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Research article

THE RISK OF COVID-19 SEVERITY IN PATIENTS WITH MS APPEARS TO BE ASSOCIATED WITH IMMUNOTHERAPY

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Immunomodulatory drugs are important to control disease activity in relapsing-remitting multiple sclerosis (MS). Anti-CD20-therapy is one of such medications. In Sweden, extensive off label prescription of rituximab (RTX) in MS has been documented; it is presently prescribed for more than half of all treated MS patients. The rationale for the increasing prescription of RTX was previous data from phase II and observational studies supporting high efficacy and safety, in addition to the financial aspect. We report national data on usage of disease modifying therapies in MS patients and risk of severe COVID-19 in association with RTX exposure within this group.

The Swedish National MS Registry (SMSreg) aims to cover all patients with MS in the country, (n = approximately 18,000). After COVID-19 pandemic started in Sweden, a new section was established in it to register clinical and demographic parameters in COVID-19-infected patients. Data presented in the current report were obtained from the SMSreg.

A total of 85 out of approximately 6,000 RTX-treated Swedish MS patients had been hospitalized with COVID-19 (as reported from the SMSreg, June 16, 2021) and adjusted analyses showed a 2–3 fold increase in a risk (OR = 2.89; p = 0.001) of hospitalization for anti-CD20 treated patients. A change of praxis was introduced in Sweden in spring 2020, resulting in a majority of patients receiving RTX infusions with extended intervals in order to reduce the risk of severe COVID-19 infection.

Current Swedish registry data suggest that exposure to RTX in MS may affect the clinical outcome of COVID-19 infection. These observations have rapidly impacted use of immunomodulatory drugs in Swedish MS patients.

Key words: *multiple sclerosis, immunomodulatory therapies, infection, COVID-19, anti-CD20-therapy, rituximab, national quality health registries, Swedish Multiple Sclerosis registry.*

The current COVID-19 (SARS-CoV-2) pandemic has affected various aspects of life and healthcare all over the world. Multiple sclerosis (MS) is a chronic demyelinating neuro-inflammatory disease of the central nervous system. The incidence rates of MS are greater in countries located at higher latitudes, such as Sweden and Russia [1–3]. Since MS is an autoimmune disease, patients within this group often adhere to immunomodulatory treatment but available therapies are quite diverse and have multiple targets [4]. Regarding relapsing-remitting MS patients (RRMS), both first- and second-line

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drugs are used depending on disease activity and response to treatment. One of the second line treatments, rituximab (RTX), which is primarily used for rheumatoid arthritis (RA), has developed extensive off-label prescription use in Sweden for MS [4–8]. The mechanism of RTX is based on anti-CD20 monoclonal antibodies (mABs), which mediate destruction of CD20-expressing cells through apoptosis, complement activation and antibody dependent-cell-mediated cytotoxicity [7, 9]. A Swedish study reported a rising trend for ongoing immunotherapy with RTX from 2011 to 2016 in MS population in the country [5]. In Sweden, RTX was prescribed to 53.3 % of all MS patients that started MS disease modifying therapy (DMT) during 2017 [5]. This trend was partially explained by both efficacy of the drug, its relative safety in use as well as cost effectiveness as documented in both RA and MS cases [5, 7]. At least within the Swedish healthcare system, the difference in cost is astounding. Compared to fingolimod and natalizumab with a cost of approximately 200,000 SEK per patient per year, the same cost for RTX corresponds to 25,000 SEK per patient per year [10]. Sweden is not alone in its off-label use, RTX is also prescribed in Norway, Denmark and less frequently in Russia [8, 11, 12].

