Serological response to SARS-CoV-2 vaccination in multiple sclerosis patients treated with fingolimod or ocrelizumab: an initial real-life experience

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Abstract

Background Recent observations suggest a lack of humoral response after SARS-CoV-2 vaccination in multiple sclerosis (MS) patients treated with fingolimod or ocrelizumab.

Objectives To assess serological response to SARS-CoV-2 vaccination in MS patients receiving these disease-modifying treatments (DMTs) in a real-life setting.

Methods Retrospective clinical data collection from MS patients followed at San Raffaele Hospital MS Centre (Milan, Italy). All patients treated with fingolimod or ocrelizumab who had received a complete anti-COVID-19 vaccination course, with no clinical history suggestive of previous SARS-CoV-2 infection and with an available post-vaccination serological assay obtained at least 14 days after vaccination completion were considered for the study.

Results We collected data from 32 MS patients, 16 treated with fingolimod and 16 receiving ocrelizumab. Among the fingolimod group 10 patients (62.5%) had a positive serological response after vaccination and among ocrelizumab-treated patients a positive serological test was found in six cases (37.5%). No relation between serological response and clinical features (i.e., treatment duration, time between vaccination and last treatment dose, and white blood cells count) was identified.

Conclusions Our initial real-life experience suggests a variable antibody production in MS patients receiving these DMTs. At present, there are no sufficient data to do not recommend anti-SARS-CoV-2 vaccine in these patients.

Keywords Multiple sclerosis · COVID-19 · SARS-CoV-2 vaccination · Fingolimod · Ocrelizumab
Table 1 Clinical information and serology of fingolimod-treated group

| Patient | Sex | Age (years) | Disease duration (years) | EDSS | Vaccine | Test method | Antibody titer (U/ml) | Titer cutoff (U/ml) | Test result | Time vaccine-test (days) | WBC (×10^9/l) | Lymphocytes (×10^9/l) | Therapy duration | Previous IS |
|---------|-----|-------------|--------------------------|------|---------|-------------|----------------------|---------------------|-------------|-------------------------|----------------|-------------------------|-----------------|------------|
| 1       | F   | 36.6        | 12.5                     | 1.5  | BNT162b2 | CLIA        | 0.40                 | 1.00                | Negative    | 48                      | 4.50           | 0.50                    | 7.26            | No         |
| 2       | F   | 68.4        | 27.9                     | 4.5  | BNT162b2 | ECLIA       | 64.29                | 0.80                | Positive    | 36                      | 2.90           | 0.40                    | 3.16            | No         |
| 3       | F   | 57.8        | 19.0                     | 3.5  | BNT162b2 | CLIA        | 4.40                 | 7.10                | Negative    | 23                      | 5.31           | 0.55                    | 8.01            | No         |
| 4       | M   | 26.9        | 6.0                      | 1.0  | BNT162b2 | CLIA        | 58.00                | NA                  | Positive    | 16                      | 4.64           | 0.45                    | 4.90            | No         |
| 5       | F   | 33.2        | 5.9                      | 1.0  | BNT162b2 | CLIA        | 1.85                 | 10.00               | Negative    | 14                      | 2.54           | 0.35                    | 3.60            | No         |
| 6       | M   | 33.2        | 8.9                      | 2.0  | BNT162b2 | CLIA        | 4.10                 | 0.80                | Positive    | 59                      | 3.84           | 0.32                    | 6.44            | Yes        |
| 7       | F   | 47.8        | 14.0                     | 1.5  | BNT162b2 | ECLIA       | 0.74                 | NA                  | Negative    | 44                      | 3.36           | 0.99                    | 4.09            | No         |
| 8       | F   | 48.9        | 23.0                     | 2.0  | BNT162b2 | CLIA        | 56.20                | 15.00               | Positive    | 17                      | 2.04           | 0.31                    | 8.58            | Yes        |
| 9       | M   | 49.6        | 4.3                      | 2.5  | BNT162b2 | CLIA        | 181.00               | 15.00               | Positive    | 14                      | 6.44           | 0.95                    | 1.35            | Yes        |
| 10      | F   | 42.2        | 8.0                      | 1.5  | BNT162b2 | CLIA        | 448.00               | 33.80               | Positive    | 45                      | 3.20           | 0.40                    | 2.82            | No         |
| 11      | F   | 53.9        | 22.0                     | 6.0  | BNT162b2 | CLIA        | 0.00                 | NA                  | Negative    | 37                      | 6.59           | 0.87                    | 5.96            | No         |
| 12      | M   | 47.4        | 23.9                     | 1.5  | BNT162b2 | CLIA        | 107.30               | 50.00               | Positive    | 40                      | 3.80           | 0.38                    | 1.91            | No         |
| 13      | F   | 40.9        | 17.3                     | 1.5  | BNT162b2 | CLIA        | 7.13                 | 1.00                | Positive    | 16                      | 5.93           | 0.55                    | 6.56            | No         |
| 14      | F   | 18.2        | 5.1                      | 1.0  | mRNA-1273| CLIA        | 169.00               | 15.00               | Positive    | 43                      | 5.80           | 0.76                    | 2.63            | No         |
| 15      | F   | 40.2        | 2.4                      | 1.5  | BNT162b2 | CMIA        | 1.20                 | 7.10                | Negative    | 21                      | 3.50           | 0.30                    | 1.93            | No         |
| 16      | F   | 57.3        | 20.0                     | 6.5  | BNT162b2 | CMIA        | 14.70                | 7.10                | Positive    | 71                      | 5.04           | 0.40                    | 4.49            | No         |

