

Multiple sclerosis disease-modifying therapies and COVID-19 vaccines: a practical review and meta-analysis

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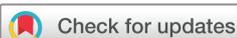
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ABSTRACT

Studies among people with multiple sclerosis (pwMS) receiving disease-modifying therapies (DMTs) have provided adequate evidence for an appraisal of COVID-19 vaccination policies among them. To synthesise the available evidence addressing the effect of MS DMTs on COVID-19 vaccines' immunogenicity and effectiveness, following the Cochrane guidelines, we systematically reviewed all observational studies available in MEDLINE, Scopus, Web of Science, MedRxiv and Google Scholar from January 2021 to January 2022 and extracted their relevant data. Immunogenicity data were then synthesised in a quantitative, and other data in a qualitative manner. Evidence from 28 studies suggests extensively lower B-cell responses in sphingosine-1-phosphate receptor modulator (S1PRM) treated and anti-CD20 (aCD20) treated, and lower T-cell responses in interferon-treated, S1PRM-treated and cladribine-treated pwMS—although most T cell evidence currently comprises of low or very low certainty. With every 10-week increase in aCD20-to-vaccine period, a 1.94-fold (95% CI 1.57 to 2.41, $p < 0.00001$) increase in the odds of seroconversion was observed. Furthermore, the evidence points out that B-cell-depleting therapies may accelerate postvaccination humoral waning, and boosters' immunogenicity is predictable with the same factors affecting the initial vaccination cycle. Four real-world studies further indicate that the comparative incidence/severity of breakthrough COVID-19 has been higher among the pwMS treated with S1PRM and aCD20—unlike the ones treated with other DMTs. S1PRM and aCD20 therapies were the only DMTs reducing the real-world effectiveness of COVID-19 vaccination among pwMS. Hence, it could be concluded that optimisation of humoral immunogenicity and ensuring its durability are the necessities of an effective COVID-19 vaccination policy among pwMS who receive DMTs.

INTRODUCTION

Global mass vaccination has been the most prominent effort of humanity to end the COVID-19 pandemic. Currently, many vaccines have been developed, all with reasonable safety and efficacy profiles (more information available at: <https://COVID-19.trackvaccines.org/agency/who>).

Among the people with multiple sclerosis (pwMS) who receive disease-modifying therapies (DMTs), the effectiveness of COVID-19 vaccination was thought to be affected—based on previous knowledge of the DMTs' immunomodulatory mechanisms of action and preliminary real-world evidence. Based on the same evidence, expert panels issued adjusted vaccination guidelines for pwMS, which mostly concerned people on sphingosine 1-phosphate receptor modulators (S1PRM), anti-CD20 therapies (aCD20), and other B-cell depleting therapies (BCDT).^{1–4}

Later on, administration of booster doses of COVID-19 vaccines was recommended due to observation of waning humoral immunity⁵ and clinical effectiveness^{6–8} over time. Among the pwMS, homologous booster doses were also used to immunise the ones who did not seroconvert following their first vaccination cycle.

Now, as several studies around the globe addressed the mentioned issues, the available real-world data is adequate for an appraisal of the initial vaccination policies of pwMS, and valuable for development of more effective ones in the future. Hence, in this systematic review and meta-analysis study, we aimed to gather and synthesise the available data and investigate the effect of DMTs on B-cell and T-cell immunogenicity and effectiveness of COVID-19 vaccines among pwMS, ultimately providing an evidence base for future research, policy making and management of pwMS receiving DMTs.

METHODS

In accordance with the Cochrane guidelines, we systematically reviewed and meta-analysed the available observational studies with the following formulation of objectives:

- Population: pwMS.
- Exposure: DMTs.
- Comparison: Being unexposed to DMTs (UX)
- Primary outcomes:
 - Vaccine-induced B-cell and T-cell responses.
 - Vaccine effectiveness.

We hereby reported and discussed the mentioned study's results in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (available from: <http://www.prisma-statement.org>). Due to restrictions in word

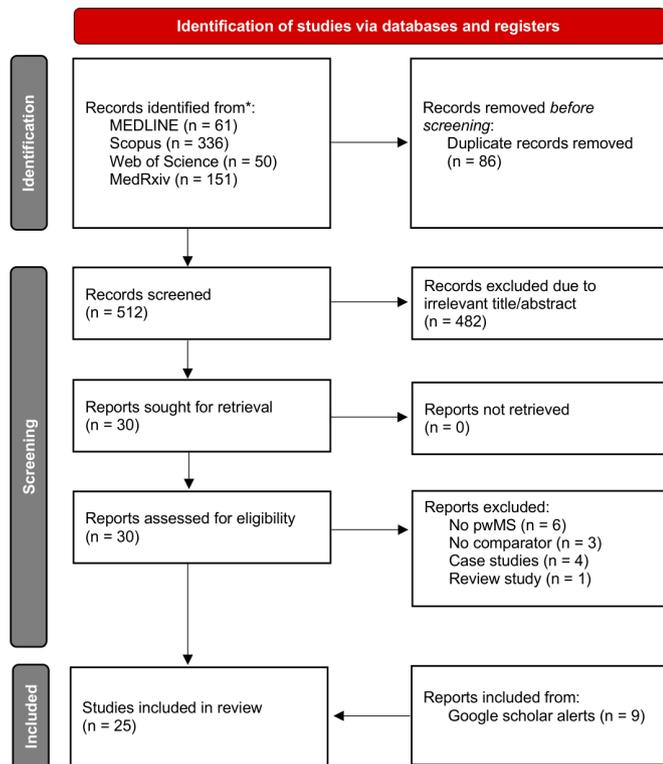


Figure 1 PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; pwMS, people with multiple sclerosis.

count, please find the further details of the methods from online supplemental material.