The potential impact on humoral immunity with RTX has raised concerns. A few studies have shown that subsets of patients treated with RTX develop hypogammaglobulinemia, which may be associated with an increased risk of severe infections [13]. In 2020 a Swedish original investigation by Luna et al. [14] studied RTX and other highly effective immune therapies used for treating MS and concluded that exposure to RTX was associated with the highest rate of serious infections. Infections may trigger both clinical exacerbations and pseudo relapses with developing reversible or irreversible deterioration of neurological performance in MS patients. Along with further data linking neurological manifestations and COVID-19, there is an interesting review over intervention of immunomodulatory therapy and whether exposure to different treatments may impact COVID-19 outcome in the current situation of the pandemic [14, 15].

The aim of this investigation was to present the current prescription of DMTs in the Swedish MS population and to report data of COVID-19 outcome in association with the use of DMTs in COVID-19 infected Swedish MS patients.

Method. The Swedish MS registry (SMSreg) was established with the purpose of ensuring high quality neurological care and treatment [16]. It has been applied in neurological departments across the country for over 20 years and covers approximately 80 % of the Swedish MS population which corresponds to a total number of about 18,000 patients. The SMSreg contains data on clinical and demographic variables, disease activity measures and immunomodulatory therapies prescribed for MS patients. The registry is regularly used by physicians and nurses in clinical patient care and often provides a basis for decision making regarding treatments. A registration module to collect data on clinical parameters related to COVID-19 infection in MS patients was put into practice in the SMSreg just after the pandemic started. The COVID-19 module was developed to gain increased knowledge about the impact produced by COVID-19 infection on the Swedish MS population [17]. The COVID-19 module allows neurologists to register data on MS patients with confirmed (positive COVID-19 PCR test or positive antibody serology) or suspected COVID-19 disease (according to the WHO criteria). The variables for registration include gender, age, date of COVID-19 disease onset, clinical symptoms, disease duration of COVID-19, current immunotherapy, last known lymphocyte count, need for hospital care / intensive care / assisted ventilation and outcome (survival / death). The data described in the present report has been obtained from the webpage of the SMSreg and from the

Visualization and Analyses Platform (VAP) in the SMSreg [16].

Results. A total number of 10,962 out of approximately 18,000 MS patients registered within the SMSreg received DMTs of which more than half of the patients were treated with RTX (52 %). The proportions of other prescribed DMTs were as follows: dimethylfumarate (11 %), natalizumab (12 %), interferon-beta (7 %), fingolimod (7 %), glatiramer acetate (4 %), teriflunomide (4 %), cladribine (1 %), alemtuzumab (1 %) and ocrelizumab (1 %), (data retrieved from the VAP, SMSreg, June, 2021) (Figure 1).

As of June 16, 2021, 971 of the nearly 18,000 MS patients within the SMSreg, were registered as COVID-19-infected, of which 127 were admitted for hospital care [16]. Of those admitted, 26 patients required intensive care and five patients had died. Furthermore, a total of 85 out of nearly 6,000 RTX-treated Swedish MS patients had been hospitalized with COVID-19. Adjusted data analyses (for age, gender, disease duration, expanded disability status scale (EDSS) and progressive disease course) showed a 2–3-fold increased risk of hospitalization (OR = 2.89, $p < 0.001$) for patients treated with anti-CD20-therapy (including RTX and ocrelizumab), (data retrieved from the SMSreg webpage) [16].

The proportions of DMT usage in the Swedish MS population have changed over time. A national trend towards a decrease in RTX usage, and an increased use of natalizumab has been observed in connection with the pandemic, (data retrieved from the VAP, SMSreg, June, 2021) (Figure 2).