WBC: white blood cells count, IS: immunosuppressants—i.e. cyclophosphamide, mitoxantrone, ECLIA: electrochemiluminescence immunoassay, CLIA: chemiluminescence immunoassay, CMIA: chemiluminescence microparticle immunoassay.
Table 2  Clinical information and serology of ocrelizumab-treated group

| Patient | Sex | Age (years) | Disease duration (years) | EDSS | Vaccine | Test method | Antibody titer (U/ml) | Titer cut-off (U/ml) | Test result | Time vaccine-test (days) | WBC ($\times 10^9$/l) | Lymphocytes ($\times 10^9$/l) | CD20 count (%) | Therapy duration (years) | Therapy cycles | Time vaccine-last dose (months) | Previous IS |
|---------|-----|-------------|--------------------------|------|---------|-------------|-----------------------|----------------------|-------------|--------------------------|----------------|---------------------------|----------------|-------------------------|--------------|----------------------------|---------------|
| 1       | F   | 50.6        | 13.4                     | 5.5  | BNT162b2| ECLIA       | <0.40                 | 0.80                 | Negative    | 37                       | 5.76          | 0.99                      | 0.00           | 1.3                     | 2            | 4.8                      | Yes          |
| 2       | F   | 30.8        | 6.8                      | 1.0  | BNT162b2| CMIA        | 2.80                  | 50.00                | Negative    | 33                       | NA            | NA                        | NA             | 2.1                     | 4            | 2.4                      | No           |
| 3       | F   | 40.0        | 14.0                     | 3.5  | BNT162b2| CMIA        | 0.30                  | NA                    | Negative    | 25                       | 4.64          | 1.22                      | 1.00           | 2.5                     | 4            | 5.0                      | No           |
| 4       | F   | 41.1        | 22.4                     | 5.5  | BNT162b2| DELFIA      | 21.00                 | 1.20                  | Positive    | 61                       | NA            | NA                        | NA             | 2.0                     | 2            | 8.2                      | Yes          |
| 5       | F   | 50.8        | 8.3                      | 6.5  | BNT162b2| ECLIA       | 98.50                 | 0.80                  | Positive    | 19                       | 6.37          | 1.60                      | 11.10          | 3.4                     | 5            | 5.4                      | Yes          |
| 6       | M   | 57.1        | 8.4                      | 5.0  | BNT162b2| ECLIA       | 238.00                | 0.80                  | Positive    | 31                       | 6.30          | 1.30                      | 2.10           | 3.4                     | 6            | 5.0                      | Yes          |
| 7       | F   | 28.0        | 3.4                      | 1.5  | BNT162b2| CLIA        | 0.05                  | 1.00                  | Negative    | 31                       | 6.60          | 1.90                      | 0.03           | 2.4                     | 4            | 3.1                      | No           |
| 8       | F   | 61.3        | 11.0                     | 6.0  | BNT162b2| ECLIA       | 0.11                  | 1.10                  | Negative    | 34                       | 5.28          | 2.35                      | 0.10           | 3.2                     | 6            | 5.8                      | No           |
| 9       | F   | 46.6        | 26.0                     | 6.5  | BNT162b2| CLIA        | 0.07                  | 10.00                 | Negative    | 66                       | NA            | NA                        | NA             | 2.7                     | 6            | 2.8                      | Yes          |
| 10      | M   | 32.3        | 14.0                     | 6.5  | BNT162b2| ECLIA       | <0.40                 | 0.80                  | Negative    | 30                       | 9.20          | 2.20                      | 0.00           | 2.5                     | 5            | 5.0                      | No           |
| 11      | M   | 23.0        | 6.1                      | 2.5  | mRNA-1273| ECLIA       | <0.40                 | 0.80                  | Negative    | 42                       | 6.50          | 2.30                      | 0.50           | 2.9                     | 5            | 4.6                      | No           |
| 12      | F   | 56.3        | 1.3                      | 4.5  | BNT162b2| CLIA        | 65.90                 | 15.00                 | Positive    | 19                       | 4.20          | 1.60                      | 0.50           | 0.0                     | 1            | 3.5                      | No           |
| 13      | M   | 43.4        | 4.3                      | 4.5  | BNT162b2| ECLIA       | <0.40                 | 0.80                  | Negative    | 18                       | 5.80          | 1.20                      | 0.00           | 2.7                     | 5            | 5.9                      | No           |
| 14      | M   | 36.8        | 10.9                     | 3.5  | BNT162b2| ECLIA       | 22.40                 | 0.80                  | Negative    | 21                       | 5.49          | 1.18                      | 0.03           | 2.1                     | 4            | 5.9                      | No           |
| 15      | F   | 64.1        | 19.5                     | 3.0  | BNT162b2| CMIA        | 155.00                | 33.80                 | Positive    | 21                       | 3.96          | 1.12                      | 0.04           | 2.1                     | 4            | 5.5                      | Yes          |
| 16      | M   | 43.2        | 25.2                     | 4.0  | BNT162b2| CMIA        | <2.20                 | 22.00                 | Negative    | 28                       | 4.33          | 1.14                      | 0.03           | 2.2                     | 4            | 4.2                      | Yes          |