RESULTS AND DISCUSSION

Overall, data from 28 studies (5025 pwMS and 1635 healthy controls) were synthesised (figure 1, table 1). One study⁹ was excluded despite containing eligible participants because their data could not be extracted. The studies differed in outcome measurement methods, settings, number of participants and the administered vaccines. The assessed vaccines used either mRNA (BNT162b2, mRNA-1273), adenoviral vector (AV) (Ad26.COVS.2, ChAdOx1) or inactivated (CoronaVac, BBIBP-CorV) platforms. Other prominent points of heterogeneity were the used assays, the number/types of assessed DMTs, the usage of different comparators (eg, healthy participants, pwMS on no DMT), and the time points of obtaining samples from participants.

The results of individual studies, heterogeneity tests, forest and funnel plots, and the detailed rationale behind each quality assessment—based on National Institutes of Health tools—is accessible from online supplemental file 2. The pooled measures are summarised in both table 2 and figure 2. The certainty of evidence, assessed using the Grades of Recommendations, Assessment, Development and Evaluation approach, is presented in the following paragraphs, and along its explicit rationale in table 2.

Effect of DMTs on COVID-19 vaccines' immunogenicity

Interferons

Based on evidence with moderate certainty, interferons (IFNs) do not decrease the odds of seroconversion (OR (95% CI): 0.84 (0.38 to 1.83), $p=0.66$) (online supplemental figure 1). All

pwMS on IFN in four studies^{10–13} seroconverted; they showed similar postvaccination antibody concentrations with the UX people, except in one study, in which they showed significantly higher concentrations of anti-Spike (S) receptor binding domain IgG compared with healthy controls.¹³ The authors suggested that IFN-beta 1a therapy may promote the postvaccination antibody responses in pwMS, however, this finding was not observed in other studies.

One study¹⁴ pointed that the extent of interferon-gamma release responses to the S antigen is lower in samples from IFN-treated pwMS compared with healthy controls (OR (95% CI): 0.02 (0.00 to 0.28), $p<0.01$), suggesting with very-low certainty that IFNs blunt the vaccine's T-cell immunogenicity. The investigators attributed the blunt to both CD4+ and CD8+ subpopulations based on a flow cytometric analysis.¹⁴ Further replication is warranted to add to the certainty of this finding.

Glatiramer acetate

Evidence suggests with moderate certainty that glatiramer acetate (GA) does not affect the odds of post-vaccination seroconversion (OR (95% CI): 0.87 (0.31 to 2.42), $p=0.79$) (online supplemental figure 2). GA-treated pwMS who remained seronegative after vaccination were only present in two studies^{15 16} and all received inactivated vaccination; however, their postvaccination antibody concentrations were similar with UX people in those studies.

Activation-induced marker (AIM) assay in one study with limited sample size¹⁷ (very low-certainty evidence) suggested that GA affects vaccine immunogenicity neither in CD4+ (OR not measurable) nor CD8+ (OR (95% CI): 0.62 (0.04 to 9.00), $p=0.72$) subpopulations of T-cells. Furthermore, it is worth mentioning that adequate interferon-gamma release responses were present after SARS-CoV-2 infection in GA-treated people,¹⁸ suggesting favourable T-cell responses.

Dimethyl fumarate

Evidence with moderate certainty did not confirm any effect of dimethyl fumarate (DMF) on odds of postvaccination seroconversion (OR (95% CI): 1.98 (0.96 to 4.09), $p=0.07$) (online supplemental figure 3). All of the pwMS on DMF in seven studies^{10 12 13 16 17 19 20} seroconverted following mRNA or inactivated vaccination; postvaccination antibody concentrations of whom were similar to UX people.

Evidence on T-cell responses among DMF-treated pwMS was limited to one study with a limited sample size¹⁷ (very-low-certainty evidence), which by using AIM assays, did not confirm any effect of DMF on the vaccine-induced responses of CD4+ (OR not measurable) and CD8+ (OR (95% CI): 3.78 (0.18 to 78.38), $p=0.39$) subpopulations of T-cells. Interferon-gamma release responses were sufficient in DMF-treated pwMS after SARS-CoV-2 infection, suggesting adequate T-cell response.¹⁸

Teriflunomide

A slightly negative effect of teriflunomide (TERI) was observed on post-vaccination seroconversion odds (OR (95% CI): 0.38 (0.16 to 0.90), $p=0.03$) (online supplemental figure 4); this finding is composed of very low certainty due to inadequate number of studies and considerable heterogeneity. The cause of heterogeneity was suspected to lie within usage of different vaccine platforms; however, as a limited number of mRNA vaccine studies had measurable relative effects, their pooled measures resulted in a wide confidence limit, and the difference between the inactivated and mRNA measures did not reach

