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Multiple Sclerosis and Related Disorders

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Review article

Effects of MS disease-modifying therapies on responses to vaccinations: A review.

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A B S T R A C T

Background: : Development of long-term immunologic memory relies upon humoral and cellular immune responses. Vaccinations aim to stimulate these responses against pathogens. Several studies have evaluated the impact of multiple sclerosis disease-modifying therapies on immune response to vaccines. Findings from these studies have important implications for people with multiple sclerosis who require vaccination and are using disease-modifying therapies.
Methods: : Searches using PubMed and other engines were conducted in May 2020 to collect studies evaluating the impact of various disease-modifying therapies on immune responses to vaccination.
Results: : Several studies demonstrated preserved immune responses in people treated with beta-interferons to multiple vaccine types. Limited data suggest vaccine responses to be preserved with dimethyl fumarate treatment, as well. Vaccine responses were reduced to varying degrees in those treated with glatiramer acetate, teriflunomide, sphingosine-1-phosphate receptor modulators, and natalizumab. The timing of vaccination played an important role in those treated with alemtuzumab. Humoral vaccine responses were significantly impaired by B cell depleting anti-CD20 monoclonal antibody therapies, particularly to a neoantigen. Data are lacking on vaccine responses in patients with multiple sclerosis taking cladribine and high-dose corticosteroids. Notably, the majority of these studies have focused on humoral responses, with few examining cellular immune responses to vaccination.
Conclusions: : Prior investigations into the effects of individual disease-modifying therapies on immune responses to existing vaccines can serve as a guide to expected responses to a SARS-CoV-2 vaccine. Responses to any vaccination depend on the vaccine type, the type of response (recall versus response to a novel antigen), and the impact of the individual disease-modifying therapy on humoral and cellular immunity in response to that vaccine type. When considering a given therapy, clinicians should weigh its efficacy against MS for the individual patient versus potential impact on responses to vaccinations that may be needed in the future.

1. Introduction

Multiple sclerosis (MS) is an immune-mediated demyelinating central nervous system (CNS) condition characterized by attacks of neurologic symptoms disseminated in space and time that often leads to disability. MS affects over 600,000 people in the United States with enormous costs to society. (Wallin et al., 2019) MS disease-modifying therapies (DMTs) act on the immune system, by modulation or suppression. This review assesses the current evidence regarding the impact of MS DMTs on immune responses to existing vaccinations, highlighting implications for response to a potential vaccine against SARS-CoV-2.

An effective immune response that provides long-term immunologic memory is driven primarily by the adaptive immune system, consisting of B cells (responsible for humoral, or antibody-mediated, immunity) and T cells (responsible for cell-mediated immunity). When stimulated in the presence of their target antigen, B and T cells clonally expand, with some transforming into memory cells, able to rapidly proliferate and become effector cells upon re-exposure to their target antigen. Upon activation, B cells can also differentiate into plasma cells that generate initially IgM and then IgG antibodies specific to the antigen. (2) Table 1 summarizes vaccine types and how the immune responses they generate differ.

Humoral responses to vaccines are generally measured using titers of IgG antibodies against the particular antigen, though use of the hemagglutination inhibition (HI) assay is an exception. (Ayling et al.,

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Table 1
Types of vaccines.

Vaccine type	Examples	Mechanism to generate immune response	Advantages	Disadvantages
Inactivated	Influenza (IM)[a,b], polio (IM)	Uses entire pathogen that has been killed with chemicals, heat, or radiation	Stable and safe (no live virus present)	Induces a weaker immune response, generally requires an adjuvant or additional booster doses
Live attenuated	MMR, varicella, influenza (nasal), polio (PO), yellow fever	Uses entire pathogen that has been weakened in the laboratory	Induces strong humoral and cellular responses, conferring long-term immunity with one or two doses	Generally contraindicated in those with weakened immune systems due to risk of generating disease
Subunit – polysaccharide[c]	PPSV23	Uses the most immunogenic components of the pathogen	Stable and safe (no live virus present)	Expensive, must determine which combination of antigens will generate an effective immune response
Subunit – protein	HBV, HPV			
Conjugate[c]	HiB, PCV13, MCV4	Uses a protein antigen attached to a polysaccharide coating from the pathogen	Induces a more effective immune response than use of polysaccharide antigen alone	
Toxoid[c]	Tetanus, diphtheria	Uses inactivated bacterial toxins	Stable and safe (no live bacteria present)	Not highly immunogenic
Nucleic acid	N/A	Uses RNA or DNA encoding for the target antigen for antigen production	Inexpensive and stable	Not highly immunogenic, limited to protein antigens
Recombinant vector	N/A	Uses a viral vector to introduce genetic material to cells	More specific delivery of genes to target cells	May induce neutralizing antibodies, limiting their effect

