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ORIGINAL ARTICLE

Antibody response elicited by the SARS-CoV-2 vaccine booster in patients with multiple sclerosis: Who gains from it?

Irene Schiavetti[1] | Matilde Inglese[2,3] | Jessica Frau[4] | Elisabetta Signoriello[5] | Francesca Caleri[6] | Maria Laura Stromillo[7] | Maria Teresa Ferrò[8] | Maria Teresa Rilla[9] | Ilaria Gandoglia[10] | Paola Gazzola[11] | Giampaolo Brichetto[12] | Livia Pasquali[13] | Luigi Grimaldi[14] | Monica Ulivelli[15] | Fabiana Marinelli[16] | Susanna Cordera[17] | Marinella Clerico[18] | Antonella Conte[19,20] | Marco Salvetti[20,21] | Mario Alberto Battaglia[22,23] | Diego Franciotta[24] | Antonio Uccelli[2,3] | Maria Pia Sormani[1,2] | CovaXiMS Study Group

[1]Section of Biostatistics, Department of Health Sciences, University of Genoa, Genoa, Italy

[2]IRCCS Ospedale Policlinico San Martino, Genoa, Italy

[3]Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health and Center of Excellence for Biomedical Research, University of Genoa, Genoa, Italy

[4]Centro Sclerosi Multipla Binaghi, ASL Cagliari, Cagliari, Italy

[5]Centro Sclerosi Multipla, II Clinica Neurologica, Università della Campania Luigi Vanvitelli, Naples, Italy

[6]Department of Neurology, MS Center, F. Tappeiner Hospital, Merano, Italy

[7]Clinica Neurologica e Malattie Neurometaboliche, Università degli Studi di Siena, Siena, Italy

[8]Neuroimmunology, Neurological Unit, Cerobrovascular Department, Center for Multiple Sclerosis, ASST Crema, Crema, Italy

[9]Department of Neurology, Imperia Hospital, Imperia, Italy

[10]Neurology Unit, Galliera Hospital, Genoa, Italy

[11]Centro Sclerosi Multipla S.C. Neurologia Asl 3 Genovese, Genoa, Italy

[12]AISM Rehabilitation Center, Genoa, Italy

[13]Neurology Unit, Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

[14]UOC Neurologia e Centro SM Fondazione Istituto G. Giglio, Cefalù, Italy

[15]Department of Medical Sciences, Surgery, and Neurosciences, University of Siena, Siena, Italy

[16]Multiple Sclerosis Center, Fabrizio Spaziani Hospital, Frosinone, Italy

[17]Department of Neurology, Ospedale Regionale, Aosta, Italy

[18]Dipartimento di Scienze Cliniche e Biologiche, Università di Torino, Turin, Italy

[19]Department of Human Neuroscience, Sapienza University of Rome, Rome, Italy

[20]IRCCS Istituto Neurologico Mediterraneo Neuromed, Pozzilli, Italy

[21]Department of Neurosciences, Mental Health, and Sensory Organs, Center for Experimental Neurological Therapies, Sapienza University of Rome, Rome, Italy

[22]Research Department, Italian Multiple Sclerosis Foundation, Genoa, Italy

[23]Department of Life Sciences, University of Siena, Siena, Italy

[24]IRCCS Mondino Foundation, Pavia, Italy

The members of the CovaXiMS Study Group are listed in the Appendix 1.

Correspondence
Irene Schiavetti, Section of Biostatistics, Department of Health Sciences, University of Genoa, Genoa, Italy.
Email: irene.schiavetti@unige.it

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Abstract

Background and purpose: Although two doses of COVID-19 vaccine elicited a protective humoral response in most persons with multiple sclerosis (pwMS), a significant group of them treated with immunosuppressive disease-modifying therapies (DMTs) showed less efficient responses.

Methods: This prospective multicenter observational study evaluates differences in immune response after a third vaccine dose in pwMS.

Results: Four hundred seventy-three pwMS were analyzed. Compared to untreated patients, there was a 50-fold decrease (95% confidence interval [CI] = 14.3–100.0, $p < 0.001$) in serum SARS-CoV-2 antibody levels in those on rituximab, a 20-fold decrease (95% CI = 8.3–50.0, $p < 0.001$) in those on ocrelizumab, and a 2.3-fold decrease (95% CI = 1.2–4.6, $p = 0.015$) in those on fingolimod. As compared to the antibody levels after the second vaccine dose, patients on the anti-CD20 drugs rituximab and ocrelizumab showed a 2.3-fold lower gain (95% CI = 1.4–3.8, $p = 0.001$), whereas those on fingolimod showed a 1.7-fold higher gain (95% CI = 1.1–2.7, $p = 0.012$), compared to patients treated with other DMTs.