Table 1 Characteristics of included studies

Study (location)	Sample size (pwMS, HC)	Vaccine (platform)	B-cell assay (method, manufacturer)	T-cell assay (method, manufacturer)	Study quality*
Achiron <i>et al.</i> (Israel) ^{19 77 78}	503 (414, 89)	BNT162b2 (mRNA)	Serum anti-S1 IgG (ELISA, EUROIMMUN) PBMC S-induced IgG-secreting B-cells (FluoroSpot, Mabtech)	PBMC S-induced IFN-g-, IL-2-positive T-cells (FluoroSpot, Mabtech)	Good
Ali <i>et al.</i> (USA) ⁵⁸	53 (46, † 7)	BNT162b2 (mRNA) mRNA-1273 (mRNA)	Serum Anti-RBD IgG (CLIA, Siemens)	NA	Fair
Apostolidis <i>et al.</i> (USA) ³⁹	30 (20, 10)	BNT162b2 (mRNA) mRNA-1273 (mRNA)	Serum anti-S IgG (ELISA, NA) Serum anti-RBD IgG (ELISA, NA) PBMC S-induced IgG-secreting B-cells (Cell Probe, NA)	PBMC S-induced activation marker-positive T-cells (AIM, NA)	Fair
Bigaut <i>et al.</i> (France) ⁹	28 (28, 0)	BNT162b2 (mRNA) mRNA-1273 (mRNA)	Serum anti-RBD IgG (CMIA, Abbot; ECLIA, Roche)	NA	Fair
Brill <i>et al.</i> (Israel) ⁴⁰	112 (72, 40)	BNT162b2 (mRNA)	Serum anti-S IgG (CLIA, DiaSorin) Serum anti-RBD IgG (CMIA, Abbot)	PBMC S/N-induced IFN-g-positive T-cells (ELISpot, Oxford Immunotec)	Fair
Capone <i>et al.</i> (Italy) ¹⁰	140 (140, 0)	BNT162b2 (mRNA)	Serum anti-RBD IgG (CMIA, Abbot)	NA	Good
Capuano <i>et al.</i> (Italy) ³⁰	57 (26, 31)	BNT162b2 (mRNA)	Serum anti-S IgG (CLIA, DiaSorin)	NA	Good
Disanto <i>et al.</i> (Switzerland) ²¹	116 (116, 0)	BNT162b2 (mRNA) mRNA-1273 (mRNA)	Serum anti-RBD IgG (CMIA, Abbot)	NA	Good
Etemadifar <i>et al.</i> (Iran) ¹⁵	358 (144, 214)	BBIBP-CorV (Inactivated)	Serum anti-S IgG (ELISA, Pishdazteb)	NA	Good
Gadani <i>et al.</i> (USA) ¹¹	101 (101, 0)	BNT162b2 (mRNA) mRNA-1273 (mRNA) Ad26.COV2.S (AV)	Serum anti-S1 IgG (ELISA, EUROIMMUN)	PBMC S-induced IFN-g-positive T-cells (FluoroSpot, Mabtech)	Fair
Gallo <i>et al.</i> (Italy) ⁷⁹	59 (4, 55)	BNT162b2 (mRNA)	Serum anti-S IgG (CLIA, DiaSorin)	NA	Fair
Giossi <i>et al.</i> (Italy) ¹²	312 (39, 273)	BNT162b2 (mRNA)	Serum anti-RBD IgG (CMIA, Abbot)	NA	Fair
Katz <i>et al.</i> (USA) ⁴³	48 (48, 0)	BNT162b2 (mRNA) mRNA-1273 (mRNA) Ad26.COV2.S (AV)	Serum anti-RBD IgG (ECLIA, Roche)	Rearranged TCR gene sequences (M-PCR, Adaptive Biotechnologies)	Fair
König <i>et al.</i> (Norway) ²³	1155 (528, 627)	BNT162b2 (mRNA) mRNA-1273 (mRNA) ChAdOx1 (AV)	PBMC S-induced IgG-secreting B-cells (BBFCA, NA) PBMC RBD-induced IgG-secreting B-cells (BBFCA, NA)	NA	Fair
Madelon <i>et al.</i> (Switzerland) ⁴¹	48 (26, 22)	BNT162b2 (mRNA) mRNA-1273 (mRNA)	Serum anti-RBD IgG (ECLIA, Roche)	PBMC S-induced activation marker-positive T-cells (AIM, NA)	Fair
Maniscalco <i>et al.</i> (Italy) ¹³	149 (125, 24)	BNT162b2 (mRNA)	Serum anti-RBD IgG (ECLIA, Roche)	NA	Good
Ozakbas <i>et al.</i> (Turkey) ¹⁶	591 (547, 44)	BNT162b2 (mRNA) CoronaVac (Inactivated)	Serum anti-RBD IgG (CMIA, Abbot)	NA	Good
Pitzalis <i>et al.</i> (Italy) ²²	975 (912, 63)	BNT162b2 (mRNA)	Serum anti-RBD IgG (ECLIA, Roche)	NA	Fair
Pompsch <i>et al.</i> (Germany) ⁴²	30 (10, 20)	BNT162b2 (mRNA)	Serum anti-S1 IgG (ELISA, EUROIMMUN)	S/N/M-induced IFN-g-positive T-cells (ELISpot, Miltenyi Biotec)	Fair
Sabatino <i>et al.</i> (USA) ¹⁷	80 (67, 13)	BNT162b2 (mRNA) mRNA-1273 (mRNA) Ad26.COV2.S (AV)	PBMC S-induced IgG-secreting B-cells (BBFCA, NA) PBMC RBD-induced IgG-secreting B-cells (BBFCA, NA)	PBMC S-induced activated T-cells (AIM; ICS; pMHC, NA)	Fair
Sormani <i>et al.</i> (Italy) ^{20 57}	780 (780, 0)	BNT162b2 (mRNA) mRNA-1273 (mRNA)	Serum anti-RBD IgG (ECLIA, Roche)	NA	Good
Tallantyre <i>et al.</i> (UK) ²⁴	473 (473, 0)	BNT162b2 (mRNA) ChAdOx1 (AV) Ad26.COV2.S (AV)	Serum anti-RBD IgG (ELISA, Kantaro Biosciences; GloBody, NA)	PBMC S/N/M-induced IFN-g-positive T-cells (ELISpot, ImmunoServ Ltd.)	Fair
Tortorella <i>et al.</i> (Italy) ¹⁴	186 (108, 78)	BNT162b2 (mRNA) mRNA-1273 (mRNA)	Serum anti-RBD IgG (NR) Neutralising antibodies (MNA, NA)	Whole blood S-induced IFN-g (ELISA, ProteinSimple)	Fair
Türkoğlu <i>et al.</i> (Turkey) ²⁵	59 (34, 25)	CoronaVac (Inactivated)	Serum anti-S1 IgG (ELISA, EUROIMMUN)	NA	Fair
Van Kempen <i>et al.</i> (Netherlands) ⁸⁰	87 (87, 0)	mRNA-1273 (mRNA)	Serum anti-RBD IgG (ELISA, NR)	NA	Fair
Studies with no comparators					
Guerrieri <i>et al.</i> (Italy) ⁸¹	32 (32, 0)	BNT162b2 (mRNA) mRNA-1273 (mRNA)	Various assays	NA	NA
Novak <i>et al.</i> (Denmark, USA) ⁸²	60 (60, 0)	mRNA vaccines	Serum anti-RBD IgG (CMIA, Abbot)	NA	NA
Grothe <i>et al.</i> (Germany) ³⁵	38 (38, 0)	BNT162b2 (mRNA) mRNA-1273 (mRNA) ChAdOx1 (AV)	Serum anti-S IgG (CLIA, DiaSorin)	NA	NA

