 subjects (22%) had infections during the follow-up period of which four cases (4.8%) required hospitalization. Alcalá et al reported 14/90 (16%) subjects with common infections, none of

**FIGURE 3** Efficacy of rituximab for multiple sclerosis (MS) evaluated by new lesions on MRI, managed at a general hospital in Helsingborg, Sweden (n = 76). Subjects with relapsing-remitting MS are shown with blue arrows and progressive MS with red arrows. Follow-up scans were compared with the most recent previous MRI. Yellow dots denote scans with enhancement in ≥1 lesion at a single MRI evaluation, and black dots denote new lesions without enhancement.
which were categorized as severe. Yamout et al reported infections among 14/89 (15.7%) subjects, including one severe (1.1%). The higher incidence of mild infectious adverse events in our study might be explained by differences between countries’ documentation routines and access to relevant information in medical records.

Salzer et al reported a lower incidence of infections than our study, seen in 9.2% and 34% of subjects, respectively. In contrast to our report, they did not count lower urinary infections and respiratory tract infections as the data had low sensitivity in their material. This probably explains at least part of the difference. More importantly, safety—that is, the number of serious infectious adverse events—differed. Saltzer et al reported 1.7% vs the 4.8% reported in our study. A selection bias due to the limited number of subjects in our study may explain this difference. However, our numbers are similar to those found in the early randomized controlled trials (RTCs) of RTX for MS, where serious infections associated with RTX treatment occurred in 2.9% and 4.5% of subjects.8,9 We are aware of that Salzers’ study and both RTCs used the Common Terminology Criteria for Adverse Events scale (CTCAES) for classification of adverse events. In our simplified although comparable scale, hospitalizations and life-threatening consequences correspond to moderate or severe adverse events, which are criteria included in grade 3 and grade 4 events in the CTCAES.

We also present, to our knowledge, the first Swedish case of late-onset neutropenia (LON) in connection with RTX treatment for MS. There has only been one previous report on the subject of LON among RTX-treated subjects with MS.19 Treatment was discontinued and switched to dimethyl fumarate, in contrast to our patient’s regime of a combination of G-CSF and yearly RTX infusions. The treatment decision by clinicians at Helsingborg general hospital was supported by studies of RTX in hematologic malignancies suggesting that concurrent therapy with RTX and G-CSF is not only well-tolerated, but actually enhances the B cell–depleting effect of RTX without an increase in adverse RTX toxicity.20,21 Our findings strengthen the assertion that vigilance for adverse events due to RTX immunogenicity is warranted, as the incidence of LON in rheumatologic

### Table 2

| Adverse events                              | Mild (pts n = 21) | Moderate (pts n = 5) | Severe (pts n = 1) | Total (pts n = 26) |
|---------------------------------------------|-------------------|----------------------|-------------------|-------------------|
| Infectious                                  |                   |                      |                   |                   |
| UTI                                         | 8                 | 1                    | -                 | 9                 |
| Pneumonia                                   | 5                 | 1                    | 1                 | 7                 |
| Eye infection                               | 7                 |                      | -                 | 7                 |
| Viral infection                             | 6                 |                      | -                 | 6                 |
| Lyme disease                                | 1                 |                      | -                 | 1                 |
| Fungal                                      | 1                 |                      | -                 | 1                 |
| URI                                         | 2                 |                      | -                 | 2                 |
| Impetigo                                    | 1                 |                      | -                 | 1                 |
| Tonsillitis                                 | 1                 |                      | -                 | 1                 |
| Influenza                                   | 1                 | 1                    | -                 | 2                 |
| Toe infection                               | 1                 |                      | -                 | 1                 |
| Sinusitis                                   | 1                 |                      | -                 | 1                 |
| Herpes zoster                               | 1                 |                      | -                 | 1                 |
| Other                                       |                   |                      |                   |                   |
| Dermatologic                                | 6                 |                      | -                 | 6                 |
| Abdominal pain                              | 6                 |                      | -                 | 6                 |
| Chest pain                                  | 4                 |                      | -                 | 4                 |
| Vertigo                                     | -                 | 1                    | -                 | 1                 |
| Syncope                                     | -                 | 1                    | -                 | 1                 |
| DVT                                         | 1                 |                      | -                 | 1                 |
| Total                                       | 53                | 5                    | 1                 | 59                |

Note: Adverse events were categorized as follows: mild = with no or minor need for intervention, moderate = with hospitalization but without persistent disability, or severe = potentially life-threatening.