Conclusions: All pwMS increased their serum SARS-CoV-2 antibody levels after the third vaccine dose. The mean antibody values of patients treated with ocrelizumab/rituximab remained well below the empirical "protective threshold" for risk of infection identified in the CovaXiMS study (>659 binding antibody units/mL), whereas for patients treated with fingolimod this value was significantly closer to the cutoff.

KEYWORDS
anti-CD20, booster dose, COVID-19, fingolimod, multiple sclerosis, SARS-CoV-2 vaccine

INTRODUCTION

The abnormal regulation of immunity in persons with multiple sclerosis (pwMS) has raised several questions about the evaluation of their vaccine-induced immune responses. Although most patients reach an efficient and long-lasting humoral response (up to 6 months) after two doses of COVID-19 vaccine, a significant proportion of pwMS treated with immunosuppressive disease-modifying therapies (DMTs) resulted in a reduced humoral response [1–3]. In addition, in a cohort of almost 20,000 vaccinated pwMS, the cumulative incidence of "delta" breakthrough infection at 8 months follow-up was 4.3%, with significant differences in infection rates among DMTs [4].

The current study was conducted on a large cohort of pwMS who received a three-dose vaccination against SARS-CoV-2 to evaluate differences in their antibody-specific immunogenic response, considering the potential detrimental effect of their current treatments.

OBJECTIVE

This study investigated the immunogenic response among patients who received a three-dose vaccination against SARS-CoV-2. The aim was to evaluate the differences among treated pwMS in serum levels and actual gain of SARS-CoV-2 receptor binding domain (RBD) antibodies elicited by the COVID-19 vaccine booster (third dose).

METHODS

Study design and participants

This is a multicenter prospective observational substudy of the larger CovaXiMS (Covid-19 Vaccine in Multiple Sclerosis) [3] project, which included a subgroup of adult pwMS with three-dose vaccination.

All patients agreed to provide a serum sample before the first dose, 1 month after the second dose, and then two more samples just before and 1 month after the third dose. Exclusion and inclusion criteria and details on the methods for assessment of antibody responses and their cutoff of positivity have been previously reported elsewhere [3].

All data were collected in an electronic case report form.

Statistical analysis

Categorical variables are described as frequency with percentage, whereas continuous variables are reported as mean with SD or median with interquartile range. The distribution of antibody levels was normalized with a log10 transformation [5].

A linear regression model, adjusted for demography data, disease characteristics, vaccine type, and levels of antibodies after the second vaccine dose, was used to compare the antibody response after vaccine booster across patients treated with different DMTs.

The same model (in this case unadjusted for antibody levels after the second dose of vaccine) was used to evaluate the actual gain in antibody level after the third dose of anti-CD20 and fingolimod compared to other DMTs.

Differences were considered statistically significant when $p < 0.05$.

The results of the multivariable analysis were expressed by beta coefficients with standard error and geometric mean (multiplicative factor with respect to the reference level of each covariate) with 95% confidence interval (CI).

RESULTS

One thousand nine hundred twenty pwMS were selected and enrolled to participate in the CovaXiMS study. Between 4 March 2021 and 30 June 2022, 473 of them (24.6%) provided a set of serum before the first dose, 1 month after the second dose, and two additional samples just before and 1 month after the third dose. Their baseline demographic and clinical characteristics are reported in Table 1.

Almost all patients achieved a high response to the vaccine after the third dose, although lower values were recorded for patients treated with fingolimod, ocrelizumab, and rituximab, whose mean values remained under the cutoff discriminating patients at a higher risk of infection [6] (Figure 1).

Compared to untreated patients, a 50-fold decrease (95% CI = 14.29–100.00, $p < 0.001$) in antibody levels after the booster was attributable to rituximab effects, a 20-fold decrease (95% CI = 8.33–50.00, $p < 0.001$) to ocrelizumab, and a 2.32-fold decrease (95% CI = 1.18–4.55, $p = 0.015$) to fingolimod.

In addition, the booster-related levels were significantly influenced by sex, with a relative 1.47-fold decrease in females compared to males (95% CI = 1.08–1.96, $p = 0.012$). An association was also found between the postbooster antibody levels and the antibody levels after the second dose, with a 3.85-fold increase (95% CI = 3.15–4.72, $p < 0.001$) for each log10 unit increase in post-second dose levels (Table 2).