* Assessed with National Institutes of Health quality assessment tools (The rationale of judgements are presented in an online supplemental file 2; The used criteria are available at: <https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools>). Good means least risk of bias; Fair, low risk of bias and Poor, moderate/high risk of bias.

† Including two participants with neuromyelitis optica and two with optic neuritis. AIM, activation-induced marker; AV, adenoviral vector; BBFCA, bead-based flowcytometry assay; CLIA, chemiluminescent immunoassay; CMIA, chemiluminescence microparticle immunoassay; ECLIA, electrochemiluminescence immunoassay; HC, healthy controls; ICS, intracellular cytokine staining; IFN-g, interferon-gamma; IL, interleukin; M, membrane protein; MNA, micronutralisation assay; M-PCR, multiplex PCR; mRNA, messenger RNA; N, nucleocapsid protein; NA, not applicable; NR, not reported; PBMC, peripheral blood mononuclear cells; pMHC, peptide major histocompatibility complex; pwMS, people with multiple sclerosis; RBD, receptor-binding domain; S, spike protein.

statistical significance ($\chi^2=2.91, p=0.09$). Nevertheless, considering that all of the TERI-treated pwMS seroconverted after mRNA vaccination,^{10 12 16 19–22} the suggested blunt may not be generalisable to the mRNA-vaccinated pwMS receiving TERI.

Furthermore, in comparison to UX people, TERI-treated pwMS had lower postvaccine antibody concentrations—regardless of the vaccine platform; this difference reached statistical significance only in one study.²² TERI’s mechanism of action—which

Table 2 Summary of findings

Factors (ref)	Post-vac outcomes							
	B-cell response				T-cell response			
	Seroconversion		IFN-g release		CD4 +AIM+		CD8 +AIM+	
	OR (95% CI)	P value (certainty*)	OR (95% CI)	P value (certainty*)	OR (95% CI)	P value (certainty*)	OR (95% CI)	P value (certainty*)
DMT (UX)								
-IFN	0.84 (0.38 to 1.83)	0.66 Moderate ^{1,2}	0.02 (0.00 to 0.14)	<0.01 very low ^{2,4,5}	Ni		Ni	
-GA	0.87 (0.31 to 2.42)	0.79 Moderate ^{1,2}	Ni		NE		0.62 (0.04 to 9.00)	0.72 very low ^{1,2,4,5}
-DMF	1.98 (0.96 to 4.09)	0.07 Moderate ^{1,2}	Ni		NE		3.78 (0.18 to 78.38)	0.39 very low ^{1,2,4,5}
-TERI	0.38 (0.16 to 0.90)	0.03 very low ^{2,3}	Ni		Ni		Ni	
-S1PRM	0.04 (0.03 to 0.06)	<0.00001 High ¹	0.04 (0.02 to 0.07)	<0.00001 Low ^{1,2,3}	0.01 (0.00 to 0.18)	0.001 very low ^{2,4,5}	0.95 (0.08 to 10.71)	0.97 very low ^{1,2,4,5}
-NTZ	0.53 (0.24 to 1.18)	0.12 Low ^{1,2,4}	1.00 (0.20 to 5.12)	1.00 very low ^{1,2,4,5}	NE		3.95 (0.23 to 69.44)	0.35 very low ^{1,2,4,5}
-CLAD	0.41 (0.15 to 1.11)	0.08 Low ^{1,2,5}	0.01 (0.00 to 0.04)	<0.00001 Low ^{1,2,5}	Ni		Ni	
-ALEM	0.32 (0.10 to 0.96)	0.04 Very Low ^{2,3}	Ni		Ni		Ni	
-aCD20	0.05 (0.04 to 0.06)	<0.00001 High ¹	1.12 (0.62 to 2.05)	0.70 Moderate ^{1,3}	1.13 (0.17 to 7.61)	0.90 Moderate ^{1,2}	2.54 (0.89 to 7.27)	0.08 Moderate ^{1,5}
aCD20 infusion-to-vac (per 10 weeks)	1.94 (1.57 to 2.41)	<0.00001 High ¹	Ni		Ni		Ni	

Results with p<0.05 are bolded.