Abbreviations: Hemophilus influenzae type B (HiB); Hepatitis B virus (HBV); human papilloma virus (HPV); intramuscular (IM); measles/mumps/rubella (MMR); oral (PO); quadrivalent meningococcal conjugate (MCV4); 13-valent pneumococcal conjugate (PCV13); 23-valent pneumococcal polysaccharide (PPSV23).

[a] Influenza vaccines typically include 2 influenza A antigens and one influenza B antigen per season.
[b] 2009 influenza vaccine contained new H1N1 influenza A strain that had led to "swine flu" pandemic.
[c] Unlikely to be used for SARS-CoV-2 vaccine.

Table 2
Studies of MS DMT effects on immune responses to vaccinations.

DMT	Mechanism of action	Type of study	Patient description	Control group	Intervention(s)	Outcome measure(s)	Result(s)	Support	Level of Evidence	Citation	Summary
Beta-interferons	Inhibition of T cell activation and proliferation; apoptosis of autoreactive T cells; induction of regulatory T cells; inhibition of leukocyte migration across BBB; cytokine modulation	Prospective, non-randomized, open label study	86 relapsing MS patients taking IFN beta	77 untreated MS patients	Inactivated seasonal influenza vaccine	HI titer ≥ 40	No significant difference in proportion reaching HI titer ≥ 40	Industry supported	Level 3	(Schwid et al., 2005)	Vaccine responses were not adversely affected by beta-interferon treatment.
		Non-randomized, open label, parallel group observational study	128 relapsing MS patients taking IFN beta (n = 46), teriflunomide 7 mg/day (n = 41), teriflunomide 14 mg/day (n = 41)	None	Inactivated seasonal influenza vaccine	HI titer ≥ 40	Lower (but non-significant) rates of HI titers ≥ 40 for one influenza antigen in teriflunomide 14 mg/day group Lower post/pre vaccination GMT ratio in both teriflunomide dose groups	Industry supported	Level 3	(Bar-Or et al., 2013)	
		Prospective observational open-label study	26 relapsing MS patients taking IFN beta	33 healthy controls	Inactivated seasonal influenza vaccine	Anti-influenza IgM/IgG pre- and post-vaccination (measured by ELISA)	No significant difference in vaccine-induced humoral immune responses	Investigator initiated, industry supported	Level 3	(Mehling et al., 2013)	
		Retrospective, non-randomized, observational study	H1N1 analysis: RRMS patients taking IFN beta (n = 36), GA (n = 37), natalizumab (n = 17), mitoxantrone (n = 11) Seasonal influenza analysis: RRMS patients taking IFN beta (n = 17), GA (n = 12), natalizumab (n = 8), mitoxantrone (n = 4)	H1N1 analysis: 216 healthy controls Seasonal influenza analysis: 73 healthy controls	Inactivated H1N1 influenza vaccine Inactivated seasonal influenza vaccine	HI titer ≥ 40	H1N1 analysis: Similar proportion reaching HI titer ≥ 40 of IFN beta and healthy controls, but reduced proportion in GA, natalizumab, and mitoxantrone groups Seasonal influenza analysis: Higher proportion reaching HI titer ≥ 40 against multiple influenza A strains in IFN beta group compared to GA, natalizumab, and mitoxantrone groups	No industry support	Level 3	(Olberg et al., 2014)	
		Prospective observational study	Mainly RRMS patients taking IFN beta-1a/1b (n = 25), GA (n = 23), fingolimod (n = 15), natalizumab (n = 12); untreated (n = 12)	62 healthy controls	Inactivated seasonal influenza vaccine	HI titer ≥ 40	No significant difference in proportion reaching HI titer ≥ 40 between IFN beta, GA, and untreated MS patients compared to HC; reduced rates in fingolimod and natalizumab groups	No industry support	Level 3	(Olberg et al., 2018)	
		Open-label non-randomized study	71 RRMS patients taking IFN beta (n = 33) and DMF (n = 38)	None	Tetanus-diphtheria toxoid vaccine 23-valent	Proportion with ≥ 2-fold rise in antigen-specific	No difference between IFN beta and DMF groups in proportion with ≥ 2-	Industry supported	Level 3	(Von Hehn et al., 2018)	