Figure 2 shows the differences in the gain in antibody levels after the booster compared to second-dose levels among different DMTs. Patients treated with fingolimod showed an approximate 15-fold increase in antibody levels, almost fivefold increase for all anti-CD20 DMTs combined, and almost 10-fold increase for the remaining DMTs.

Table 3 explains these results with a multivariable regression model. A 2.32-fold lower gain (95% CI = 1.43–3.84, $p = 0.001$) was found in anti-CD20-treated patients compared to other treatments; in contrast, patients treated with fingolimod showed a 1.74-fold higher gain (95% CI = 1.13–2.69, $p = 0.012$) compared to those treated with other DMTs. Finally, a lower gain was observed in females than in males (1.47-fold lower, 95% CI = 1.08–1.96, $p = 0.008$).

TABLE 1 Baseline demographic and clinical characteristics of the included patients ($N = 473$).

Age, years, mean (SD)	47.6 (12.59)
Female sex, *n* (%)	331 (70.0%)
BMI, kg/m^2, mean (SD)	24.2 (4.79)
Caucasian ethnicity, *n* (%)	471 (99.6%)
Presence of relapse in the previous 3 months	12 (2.5%)
MS phenotype, *n* (%)	
Relapsing–remitting MS	405 (85.6%)
Secondary progressive MS	45 (9.5%)
Primary progressive MS	23 (4.9%)
EDSS, median [IQR]	1.5 [1.0–3.0]
MS disease duration, years, median [IQR]	11.0 [5.0–17.0]
Disease-modifying therapy, *n* (%)	
Dimethyl fumarate	78 (16.5%)
Fingolimod	73 (15.4%)
Interferon	69 (14.6%)
Ocrelizumab	51 (10.8%)
Natalizumab	45 (9.5%)
Glatiramer acetate	41 (8.7%)
Never treated	37 (7.8%)
Teriflunomide	35 (7.4%)
Cladribine	18 (3.8%)
Alemtuzumab	9 (1.9%)
Rituximab	8 (1.7%)
Azathioprine	6 (1.3%)
Other	3 (0.6%)
Recent use of methylprednisolone	5 (1.1%)
Positivity for N antibody before vaccination	33 (7.0)
Vaccine type, *n* (%)	
BNT162b2	383 (81.0%)
mRNA-1273	90 (19.0%)

Abbreviations: BMI, body mass index; EDSS, Expanded Disability Status Scale; IQR, interquartile range; MS, multiple sclerosis.

DISCUSSION

In this study, we measured serum levels of antibody response to RBD of the SARS-CoV-2 spike 1 protein before and after the third dose of mRNA-based vaccine (BNT162b2 or mRNA-1273) in a large cohort of pwMS.

These results confirm the evidence of a weaker humoral response to the first two doses of vaccine in pwMS treated with ocrelizumab, rituximab, and fingolimod [3, 7, 8].

After the third booster vaccine dose, all patients increased their antibody levels, but the average antibody values of patients treated with ocrelizumab and rituximab still remained below the empirical "protective threshold" for risk of infection (>659 binding antibody units/mL) identified in previous studies [6], whereas the mean antibody value was significantly closer to the cutoff in patients on

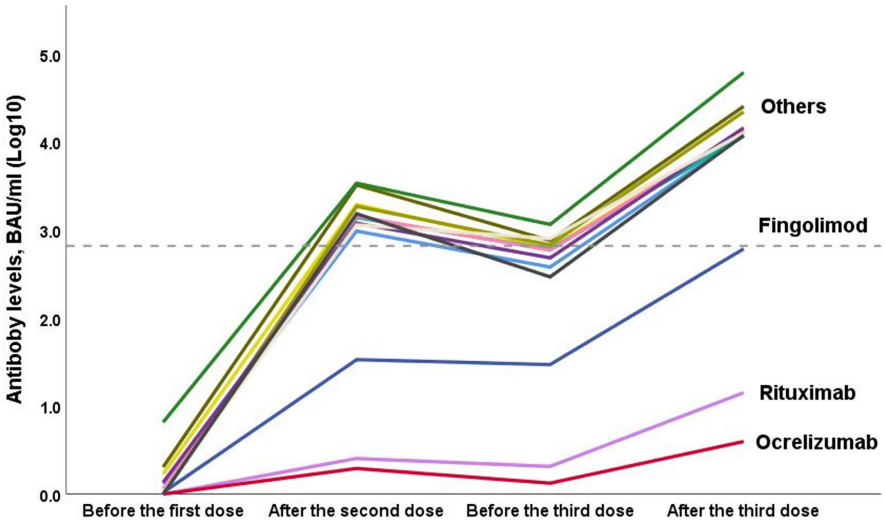

FIGURE 1 Antibody levels (log10 transformation) over time among patients treated with different disease-modifying therapies. BAU, binding antibody units.