Abbreviations: DVT, deep vein thrombosis; pts, patients; URI, upper respiratory infection; UTI, urinary tract infection.

1 One mild adverse event and one moderate adverse event were seen in a single subject at different time points.

2 Subject with a late-onset neutropenia concomitantly with pneumonia.
conditions has been reported to be 5%-7% and in hematologic malignancies 3%-27%.22,24

Twelve subjects in our study discontinued treatment, in one case due to antidrug antibodies (ADAs) against RTX. In our case, it may be a coincidence that this very patient did not experience any CWD or relapses while on RTX. However, in a cross-sectional study by Dunn et al.,25 samples were collected from 339 RTX-treated subjects with MS to determine the clinical relevance of ADA. The authors showed that RTX was associated with a high degree of ADA, which in turn correlated significantly with incomplete B-cell depletion. However, no clinical significance of ADA could be ascertained. There is no consensus on the matter of whether RTX treatment should be stopped based on the presence of ADA when evidence of disease activity is absent, as previously discussed in an article by Phiel and Hillert.2

As pointed out in our introduction, there is a rapid increase in the use of RTX for MS in Sweden, not only as an alternative when previous DMT was ineffective, but also as a first-line therapy. By June 2017, over 50% of all treatment naïve subjects with MS in Sweden received RTX as their first DMT.3 This growth has recently resulted in the Swedish Ministry of Health and Social Affairs planning a risk-benefit analysis of off-label RTX use, underlining the importance of our study.

4.1 | Limitations

Although data were extracted retrospectively, we would like to emphasize that it was originally collected prospectively and recorded in the Swedish MS registry during outpatient visits. The most important limitation, besides the retrospective design with lack of control group, is that the observed cohort was 83 subjects which gives the statistical results less impact in comparison with larger registry studies. However, the results are concordant with previous studies which indicate reliability. Secondly, no radiologists were involved in the research group for a blinded re-evaluation of MRI investigational images as part of our study; instead, MRI data were extracted from medical charts. This creates another layer of interpretation which may result in a margin of error. This implies an uncertainty, particularly regarding the correct number of new non-enhancing lesions, and we therefore analyzed MRI lesions as a binary outcome. Last, the irregular entry of EDSS scores by the clinicians documenting visits to the outpatient clinic in the medical charts is a limitation. A number of subjects lacked sufficient documentation, and proper conclusions from an analysis of the EDSS scores were therefore considered inappropriate.

5 | CONCLUSIONS

Rituximab was a frequently used off-label therapy against MS at Helsingborg General Hospital, often as a first-line treatment. This study shows that RTX for MS is as effective and safe at general hospital level compared with previous reports from university hospital-based studies. Most adverse events and reactions seem to be mild and require little or no intervention. However, the number of serious adverse events found in our cohort underlines the importance of monitoring to identify secondary immunosuppressive-related infectious adverse events and signs of negative treatment-related immunogenicity at an early stage (see Data Availability Statement).