*Based on GRADE approach (Baseline: moderate due to observational nature of studies; ▲upgrade; ▼downgrade): 1. ▲Result in line with quantitative analyses in individual studies; 2. ▼Low count of studies with measurable relative effect; 3. ▼ Inconsistency; 4. ▼ Risk of missing results and 5. ▼ Imprecision.

aCD20, anti-CD20 therapies; AIM, activation-induced marker; ALEM, alemtuzumab; CLAD, cladribine; DMF, dimethyl fumarate; DMT, disease-modifying therapy; GA, glatiramer acetate; GRADE, Grades of Recommendations, Assessment, Development and Evaluation; IFN, interferons; IFN-g, interferon-gamma; NE, not estimable; Ni, no information; NTZ, natalizumab; ref, reference; S1PRM, sphingosine-1-phosphate receptor modulators; TERI, teriflunomide; UX, unexposed; vac, vaccination.

involves inhibition of rapidly dividing cells, including activated B-cells—may explain this observation.

Furthermore, no study was found addressing the vaccine-induced T-cell responses in TERI-treated pwMS; this is therefore encouraged in future studies.

Sphingosine-1-phosphate receptor modulators

S1PRM extensively decrease the odds of post-vaccine seroconversion (OR (95% CI): 0.04 (0.03 to 0.06), p<0.00001) (online supplemental figure 5), according to evidence with high certainty. In all of the included studies,^{10 11 13–16 19–25} the S1PRM-treated pwMS had significantly lower concentrations of post-vaccine

antibodies when compared with UX people; the effect measures were, however, heterogenous. Therefore, evidence indicates with moderate certainty that pwMS on S1PRM are 25 times (95% CI: 16.66 to 33.33) less likely to show anti-S1, and 8.33 times (95% CI: 3.70 to 20) less likely to show anti-S seroconversion following COVID-19 vaccination ($\chi^2=7.24$, p<0.01). In contrast to the healthy population, evidence suggests with low certainty—due to limited count of inactivated vaccine studies—that inactivated-vaccinated S1PRM-treated pwMS are more likely to seroconvert compared with the mRNA-vaccinated and AV-vaccinated ones ($\chi^2=11.97$, p<0.001). Although theoretically reasonable,²⁶ this has been contradicted in head-to-head

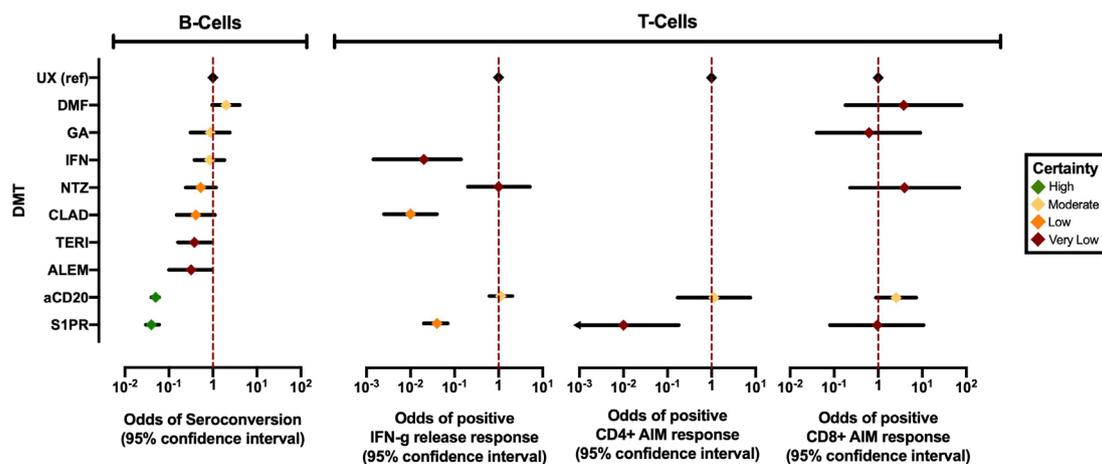


Figure 2 Summary forest plot of the pooled results. AIM, activation-induced marker; aCD20, anti-CD20 therapies; ALEM, alemtuzumab; CLAD, cladribine; DMF, dimethyl fumarate; GA, glatiramer acetate; IFN, interferons; IFN-g, interferon-gamma; NTZ, natalizumab; ref, reference; S1PR, sphingosine-1-phosphate receptor modulators; TERI, teriflunomide; UX, unexposed.

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mRNA-AV²⁴ and mRNA-inactivated¹⁶ immunogenicity comparisons. Hence, more replication of inactivated/mRNA/AV comparisons among S1PRM-treated pwMS is encouraged.

Furthermore, interferon-gamma release assays in two studies^{14 19} suggested with low certainty that S1PRM blunt vaccine-induced T-cell responses (OR (95% CI): 0.04 (0.02 to 0.07), $p < 0.00001$) (online supplemental figure 6). AIM assay in another study¹⁷ confirmed this blunt in the CD4+ (OR (95% CI): 0.01 (0.00 to 0.18), $p = 0.001$), but not in the CD8+ (OR (95% CI): 0.95 (0.08 to 10.71), $p = 0.97$) subpopulations of T-cells.