TABLE 2 Multivariable analysis assessing factors associated with antibody levels 4 weeks after the third dose.

Parameter	Beta coefficient (SE)	Geometric mean (95% CI)[a]	*p*
Age, 10 years	0.02 (0.03)	1.04 (0.90–1.20)	0.62
Sex, female vs. male	−0.17 (0.07)	0.68 (0.51–0.92)	0.012
MS phenotype	0.19 (0.12)	1.54 (0.91–2.61)	0.11
Disease duration > 10 years	−0.04 (0.07)	0.92 (0.68–1.25)	0.59
EDSS	−0.03 (0.02)	0.93 (0.84–1.03)	0.16
Disease-modifying therapy			
No therapy	Ref.		
Cladribine	−0.11 (0.21)	0.77 (0.30–1.94)	0.58
Teriflunomide	0.13 (0.15)	1.34 (0.67–2.66)	0.41
Rituximab	−1.68 (0.27)	0.02 (0.01–0.07)	<0.001
Ocrelizumab	−1.28 (0.19)	0.05 (0.02–0.12)	<0.001
Natalizumab	0.04 (0.15)	1.10 (0.55–2.19)	0.79
Interferon	0.14 (0.13)	1.38 (0.76–2.51)	0.28
Fingolimod	−0.37 (0.15)	0.43 (0.22–0.85)	0.015
Glatiramer acetate	−0.02 (0.14)	0.96 (0.50–1.83)	0.91
Dimethyl fumarate	−0.07 (0.13)	0.85 (0.46–1.55)	0.59
Other	0.02 (0.19)	1.05 (0.45–2.49)	0.91
Antibody level after the second dose, log10	0.59 (0.04)	3.85 (3.15–4.72)	<0.001
Days between second and booster dose	0.00 (0.00)	1.00 (1.00–1.01)	0.36
Vaccine type			
mRNA-1273	Ref.		
BNT162b2	−0.04 (0.07)	0.91 (0.65–1.28)	0.60

Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale; Ref., reference.
[a]A 1.47-fold decrease (95% CI = 1.08–1.96) for females compared to males, a 2.32-fold decrease (95% CI = 1.18–4.55) for fingolimod effect, a 20-fold decrease (95% CI = 8.33–50) for ocrelizumab, and a 50-fold decrease (95% CI = 14.29–100.00) for rituximab.

fingolimod. These findings are in line with previous published data on breakthrough infections [6].

During the delta wave, the probability of infection had been much higher in pwMS treated with anti-CD20 and fingolimod than in those on other treatments. However, during the omicron wave considered here, this probability remained higher in patients taking anti-CD20, whereas it was overlapping (and lower than anti-CD20) in pwMS taking fingolimod and other treatments. It should be noted that in Italy, the advent of the omicron variant was preceded by the introduction of the booster dose. Moreover, recent data demonstrated

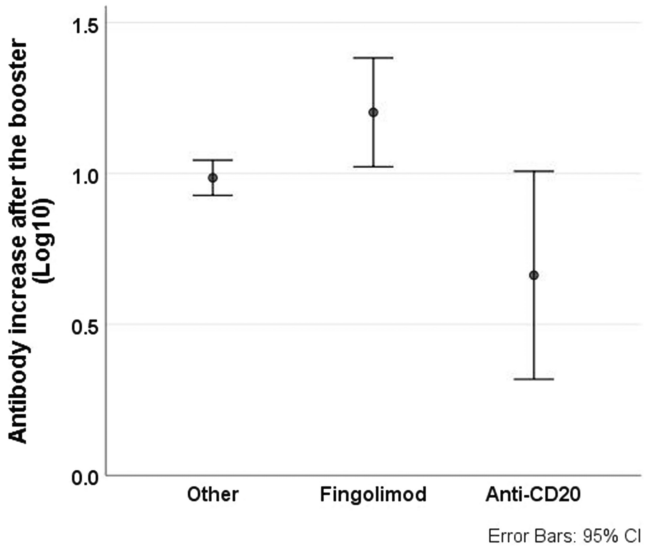

FIGURE 2 Antibody increase after the booster dose (log10 transformation) among patients treated with different disease-modifying therapies. CI, confidence interval.

