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## Correspondence

## COVID-19 vaccines in multiple sclerosis treated with cladribine or ocrelizumab



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## ABSTRACT

Since the recent approval of vaccines against COVID-19, efficacy concerns emerged for MS patients treated with immunosuppressive drugs. We report our experience in four patients, under cladribine (two) or under ocrelizumab (two) treatment, all with low lymphocyte count, three of them vaccinated after 3 months from the last dose with good immune response, one (under ocrelizumab) after 2 months, without developing an appropriate title of antibodies. This experience suggests that the discriminant for the response to the vaccine is not the lymphocyte count but the timing of the vaccination.

In the last year, since the appearance of Coronavirus disease (COVID-19) in the Chinese city of Wuhan on December 2019 to its diffusion through the world, vaccines have been considered the most important strategy to counteract the spread of the disease (Hodgson et al., 2021). Since the first phase of COVID-19 global pandemic, clinicians and researchers were particularly concerned about the possible effects of COVID-19 in MS patients treated with a disease modifying therapy (DMT). Immunomodulatory or immunosuppressive effects of DMTs could in principle make MS patients more susceptible to severe forms of disease. This concern was however mitigated by the clinical evidence that treated MS patients do not develop more severe COVID-19 compared with healthy population, supporting the idea that most DMTs can be safely administrated during the pandemic (Sormani et al., 2021). In the last months, introduction of vaccines into clinical practice brought to clinicians' attention a further issue regarding the efficacy of vaccines in the DMT-treated population (Sellner and Rommer, 2021). First of all, the question is whether MS patients treated with a DMT are able to produce appropriate T and B cell responses to the vaccine. The next question is how to identify the ideal timing for vaccination in patients elected to start a DMT therapy, or already treated with a given DMT. Unfortunately, large scale experience on immune response against COVID-19 vaccines is still lacking and there are no approved guidelines to lead the clinician to the correct administration of COVID-19 vaccines in MS patients treated with DMT (Sellner and Rommer, 2021). Regarding efficacy of vaccines in MS patients, several studies demonstrated no difference in T and B cell response to vaccination in MS patients and healthy subjects (Lebrun and Vukusic, 2019).

Previous evidence with influenza vaccines demonstrated that most of DMT-treated patients can be safely vaccinated, obtaining an immunization comparable to healthy subjects (Olberg et al., 2018). In particular, patients treated with first and second line drugs including dimethyl fumarate (von Hehn et al., 2018), interferons (Olberg et al., 2018), glatiramer acetate (Olberg et al., 2018), teriflunomide (Korsukewitz et al., 2020) and fingolimod (Olberg et al., 2018) are able to produce an adequate immune response against antigens presented during vaccination. This information is not always present with other infusive or oral immunosuppressive treatments such as the anti-CD-20 monoclonal

antibody ocrelizumab and the adenosine-deaminase inhibitor cladribine. In particular for cladribine, it appears reasonable to vaccinate the patient only when lymphocyte absolute count is reconstituted, usually in 3–6 months from the last administration (Korsukewitz et al., 2020), whereas for ocrelizumab there is indication to vaccinate the patients 3 months after the last infusion (Bar-Or et al., 2020).

In our clinical experience with cladribine and ocrelizumab, there were initial concerns regarding the proposed timelines, as they are not always associated with a complete reconstitution of lymphocyte count (Bar-Or et al., 2020). Moreover, previous studies demonstrated that less than 20% of MS patients treated with ocrelizumab generate an antibody response when naturally infected by COVID-19 (Zabalza et al., 2021). Here we share our first data of patients treated in everyday clinical practice. We observed that two patients (both young females; the first patient was 37 years old, previously untreated, EDSS: 1; the second patient was 31 years old; previously treated with interferon and fingolimod; EDSS: 1) under cladribine, and treated respectively with adenoviral vector-based vaccine (AstraZeneca®) and mRNA vaccine (Pfizer-BioNTech®) after three months from the second cycle of treatment, produced a protective antibody response despite an incomplete reconstitution of the absolute values of circulating lymphocytes (respectively  $0.65 \cdot 10^3/\mu\text{L}$  and  $1.1 \cdot 10^3/\mu\text{L}$ ). Similarly, a female patient treated with ocrelizumab (age: 64; previously treated with teriflunomide; EDSS: 6.5) and successively vaccinated after 3 months from the last infusion was able to produce a protective antibody response against COVID-19 spike protein although low CD19 count ( $0.07/\mu\text{L}$ ). Conversely, another young female patient treated with ocrelizumab (age: 46; previously treated with interferon and teriflunomide; EDSS: 6.5) with similar low CD 19 count ( $0.2/\mu\text{L}$ ) was vaccinated after 2 months from the last infusion and was not able to produce a protective antibody response against COVID-19 spike protein. This observation is consistent with another case of patient treated with ocrelizumab that did not develop an effective immune response when they received the second dose of COVID-19 vaccination (Pfizer-BioNTech®) nine days after last infusion (Khayat-Khoei et al., 2021).

In conclusion this evidence, although limited, seems to suggest that while leukocyte count may be an unreliable marker to establish the

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correct timing of COVID 19 vaccination in patients treated with cladribine or ocrelizumab, it may be important to indicate vaccination at least three months after drug administration.

### Ethical approval

The Ethic Committee of Neuromed Research Institute in Pozzilli, Italy (cod. 10–17) approved the study according to the Declaration of Helsinki.

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### Declaration of Competing Interests

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