Additionally, among the pwMS on S1PRM who failed to seroconvert following their initial vaccination cycle, one study showed that administration of booster doses increased anti-S1 antibody concentrations, but promoted seroconversion only in 2/29 (7%).²⁷

S1PRM inhibit the trafficking of lymphocytes and restricts them to lymphatics; this causes peripheral lymphopenia in pwMS on S1PRM, which may explain the lower T-cell reactivity observed in their peripheral blood samples. In addition, an inhibitive effect of S1PRM on T-cell activation has previously been documented.²⁸ Blunted humoral responses could also be explained by the former reason (lymph-restricting effect of S1PRM); lymph flows one-way from peripheral to central areas, therefore, lymph-trapped lymphocytes in S1PRM-treated pwMS are unable to traffic to peripheral areas, and hence, are not properly exposed to the immunising materials of the vaccines. This may sound more reasonable when considering the immunising effect of systemic SARS-CoV-2 infection among S1PRM-treated pwMS.^{26 29} Another hypothesis is that S1PRM interact directly with the lipid nanoparticles used in mRNA vaccines,²⁶ however, this hypothesis could not explain humoral blunts after other vaccine platforms.

Natalizumab

Natalizumab (NTZ) did not affect the post-vaccine seroconversion odds significantly (OR (95% CI): 0.53 (0.24 to 1.18), $p = 0.12$) (online supplemental figure 7), suggests evidence with low certainty. All NTZ-treated pwMS in seven studies seroconverted following vaccination^{10 11 17 19 20 22 30}; while being similar in others, one of the studies²² showed a significantly lower post-vaccine antibody concentration in pwMS on NTZ compared with UX people.

Neither interferon-gamma release¹¹ nor AIM¹⁷ assays suggested a blunting effect of NTZ on vaccine-induced T-cell responses (very-low-certainty evidence).

NTZ, an anti- $\alpha 4$ -integrin monoclonal antibody, implements its effect by inhibiting lymphocyte extravasation; unlike S1PRM, it does not trap the lymphocytes in the lymphatic system—that is, it does not cause peripheral lymphopenia. Although their trafficking abilities are inhibited, the preserved presence of lymphocytes in blood flow—which, unlike the lymph flow, can be from central to peripheral areas as well—may be the reason NTZ does not blunt vaccination-induced immunisation as much as S1PRM (another class of lymphocyte trafficking inhibitor DMTs).

Cladribine

With the current guidelines, cladribine (CLAD) minimally affects the odds of postvaccine seroconversion (OR (95% CI): 0.41 (0.15 to 1.11), $p = 0.08$) (online supplemental figure 8); however, the certainty of this finding is low due to limited number of studies with measurable relative effect and imprecision of the pooled measure. All of the available studies have measured anti-S1

IgG, and no evidence was found regarding anti-S seroconversion. In five studies,^{10 13 14 16 20} all CLAD-treated pwMS seroconverted following vaccination with similar concentrations of postvaccination antibodies with the UX people. Assessment of vaccination-induced T-cell response was limited to one study¹⁴ (very-low-certainty evidence); samples from vaccinated CLAD-treated pwMS in that study showed significantly lower extents of S-induced interferon-gamma release response compared with the UX people (OR (95% CI): 0.01 (0.00 to 0.04), $p < 0.00001$).

Compared with its effect on the T-cell lineage, CLAD's effect on the B-cells is more extensive but less durable.^{31–34} As interpreted, this has been translated into proper humoral despite blunted cellular responses to COVID-19 vaccination in CLAD-treated pwMS. Furthermore, the time since the last CLAD dose theoretically affects humoral responses; This was suggested especially by Achiron *et al* study¹⁹ but did not reach statistical significance, and was not confirmed by other studies.^{20 22 35} It seems the implemented guidelines^{1–4} have suggested an adequate time window between CLAD administration and vaccination to prevent blunted humoral responses, making the probable effect unmeasurable. Additionally, although CLAD depletes the memory B-cells,³⁶ a preliminary study suggested its subsequent doses will not alter pre-existing humoral memory.³⁷ Still, there is limited evidence that the longevity of vaccine-induced humoral responses is lower in pwMS on CLAD¹⁹; this should be interpreted with caution as more time is generally required for an accurate assessment of longer-term responses. Replicative studies measuring the immunity waning speed in these pwMS after COVID-19 vaccination are, therefore, warranted to determine whether they require personalised booster schedules.

Alemtuzumab

With statistical significance but by a low extent, alemtuzumab (ALEM) was shown to negatively impact post-vaccine seroconversion odds (OR (95% CI): 0.32 (0.10 to 0.96), $p = 0.04$) (online supplemental figure 9); although, due to limited number of studies and imprecision of the pooled measures, the certainty of this evidence is considered very low. All studies measured anti-S1 IgG responses, except for one which assessed anti-S seroconversion; its data could not be extracted.²³ The ALEM-treated pwMS showed 100% seroconversion rates in three studies^{10 20 22} with similar concentrations of post-vaccination antibodies to the UX people.

Vaccination-induced T-cell responses were not assessed in any of the included studies, still, ALEM's durable effect of T-cell lineage³⁸ (similar to CLAD) suggests that it has blunting effect on vaccine-induced T-cell immunity.

ALEM, an anti-CD52 monoclonal antibody, is known to significantly deplete B- and T-cells shortly after administration. ALEM's short-term effect on B-cell and T-cell dynamics is relatively similar to CLAD.^{34 38} Hence, although the time from the last ALEM infusion affects seroconversion,¹⁹ this effect is currently not measurable as the implemented guidelines^{1–4} seem to have recommended an adequate time window between ALEM infusion and vaccination. Similar to other BCDT, further studies measuring comparative immunity waning speeds in ALEM-treated pwMS are needed to determine whether they require more frequent boosters.