TABLE 3 Multivariable analysis assessing factors associated with change in antibody levels 4 weeks after the third dose.

Parameter	Beta coefficients (SE)	Geometric mean (95% CI)[a]	*p*
Age, 10 years	0.04 (0.03)	1.10 (0.95–1.27)	0.22
Sex, female vs. male	−0.19 (0.07)	0.64 (0.46–0.89)	0.008
MS phenotype, progressive vs. RR	0.03 (0.13)	1.07 (0.61–1.89)	0.82
Disease duration > 10 years	−0.03 (0.07)	0.93 (0.67–1.30)	0.67
EDSS	0.01 (0.02)	1.02 (0.91–1.14)	0.70
Disease-modifying therapy			
Other (Ref.)			
Anti-CD20	−0.37 (0.11)	0.43 (0.26–0.70)	0.001
Fingolimod	0.24 (0.10)	1.74 (1.13–2.69)	0.012
Days between second and booster dose	0.00 (0.00)	1.00 (1.00–1.01)	0.26
Vaccine type			
mRNA-1273	Ref.		
BNT162b2	0.08 (0.08)	1.20 (0.83–1.74)	0.32

Abbreviations: CI, confidence interval; EDSS, Expanded Disability Status Scale; MS, multiple sclerosis; RR, relapsing–remitting.

[a]A 1.56-fold decrease (95% CI = 1.05–0.79) for females compared to males, a 2.32-fold decrease (95% CI = 1.43–3.84) for anti-CD20.

that compared to the second dose of COVID-19 vaccine, the third dose resulted in a strong release of neutralizing antibodies against the omicron variant [9].

The different levels of humoral responses among pwMS could be explained by the different mechanisms of action of DMTs on the immune system [10]. Whereas treatment with fingolimod resulted in undetectable SARS-CoV-2-specific memory B- and T-cell immune responses, with an enhanced humoral response after the booster dose [11], anti-CD20 drugs deplete all circulating B cells, resulting in a weaker humoral response after the COVID-19 vaccine.

However, several studies have proved that in patients treated with anti-CD20 there was a strong T-cell response after the third dose, demonstrating the importance of a booster dose and confirming that even in this group of patients, a three-dose vaccination strategy can protect against the severe complications of COVID-19 infection [12–15].

In conclusion, the results of this study show that a third dose of COVID-19 mRNA vaccine is associated with a modest increase in the levels of humoral responses in MS patients under different DMTs, thus confirming the importance of an additional dose of vaccine also for patients with weak immunity priming.

AUTHOR CONTRIBUTIONS

Irene Schiavetti: Conceptualization; writing – original draft; methodology; software; formal analysis; data curation. **Matilde Inglese:** Investigation; data curation. **Jessica Frau:** Data curation; investigation. **Elisabetta Signoriello:** Investigation; data curation. **Francesca Caleri:** Investigation; data curation. **Maria Laura Stromillo:** Investigation; data curation. **Maria Teresa Ferrò:** Investigation; data curation. **Maria Teresa Rilla:** Investigation; data curation. **Ilaria Gandoglia:** Investigation; data curation. **Paola Gazzola:** Investigation; data curation. **Giampaolo Brichetto:** Investigation; data curation. **Livia Pasquali:** Data curation; investigation. **Monica Ulivelli:** Investigation; data curation. **Fabiana Marinelli:** Data curation; investigation. **Susanna Cordera:** Investigation; data curation. **Marinella Clerico:** Data curation; investigation. **Antonella Conte:** Investigation; data curation. **Marco Salvetti:** Data curation; investigation; supervision. **Mario Alberto Battaglia:** Investigation; data curation; supervision. **Diego Franciotta:** Data curation; investigation. **Antonio Uccelli:** Investigation; conceptualization; supervision. **Maria Pia Sormani:** Conceptualization; methodology; supervision; formal analysis.