WBC white blood cells count, IS immunosuppressants—i.e. cyclophosphamide, mitoxantrone, ECLIA electrochemiluminescence immunoassay, CLIA chemiluminescence immunoassay, CMIA chemiluminescence microparticle immunoassay, DELFIA dissociation-enhanced lanthanide fluorescent immunoassay
Our experience, in comparison to previously published data [8], suggests that humoral response to SARS-CoV-2 vaccination might be highly variable, even in patients treated with fingolimod or ocrelizumab. As a consequence, we believe that SARS-CoV-2 vaccination should be recommended also in MS patients treated with such agents. Indeed, available data are still too limited to suggest treatment discontinuation in order to favor a vaccination response, considering the significant risk of clinical relapse and MRI activity associated to second-line treatment withdrawal (at least in relapsing–remitting MS patients). Furthermore, initial reports relative to other medical conditions causing immunodeficiency suggest the possibility of an efficient cell-mediated immunity after vaccination even in the absence of a detectable humoral response [10].

Clearly, this study is not without limitations: the sample size is relatively small and data collection is retrospective, with serological exams performed with different techniques. In addition, we do not have pre-vaccinations serological tests available; northern Italy had a very high prevalence of SARS-CoV-2 infection over the last year, therefore we cannot exclude a previous asymptomatic infection possibly influencing the serological response.

In this historical moment, it is of utmost importance that a very large proportion of the population, including people with MS, adheres to mass vaccination campaigns, in order to get through the current pandemic condition. With the rapid progression of SARS-CoV-2 vaccination programs all over the world, more extensive real-life data from different geographic regions are likely to become available in the near future. The assessment, in the context of prospective clinical trials, of humoral and in particular T cell response to SARS-CoV-2 vaccination will be also crucial to tailor the clinical management of MS patients.

Declarations

Conflicts of interest This article was written in the absence of any intellectual, commercial or financial relationships that could represent a potential conflict of interest.

Ethics and patient consent All patients had signed written consent form for clinical data collection.

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