Anti-CD20 therapies

The aCD20 cause an extensive blunt on the vaccine-induced seroconversion rates (OR (95% CI): 0.05 (0.04 to 0.06), $p < 0.00001$) (online supplemental figure 10). The certainty of

this finding is considered high as it was suggested by all studies; however, the studies had heterogeneous effect measures. Therefore, it could be indicated with moderate certainty that with the current guidelines, pwMS on aCD20 are 20 times (95% CI: 16.66 to 25) less likely to seroconvert for anti-S1, and 12.5 times (95% CI: 7.69 to 20) less likely to seroconvert for anti-S antibodies ($\chi^2=2.76$, $p=0.10$) following COVID-19 vaccination. Furthermore, evidence indicates with high certainty that every 10 week delay in subsequent aCD20 infusion is associated with a 1.94-time (95% CI: 1.57 to 2.41, $p<0.00001$) increase in seroconversion odds of aCD20-treated pwMS (online supplemental figure 11). A possible publication bias may be present regarding this measure, as indicated by asymmetric funnel plot (online supplemental figure 11).

Regarding the T-cell responses, aCD20 affected neither the interferon-gamma release responses (OR (95% CI): 1.12 (0.62 to 2.05), $p=0.70$) (online supplemental figure 12), nor the AIM responses of CD8+ (OR (95% CI): 2.54 (0.89 to 7.27), $p=0.08$) (online supplemental figure 13) and CD4+ (OR (95% CI): 1.13 (0.17 to 7.61), $p=0.90$) T-cell subpopulations. Quantitative analyses in most studies^{11 14 17 24 39–42} were in line with the dichotomised evidence. Multiplex PCR assay in one study⁴³ indicated positive adaptive T-cell responses among 100% of postvaccine seronegative aCD20-treated pwMS.

Furthermore, the preliminary evidence indicates significant decline in seropositivity rates of pwMS on aCD20 6 months after their second dose.^{44 45} Homologous mRNA boosters in pwMS on aCD20 promoted T-cell responses,⁴⁶ while humoral responses were still heavily dependent on the serostatus following the first vaccination cycle, and the B-cell dynamics at the time of booster administration.^{27 45–47} In other words, among the aCD20-treated pwMS not seroconverting after their initial vaccination cycle, the booster doses promoted humoral immunisation only if their B-cells were reconstituted. Studies among people on aCD20 with diseases other than MS^{48 49} support the same conclusion.

As the B-cells are the main expressors of the CD20 marker, the anti-CD20 monoclonal antibodies primarily affect the B-cell compartment of the immune system—although some recent literature suggests that their effectiveness in MS may stem from their effect on subsets of ‘rogue’ CD20+ T cells.⁵⁰ Similar to pwMS on other DMTs, the COVID-19 vaccines’ immunogenicity among pwMS on aCD20 could be considered a translation of the previously-determined B-cell and T-cell dynamics in them,^{34 51} based on which the current guidelines recommended a 12-to-36-week window between aCD20 infusion and COVID-19 vaccination.^{1–4} However, the presented evidence suggests that the mentioned interval, although increases the odds, will not be adequate to reverse the humoral blunts in pwMS on aCD20 (figure 3). The alterations in the dynamics of B-cells in people receiving aCD20 last for years according to the unpublished results from the NCT00676715 phase-II extension trial,⁵² suggesting durable, long-lasting benefits of aCD20 without subsequent dosing.⁵³ However, this durable effect of aCD20 has shown to be able to alter vaccine immunogenicity for as long as 3 years, as observed in people with haematological malignancies.⁵⁴ Hence, prior B-cell profiling and post-vaccination serological screening may be the necessities of an effective personalised vaccination strategy in pwMS who received aCD20 at any time point within 3 years.

Vaccine types

Based on phase-III data, the efficacy profiles of different available COVID-19 vaccine types (ie, mRNA, AV, inactivated and

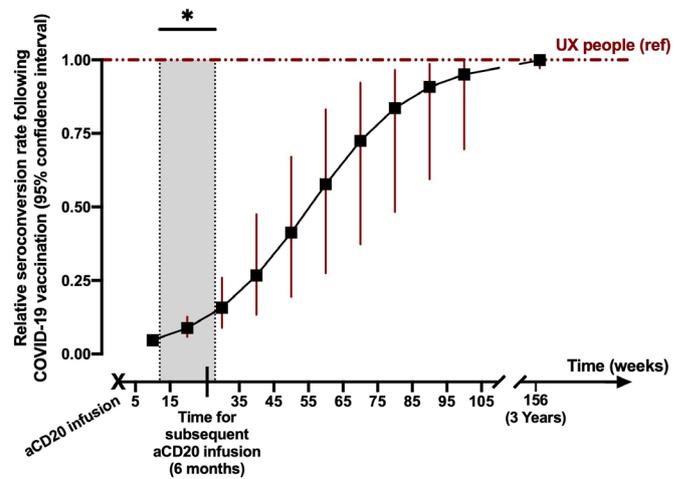


Figure 3 Schematic curve showing the association of post-vaccination seroconversion rates with time since last anti-CD20 infusion. *Current guideline recommendations on minimum delay of vaccination after anti-CD20 infusion. UX, unexposed.