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CONFLICT OF INTEREST STATEMENT

F.C. has received honoraria for lectures or presentations from Biogen, Merck, Teva, Novartis, Sanofi-Genzyme, and Roche; has received support for attending meetings and travel grants from Biogen, Merck, Teva, Novartis, Sanofi-Genzyme, and Roche; and has received honoraria for participation on advisory boards from Biogen, Merck, Teva, Novartis, Sanofi-Genzyme, and Roche. M.C. has received grants and consulting fees from Merck, Biogen, Novartis, Sanofi-Genzyme, Roche, and Almirall. A.C. reports speaking honoraria from Merck, Sanofi, Novartis, Biogen, Roche, Bristol Myers Squibb, and Almirall and has received research support from

Roche, Biogen, and Merck. J.F. serves on scientific advisory boards for Biogen, Merck, Genzyme, and Novartis and has received honoraria as a speaker from Merck, Biogen, Novartis, Genzyme, Teva, and Alexion. Matilde Inglese has received grants or contracts from FISM, INAIL, and the European Union. M.L.S. has received personal compensation for speaking or consultancy from Biogen, Teva, Genzyme, Merck, Mylan, Novartis, and Roche. F.M. has received consultancy fees or speaker compensation from Sanofi, Bristol, Biogen Idec, and Novartis. L.P. has received personal compensation for speaking or consultancy from Sanofi, Novartis, Merck, Alexion, and Biogen and has received support for attending meetings from Sanofi and Merck. M.S. has received grants or contracts from Biogen, Merck, and Novartis and has received payments or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Biogen, Merck, Novartis, Roche, and Sanofi. I.S. has acted as a paid consultant to Associazione Commissione Difesa Vista, Eye Pharma, Hippocrates Research, and D.M.G. Italia. E.S. has received speaker honoraria and/or consultancy fees from Biogen, Teva, Genzyme, Merck, Novartis, Almirall, and Roche. M.P.S. has received consulting fees from Roche, Biogen, Merck, Novartis, Sanofi, Celgene, Immunic, Geneuro, GSK, and Medday; has received payment or honoraria for lectures, presentations, speakers' bureaus, manuscript writing, or educational events from Roche, Biogen Merck, Novartis, Sanofi, and Celgene; and has participated on a data safety monitoring board or advisory board for Roche, Sanofi, Novartis, and Merck. A.U. has received grants (to his institution) from FISM, Biogen, Roche, Alexion, and Merck Serono and has participated on a data safety monitoring board or advisory board (to his institution) for BD, Biogen, Iqvia, Sanofi, Roche, Alexion, and Bristol Myers Squibb. M.U. has received consulting fees from Biogen, Novartis, and Serono. None of the other authors has any conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

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

ETHICS STATEMENT

The study was conducted in accordance with the principles of the Declaration of Helsinki. The protocol was approved by the regional ethics committee (CER Liguria: 5/2021, DB id 11169, 21/01/2021) and by the centralized national ethics committee AIFA/Spallanzani (Parere n 351, 2020/21). All participants provided written informed consent prior to enrollment in the study.

ORCID

Irene Schiavetti https://orcid.org/0000-0002-5460-2977
Jessica Frau https://orcid.org/0000-0001-9068-9144
Elisabetta Signoriello https://orcid.org/0000-0001-5753-6752
Ilaria Gandoglia https://orcid.org/0000-0003-4429-914X
Giampaolo Brichetto https://orcid.org/0000-0003-2026-3572
Monica Ulivelli https://orcid.org/0000-0003-3463-6341
Antonella Conte https://orcid.org/0000-0002-6338-2961