It was anticipated that the current highly effective immunomodulatory therapies, such as anti-CD20-therapy, might impact the COVID-19 outcome amongst MS patients. The association between anti-CD20-therapy and risk for hospitalization observed in the Swedish MS population according to the SMSreg was corroborated in an international study covering registry data

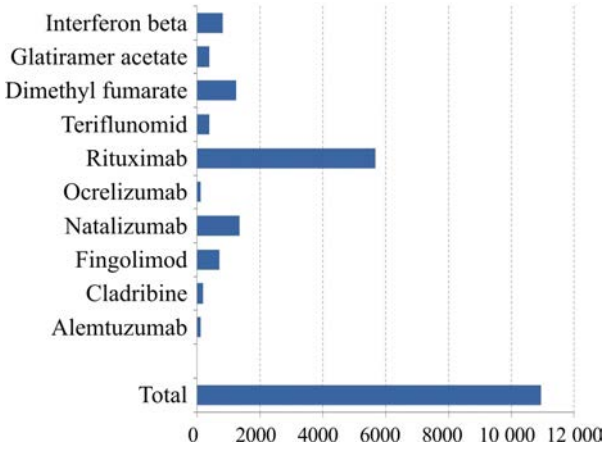

Figure 1. Number of ongoing disease-modifying therapies for MS patients in Sweden. Data retrieved from the Visualization and Analyses Platform (VAP), Swedish MS register (SMSreg), June, 2021

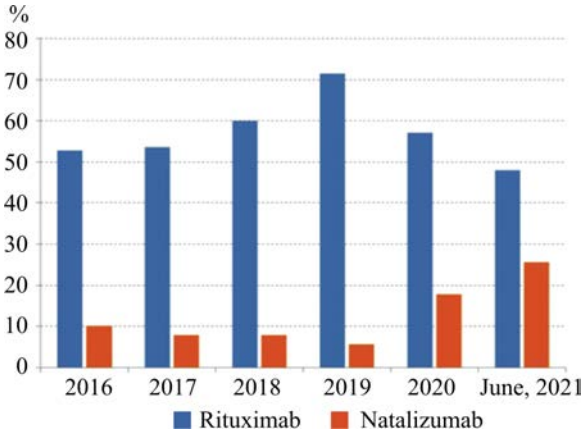

Figure 2. The proportion of MS patients that initiated treatment with rituximab and natalizumab in relation to all disease-modifying drugs during the time period January 2016 to June 2021. Data retrieved from the Visualization and Analyses Platform (VAP), Swedish MS register (SMSreg), June, 2021

from several countries [18]. A positive correlation between anti-CD20-treatment and risk of both hospital care and intensive care was described in this large international MS cohort of more than 2,000 patients with COVID-19 infection [18]. Comparable results were reported in an Italian MS study of 844 patients [19]. Another study from North America showed that MS patients treated with RTX ran an increased risk of

COVID-19 and suffering a worse disease course, compared to patients without immunomodulatory treatment [19, 20]. Similarly, a separate study showed that RTX treated MS patients ran a greater risk of severe COVID-19 compared to the general population on average during 2.5 months after recent RTX infusion [21]. A high dose of RTX (1,000 mg) was also correlated to worse COVID-19 outcomes [21].

Furthermore, in line with the results obtained via the international study using several national MS cohorts, a large global study on more than 2,800 COVID-19 infected RA patients showed that exposure to RTX correlated with worse COVID-19 outcome compared to patients treated with tumor necrosis factor inhibitors [22].

The accumulating support for an increased risk of worse COVID-19 outcome in MS patients that are treated with RTX has rapidly implicated clinical work for decision making regarding choice and timing of DMTs in this population. In Sweden, dosing intervals between RTX infusions were advised to be extended in spring 2020. The intention was to shorten the duration of B-cell depletion to possibly reduce the risk for severe COVID-19 infection. This strategy was supported by a Swedish report that described absence of recurrence in disease activity after discontinuation of RTX in MS patients [23]. In addition, data from the SMSreg have shown a recent change in the prescription of DMTs in MS including a trend of decreased usage of RTX and increased prescription of natalizumab in Sweden.

To sum up, current national data from the SMSreg and international combined registry data suggest an increased risk for a worse outcome of COVID-19 in patients exposed to anti-CD20-therapy. Choice on immunomodulatory therapy is to be made under careful consideration of other common and MS specific risk factors including disability status, to reduce the risk for severe COVID-19 infection.

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