protein based) seems to correlate to their anti-S/S1 humoral immunogenicity—both in healthy people^{55 56} and pwMS.⁵⁷ For the pwMS and in terms of efficacy, head-to-head comparisons of the available COVID-19 vaccines reveals the superiority of mRNA-1237 over BNT162b2 (both mRNA-based)^{14 20 58}—probably due to higher concentrations of active material—BNT162b2 and mRNA-1237 (mRNA) over ChAdOx1 and Ad26.COV2.S (AV),^{11 17 24 43} and BNT162b2 (mRNA) over CoronaVac (inactivated)¹⁶—although humoral immunisation did not differ significantly in pwMS on aCD20 receiving BNT162b2 and CoronaVac in Ozakbas *et al*¹⁶ study. The choice of a specific vaccine type among pwMS is encouraged and should be based on an individualised risk/benefit assessment with careful consideration of their COVID-19 risk factor profile,^{59 60} their DMT and the availability/cost-effectiveness of the vaccine.^{61 62}

Moving into the clinic

While the serum anti-S/S1 assays are deemed predictive of its neutralising activity,^{63 64} and the serum neutralising activity predictive of the clinical protection against symptomatic SARS-CoV-2 infection,⁶⁵ pwMS with adequate humoral responses—mostly on DMTs other than aCD20 and S1PRM—would theoretically show adequate protection against SARS-CoV-2. However, in the absence of humoral immunisation, it is doubted whether the adaptive T-cell responses could provide adequate protection. Currently one real-world study confirms the predictive effect of seroconversion on post-vaccination COVID-19 incidence and severity,⁵⁷ and four studies from UK, Italy and Iran indicate rising comparative incidence and severity of COVID-19 among pwMS on S1PRM and aCD20 following mass vaccination of pwMS.^{57 66–68} The registry-based UK study⁶⁶ marks a rise in COVID-19 comparative incidence among aCD20-treated and S1PRM-treated pwMS after the date the mass vaccination of pwMS was started in the area—although the study did not provide any information on the vaccination status of its individual participants. The Italian and Iranian studies^{57 67 68}—which to the best of our knowledge, were not peer-reviewed up to the time of the present study—followed up cohorts of vaccinated pwMS receiving different DMTs; they noted significant rises in both incidence and severity of breakthrough COVID-19 in aCD20-treated and S1PRM-treated pwMS compared with

the others. Based on these studies, the less-extensive humoral blunts in pwMS on TERI, ALEM and possibly CLAD, do not seem to have had any significant effect on vaccine effectiveness. Regarding the protective effect of adaptive T-cell responses, currently, the only clue lies within the Iranian study⁶⁷—although it has not been confirmed by a larger Italian study⁶⁸ and should be considered with excessive caution due to the current limitation of evidence; it showed that among the vaccinated pwMS, the ones on aCD20 experienced comparable incidence and severity of COVID-19 with those on fingolimod (an S1PRM). Unlike the S1PRM-treated pwMS, the aCD20-treated are known to be prone to a severer course of COVID-19 before vaccination^{59, 69}; robust postvaccination T-cell responses in the aCD20-treated pwMS—which is absent in the S1PRM-treated ones—may therefore, explain the unexpected comparable severity of breakthrough COVID-19 among them after vaccination. Still, it should be emphasised that the protective effect of adaptive T-cell responses in the absence of antibodies could neither be confirmed nor measured until further comparative evidence of real-world incidence and severity of COVID-19 among vaccinated aCD20-treated and unvaccinated pwMS becomes available.

CONCLUSION

The presented analyses highlight and corroborate the relevance for an optimal treatment strategy in pwMS before COVID-19 vaccination. It was demonstrated that the current vaccination strategy has failed to promote adequate humoral immunity in aCD20-treated and S1PRM-treated pwMS, which is being translated into low clinical effectiveness of COVID-19 vaccines among them—despite adequate T-cell responses in the ones on aCD20. Their susceptibility to worse COVID-19 outcomes, and the dependency of COVID-19 vaccines' humoral immunogenicity to the B-cell dynamics at the time of administration—and therefore, the timing of aCD20 infusion—stress the importance of personalising vaccination strategies for pwMS on aCD20 with respect to their B-cell profiles and aCD20 infusion timings. Theoretically and based on limited evidence, mode of action and administration method may be important factors to consider also when vaccinating S1PRM-treated pwMS. Milder humoral and considerable T-cell response blunts—also depending on dosage timings—and higher immunity waning speeds may be present in pwMS on CLAD and ALEM. It should be emphasised that these findings currently comprise of inadequate certainty; however, subject to their confirmation by further evidence, they stress the importance of earlier booster administrations among BCDDT-treated pwMS. TERI may also cause a humoral immunogenicity blunt, however, being less extensive and clinically irrelevant based on current evidence—which also comprises of low certainty—pwMS on TERI may not require countering policies other than being provided with reliable information about the importance of booster doses. Evidence to date does not indicate any significant effect of IFN, GA, DMF, and NTZ on COVID-19 vaccines' immunogenicity and effectiveness.

Additionally, similar to the healthy population,^{70–76} heterologous boosters may be more immunogenic and effective for pwMS; we unfortunately could not find any evidence in this regard. Therefore, further immunogenicity and effectiveness studies are encouraged among pwMS receiving heterologous vaccination regimens.

LIMITATIONS

Some limitations account to this study. Most important of all, it is a synthesis of observational studies which often present

low to moderate-level evidence. Most probably, this limitation will account to future reviews as well as randomised studies are doubted to be considered ethical at the current stage. Other limitations included restrictions in obtaining data from primary investigators, computational problems/restrictions in meta-analysis/meta-regression and lack or low certainty of evidence in some instances. Future updated reviews are encouraged to account for the mentioned limitations.

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