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APPENDIX 1

CovaXiMS Study Group

Alessandro Maglione (Dipartimento di Scienze Cliniche e Biologiche, Università di Torino, Turin, Italy), Alessia Di Sapio (Department of Neurology, Regina Montis Regalis Hospital, Mondovì, Italy), Alice Laroni (Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy; Ospedale Policlinico San Martino IRCCS, Genoa, Italy; Center of Excellence for Biomedical Research, University of Genoa, Genoa, Italy), Aniello Iovino (Clinica Neurologica, DSNRO Università Federico II di Napoli, Naples, Italy), Antonio Mannironi (Department of Neurology, Sant'Andrea Hospital, La Spezia, Italy), Antonio Uccelli (Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy; Ospedale Policlinico San Martino IRCCS, Genoa, Italy; Center of Excellence for Biomedical Research, University of Genoa, Genoa, Italy), Barbara Nucciarone (Department of Neurology, Sant'Andrea Hospital, La Spezia, Italy), Carlo Serrati (Department of Neurology, Imperia Hospital, Imperia, Italy), Carolina Gabri Nicoletti (Multiple Sclerosis Clinical and Research Unit, Department of Systems Medicine, Tor Vergata University and Hospital, Rome, Italy), Caterina Lapucci (Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy), Chiara Rosa Mancinelli (Centro Sclerosi Multipla ASST Spedali Civili di Brescia, Brescia, Italy), Cinzia Cordioli (Centro Sclerosi Multipla ASST Spedali Civili di Brescia, Brescia, Italy), Daiana Bezzini (Department of Life Sciences, University of Siena, Siena, Italy), Daniele Carmagnini (Centro Sclerosi Multipla Ospedale Binaghi Cagliari, ATS Sardegna, Università di Cagliari, Cagliari, Italy), Davide Brogi (S.C. Neurologia, Ospedale Santa Corona, Vinovo, Italy), Nicola De Stefano (Clinica Neurologica e Malattie Neurometaboliche, Universita' degli Studi di Siena, Siena, Italy), Diego Franciotta (Autoimmunology Laboratory, IRCCS Ospedale Policlinico San Martino, Genoa, Italy), Doriana Landi (Multiple Sclerosis Clinical and Research Unit, Department of Systems Medicine, Tor Vergata University and Hospital, Rome, Italy), Eduardo Nobile Orazio (Neuromuscular and Neuroimmunology Service, IRCCS Humanitas Research Hospital, Rozzano, Italy; Department of Medical Biotechnology and Translational Medicine, Milan University, Milan, Italy), Eleonora Cocco (Centro Sclerosi Multipla Ospedale Binaghi Cagliari, ATS Sardegna, Università di Cagliari, Cagliari, Italy), Elisabetta Signoriello (Centro Sclerosi Multipla, II Clinica Neurologica, Università della Campania Luigi Vanvitelli, Caserta, Italy), Enri Nako (Department of Neurology, Regina Montis Regalis Hospital, Mondovì, Italy), Ester Assandri (Neuroimmunology, Center for Multiple Sclerosis, Cerobrovascular Department, Neurological Unit, ASST Crema, Crema, Italy), Fabiana Marinelli (ASL Frosinone, Fabrizio Spaziani Hospital, via Armando Fabi, Frosinone, Italy), Federica Baldi (Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy), Francesca Caleri (MS Center, Department of Neurology, F. Tappeiner Hospital, Merano, Italy), Gabriele Siciliano (Department of Clinical and Experimental Medicine, Neurology Unit, University of Pisa, Pisa, Italy), Gaia Cola (Multiple Sclerosis Clinical and Research Unit, Department of Systems Medicine, Tor Vergata University and Hospital, Rome, Italy), Germana Perego (SC Neurologia ASL 4 Chiavarese, Castiglione Chiavarese, Italy), Giacomo Lus (Centro Sclerosi Multipla, II Clinica Neurologica, Università della Campania Luigi Vanvitelli, Caserta, Italy), Giampaolo Brichetto (AISM Rehabilitation Center, Genoa, Italy), Gianmarco Bellucci (Center for Experimental Neurological Therapies, Department of Neurosciences, Mental Health, and Sensory Organs, Sapienza University of Rome, Rome, Italy), Giorgio Da Rin (Laboratory Unit, IRCCS Ospedale Policlinico San Martino, Genoa, Italy), Girolama Alessandra Marfia (Multiple Sclerosis Clinical and Research Unit, Department of Systems Medicine, Tor Vergata University and Hospital, Rome, Italy; Neurology Unit, IRCCS NEUROMED, Pozzilli, Italy), Giulia Vazzoler (UOC Neurologia e Centro SM Fondazione Istituto G. Giglio, Cefalù, Italy), Giuseppe Liberatore (Neuromuscular and Neuroimmunology Service, IRCCS Humanitas Research Hospital, Rozzano, Italy), Giuseppe Trivelli (SC Neurologia ASL 4 Chiavarese, Castiglione Chiavarese, Italy), Graziella Callari (UOC Neurologia e Centro SM Fondazione Istituto G. Giglio, Cefalù, Italy), Ilaria Gandoglia (Neurology Unit, Galliera Hospital, Genoa, Italy), Irene Schiavetti (Department of Health Sciences, Section of Biostatistics, University of Genoa, Genoa, Italy), Jessica Frau (Centro Sclerosi Multipla Ospedale Binaghi Cagliari, ATS Sardegna, Università di Cagliari, Cagliari, Italy), Livia Pasquali (Department of Clinical and Experimental Medicine, Neurology Unit, University of Pisa, Pisa, Italy), Loredana Petrucci (Department of Neurology, Sant'Andrea Hospital, La Spezia, Italy), Lorena Lorefice (Centro Sclerosi Multipla Ospedale Binaghi Cagliari, ATS Sardegna, Università di Cagliari, Cagliari, Italy), Lucia Ruggiero (Clinica Neurologica, DSNRO Università Federico II di Napoli, Naples, Italy), Marco Salvetti (Center for Experimental Neurological Therapies, Department of Neurosciences, Mental Health, and Sensory Organs, Sapienza University of Rome, Rome, Italy; IRCCS Istituto Neurologico Mediterraneo Neuromed, Pozzilli, Italy), Margherita Monti Bragadin (AISM Rehabilitation Center, Genoa, Italy), Maria Chiara Buscarinu (Center for Experimental Neurological Therapies, Department of Neurosciences, Mental Health, and Sensory Organs, Sapienza University of Rome, Rome, Italy), Maria Gagliardi (Department of Neurosciences, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, Genoa, Italy), Maria Pia Sormani (Department of Health Sciences, Section of Biostatistics, University of Genoa, Genoa, Italy; IRCCS Ospedale Policlinico San Martino, Genoa, Italy/ Department of Health Sciences, Section of Biostatistics, University of Genoa, Italy), Maria Teresa Ferrò (Neuroimmunology, Center for Multiple Sclerosis, Cerobrovascular Department, Neurological Unit, ASST Crema, Crema, Italy), Maria Teresa Rilla (Department of Neurology, Imperia Hospital, Imperia, Italy), Marinella Clerico (Dipartimento di Scienze Cliniche e Biologiche, Università di Torino, Turin, Italy), Mario Alberto Battaglia (Research Department, Italian Multiple Sclerosis Foundation, Genoa, Italy; Department of Life Sciences, University of Siena, Siena, Italy), Marzia Fronza (Centro Sclerosi Multipla Ospedale Binaghi Cagliari, ATS Sardegna,