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Table 2 (*continued*)

Drug	Mechanism	Study design	Population	Comparator	Vaccine	Outcome measure	Results	Funding	Level of evidence	Reference	Notes
Glatiramer acetate	Binds HLA class II; induction of anti-inflammatory T cell responses and alterations in T cell function	Prospective, multicenter, non-randomized, observational study	MS patients (92.2% RRMS) taking beta IFN (n = 45), GA (n = 26), fingolimod (n = 6), natalizumab (n = 14)	None (various DMT arms compared to each other)	Inactivated seasonal influenza vaccine	HI titer ≥ 40 or 4-fold rise in post-vaccination HI titer	Significant difference amongst various DMT arms protected against one A strain and protected against all strains, with higher rates of protection in IFN beta (highest) and GA groups compared to fingolimod and natalizumab groups	Industry supported	Level 3	(Metze et al., 2019)	Responses to the inactivated influenza vaccine were reduced compared to healthy controls. Responses to live attenuated and subunit vaccines have not been reported for in this population.
		See above under Beta-interferons							Level 3	(Olberg et al., 2014)	Responses to multiple vaccine types probably were sufficient, if somewhat blunted.
		See above under Beta-interferons							Level 3	(Olberg et al., 2018)	
		See above under Beta-interferons							Level 3	(Metze et al., 2019)	
Teriflunomide	Inhibition of de novo pyrimidine synthesis, preventing expansion of autoreactive lymphocytes (but preserving memory cells)	See above under Beta-interferons							Level 3	(Bar-Or et al., 2013)	
		Prospective, randomized, double-blind, parallel-group study	23 healthy people taking teriflunomide 14 mg/day	23 healthy people taking placebo	Inactivated rabies vaccine (to assess neoantigen response) Candida, Trichophyton, tuberculin (to assess DTH)	Anti-rabies antibody titers Proportion with positive DTH reaction	Significantly lower GMTs at Days 31 and 38 in teriflunomide group, but all patients reached seroprotective levels No difference in DTH responses between groups	Industry supported	Level 2	(Bar-Or et al., 2015)	
Fumarates	Enhancement of Nrf2 transcriptional pathway, decreases downstream oxidative stress, inhibits NfκB pathway	See above under Beta-interferons							Level 3	(Von Hehn et al., 2018)	Toxoid and polysaccharide/conjugate vaccine responses were not significantly affected,

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Table 2 (*continued*)

	Mechanism	Study design	Population	Controls	Vaccine	Outcome measure	Result	Funding	Level	Reference	Comments
											though only one study had evaluated this.
S1P receptor modulators	Inhibition of S1P receptor to inhibit lymphocyte migration (lymphocytes remain sequestered in lymph nodes)	Open-label, observational, prospective study	14 MS patients taking fingolimod	18 healthy controls	Inactivated seasonal influenza vaccine	Anti-influenza IgM/IgG Post-vaccination frequency of γ-interferon cells with re-exposure	No significant difference in humoral or cellular responses	Industry supported	Level 4	(Mehling et al., 2011)	Responses to inactivated and toxoid vaccines were diminished in those taking fingolimod at the time of vaccination. Responses to the inactivated influenza vaccine were diminished in those taking siponimod at the time of vaccination.
		Randomized, blinded, placebo-controlled study	95 relapsing MS patients taking fingolimod	43 relapsing MS patients taking placebo	Inactivated seasonal influenza vaccine Tetanus toxoid booster	Proportion with seroprotective HI or anti-TT titers or 4-fold increase in HI or anti-TT titer	Significantly lower response rates in fingolimod group at multiple timepoints to influenza and TT vaccines	Industry supported	Level 2	(Kappos et al., 2015)	
		See above under Beta-interferons							Level 3	(Olberg et al., 2018)	
		See above under Beta-interferons							Level 4	(Metze et al., 2019)	
		Randomized, prospective, placebo-controlled study	90 healthy people taking siponimod ($n = 30$ stopped 7 days prior to vaccination; $n = 30$ took concomitantly; $n = 30$ stopped 10 days prior to vaccination and restarted 14 days after vaccination)	30 healthy people taking placebo	Inactivated seasonal influenza vaccine 23-valent pneumococcal polysaccharide vaccine	HI titer ≥ 40; post-vaccination increase in GMT ≥ 2.5-fold from baseline; proportion with ≥ 4-fold increase from baseline ≥ 2-fold increase in anti-pneumococcal IgG titer	Similar responses between groups to influenza A strains, but lower seroprotective response rate and GMTs in interrupted and concomitant siponimod groups for multiple influenza strains High response rates in all groups to PPSV23	Industry supported	Level 2	(Ufer et al., 2017)	
Natalizumab	Monoclonal antibody against α4-integrins, causing inhibition of lymphocyte migration across BBB	Prospective, observational, non-randomized study	17 RRMS patients taking natalizumab	10 healthy controls	Inactivated seasonal influenza vaccine	Proportion with ≥ 50% increase in anti-influenza IgG from baseline	No significant difference in anti-influenza IgG changes, with non-significant trend to lower titers in natalizumab group	Industry supported	Level 3	(Vågberg et al., 2012)	Inadequate vaccine responses occurred in some patients taking natalizumab.
		Randomized, open-label, prospective, controlled study	30 relapsing MS patients taking natalizumab	30 relapsing MS patients delaying initiation of natalizumab until 2 months post-vaccination	Tetanus toxoid KLH neoantigen	Proportion with ≥ 50% increase in antigen-specific IgG from baseline	No significant differences in antigen-specific IgG response rates, with non-significant trend to lower titers in natalizumab group	Industry supported	Level 3	(Kaufman et al., 2014)	
		See above under Beta-interferons							Level 3	(Olberg et al., 2014)	
		See above under Beta-interferons							Level 3	(Olberg et al., 2018)	