ACKNOWLEDGMENTS

This study was supported by independent research grants from the Stig & Ragna Gorths Foundation, Thelma Zoegas Foundation, and the Region Skåne funding organization.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interests.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Läkemedelsverket. Läkemedelsbehandling vid multipel skleros (MS) - behandlingsrekommendation: Information från Läkemedelsverket. 2015. https://lakemedelsverket.se/upload/hals-och-sjukvard/ behandlingsrekommendationen/Lakemedelsbehandling_av_multipel_skleros_MS_behandlingsrekommendation_webb.pdf. Accessed December 21, 2015.
2. Piehl F, Hillert J. Rituximab is an acceptable alternative to oc- relizumab for treating multiple sclerosis - yes. Mult Scler. 2018;24(9):1157-1159.
3. Berntsson SG, Kristoffersson A, Boström I, Feresiadou A, Burman J, Landtblom AM. Rapidly increasing off-label use of rituximab in multiple sclerosis in Sweden - outlier or predecessor? Acta Neurol Scand. 2018;138(4):327-331.
4. Lopez-Olivo MA, Amezaga Urruela M, McGahan L, Pollono EN, Suarez-Almazor ME. Rituximab for rheumatoid arthritis. Cochrane Database Syst Rev. 2015;1:CD007356.
5. Salles G, Barrett M, Foà R, et al. Rituximab in B-cell hematologic malignancies: a review of 20 years of clinical experience. Adv Ther. 2017;34(10):2232-2273.
6. Roux T, Debs R, Maisonneuve T, et al. Rituximab in chronic inflammatory demyelinating polyradiculoneuropathy with associated diseases. J Peripher Nerv Syst. 2018;23(4):235-240.
7. Tandan R, Hehir MK 2nd, Waheed W, Howard DB. Rituximab treatment of myasthenia gravis: a systematic review. Muscle Nerve. 2017;56(2):185-196.
8. Hauser SL, Waubant E, Arnold DL, et al. B-cell depletion with rituximab in relapsing-remitting multiple sclerosis. N Engl J Med. 2008;358(7):676-688.
9. Hawker K, O’Connor P, Freedman MS, et al. Rituximab in patients with primary progressive multiple sclerosis: results of a randomized double-blind placebo-controlled multicenter trial. Ann Neurol. 2009;66(4):460-471.
10. Granqvist M, Boremalm M, Poorghobad A, et al. Comparative effectiveness of rituximab and other initial treatment choices for multiple sclerosis. JAMA Neurol. 2018;75(3):320-327.
11. Bar-Or A, Pachner A, Menguy-Vacheron F, Kaplan J, Wiendl H. Teriflunomide and its mechanism of action in multiple sclerosis. Drugs. 2014;74(6):659-674.
12. Jaglowski SM, Alinari L, Lapalombella R, Muthusamy N, Byrd JC. The clinical application of monoclonal antibodies in chronic lymphocytic leukemia. Blood. 2010;116(19):3705-3714.
13. Luna G, Alping P, Burman J, et al. Infection risks among patients with multiple sclerosis treated with fingolimod, natalizumab, rituximab, and injectable therapies. JAMA Neurol. 2019. https://doi.org/10.1001/jamaneurol.2019.3365
14. Alcala C, Gascon F, Perez-Miralles F, et al. Efficacy and safety of rituximab in relapsing and progressive multiple sclerosis: a hospital-based study. J Neurol. 2018;265(7):1690-1697.
15. Scotti B, Disanto G, Sacco R, Guigli M, Zecca C, Gobbi C. Effectiveness and safety of rituximab in multiple sclerosis: an observational study from Southern Switzerland. PLoS One. 2018;13(5):e0197415.
16. Yamout BI, El-Ayoubi NK, Nicolas J, El Kouzi Y, Khoury SJ, Zeineddine MM. Safety and efficacy of rituximab in multiple sclerosis: a retrospective observational study. J Immunol Res. 2018;2018:9084759.
17. Curtis BR. Drug-induced immune neutropenia/agranulocytosis. Immunohematology. 2014;30(2):95-101.
18. Salzer J, Svenningsson R, Alping P, et al. Rituximab in multiple sclerosis: a retrospective observational study on safety and efficacy. Neurology. 2016;87(20):2074-2081.
19. Rissanen E, Remes K, Airas L. Severe neutropenia after rituximab treatment of multiple sclerosis. Mult Scler Relat Disord. 2018;20:3-5.
20. Hernandez-Izilaliturri FJ, Jupudy V, Reising S, Repasky EA, Czuczman MS. Concurrent administration of granulocyte colony-stimulating factor or granulocyte-monocyte colony-stimulating factor enhances the biological activity of rituximab in a severe combined immunodeficiency mouse lymphoma model. Leuk Lymphoma. 2005;46(12):1775-1784.
21. Torka P, Patel P, Tan W, et al. A phase II trial of rituximab combined with pegfilgrastim in patients with indolent B-cell non-hodgkin lymphoma. Clin Lymphoma Myeloma Leuk. 2018;18(1):e51-e60.
22. Monaco WE, Jones JD, Rigby WF. Rituximab associated late-onset neutropenia-a rheumatology case series and review of the literature. Clin Rheumatol. 2016;35(10):2457-2462.
23. Tesfa D, Ajeganova S, Hagglund H, et al. Late-onset neutropenia following rituximab therapy in rheumatic diseases: association with B lymphocyte depletion and infections. Arthritis Rheum. 2011;63(8):2209-2214.
24. Wolach O, Bairey O, Lahav M. Late-onset neutropenia after rituximab treatment: case series and comprehensive review of the literature. Medicine. 2010;89(5):308-318.
25. Dunn N, Juto A, Ryner M, et al. Rituximab in multiple sclerosis: frequency and clinical relevance of anti-drug antibodies. Mult Scler. 2018;24(9):1224-1233.

How to cite this article: Hellgren J, Risedal A, Källén K. Rituximab in multiple sclerosis at general hospital level. Acta Neurol Scand. 2020;141:491–499. https://doi.org/10.1111/ane.13225