Università di Cagliari, Calgiari, Italy), Massimo Del Sette (Neurology Unit, Galliera Hospital, Geno, Italy), Matilde Inglese (Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health, University of Genoa, Genoa, Italy; Ospedale Policlinico San Martino IRCCS, Genoa, Italy; Center of Excellence for Biomedical Research, University of Genoa, Genoa, Italy), Matteo Scialabba (U.O. Neurologia e Centro Sclerosi Multipla, Fondazione Istituto G. Giglio, Cefalù, Italy), Michele Bedognetti (Centro Sclerosi Multipla S.C. Neurologia Asl 3 Genovese, Genoa, Italy), Monica Ulivelli (Department of Medicine, Surgery and Neuroscience, University of Siena, Siena, Italy), Nicola De Rossi (Centro Sclerosi Multipla ASST Spedali Civili di Brescia, Brescia, Italy), Paola Gazzola (Centro Sclerosi Multipla S.C. Neurologia Asl 3 Genovese, Genoa, Italy), Rachele Bigi (Center for Experimental Neurological Therapies, Department of Neurosciences, Mental Health, and Sensory Organs, Sapienza University of Rome, Rome, Italy), Raffaele Dubbioso (Clinica Neurologica, DSNRO Università Federico II di Napoli, Naples, Italy), Roberta Reniè (Center for Experimental Neurological Therapies, Department of Neurosciences, Mental Health, and Sensory Organs, Sapienza University of Rome, Rome, Italy), Rosa Iodice (Clinica Neurologica, DSNRO Università Federico II di Napoli, Naples, Italy), Sabrina Fabbri (Centro Sclerosi Multipla S.C. Neurologia Asl 3 Genovese, Genoa, Italy), Sarah Rasia (Centro Sclerosi Multipla ASST Spedali Civili di Brescia, Brescia, Italy), Sergio Parodi (Department of Neurology, Sant'Andrea Hospital, La Spezia, Italy), Simona Rolla (Dipartimento di Scienze Cliniche e Biologiche, Università di Torino), Stefan Platzgummer (Laboratory of Clinical Pathology, F. Tappeiner Hospital, Merano, Italy), Maria Laura Stromillo (Clinica Neurologica e Malattie Neurometaboliche, Universita' degli Studi di Siena, Siena, Italy), Tiziana Tassinari (S.C. Neurologia, Ospedale Santa Corona, Pietra Ligure, Italy), Valentina Carlini (Centro Sclerosi Multipla S.C. Neurologia Asl 3 Genovese, Genoa, Italy).