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Table 2 (*continued*)

Therapy	Mechanism	Study design	Study population	Comparator	Vaccine type	Outcome measure	Results	Support	Level	Reference	Summary
		See above under Beta-interferons									
B cell depleting therapies	Monoclonal antibodies against CD20, which depletes circulating B cells	Randomized, open-label, prospective study	68 relapsing MS patients who received one dose of ocrelizumab 600 mg	34 relapsing MS patients, untreated or taking beta IFN	Tetanus toxoid KLH neoantigen 23-valent pneumococcal polysaccharide vaccine	4-fold increase in antigen-specific IgG from baseline or development of protective antibody levels	Significantly lower response rates in ocrelizumab group to TT, KLH, and PPSV23, and lower responses to PCV13 booster vaccine and seasonal influenza vaccine	Industry supported	Level 2	(Stokmaier et al., 2018)	Vaccine responses, especially to neoantigens and T cell-independent antigens, were significantly impaired by B cell depletion. (Metze et al., 2019) Level 3
		Randomized, prospective study	69 rheumatoid arthritis patients taking rituximab (1000 mg twice, given 2 weeks apart) plus methotrexate	34 rheumatoid arthritis patients taking methotrexate alone	Tetanus toxoid KLH neoantigen 23-valent pneumococcal polysaccharide vaccine Candida (to assess DTH)	Proportion with ≥ 4-fold increase in antigen-specific IgG from baseline	Similar responses between groups to TT and DTH to Candida, but significantly reduced responses to PPSV23 and KLH in RTX/MTX group compared with MTX alone	Industry supported	Level 2	(Bingham et al., 2010)	
Alemtuzumab	Monoclonal antibody against CD52, which depletes circulating autoreactive T and B cells	Prospective case-control study	24 RRMS patients taking alemtuzumab	None	Tetanus-diphtheria toxoid vaccine Inactivated poliomyelitis vaccine Hemophilus influenzae type b conjugate vaccine Quadrivalent meningococcal vaccine 23-valent pneumococcal polysaccharide vaccine	4-fold increase in antigen-specific IgG from baseline or development of protective antibody levels	Similar responses to all vaccine types in study patients compared with historical controls, though proportion responding to vaccination within 6 months after treatment was lower	No industry support	Level 3	(McCarthy et al., 2013)	Responses to multiple vaccine types were maintained in patients taking alemtuzumab in the one available study, though somewhat blunted for vaccinations within 6 months of dosing.

Abbreviations: blood-brain barrier (BBB); delayed-type hypersensitivity (DTH); dimethyl fumarate (DMF); disease-modifying therapy (DMT); enzyme-linked immunosorbent assay (ELISA); geometric mean titer (GMT); glatiramer acetate (GA); healthy controls (HC); hemagglutination inhibition (HI); human leukocyte antigen (HLA); immunoglobulin G (IgG); immunoglobulin M (IgM); interferon (IFN); keyhole limpet hemocyanin (KLH); methotrexate (MTX); multiple sclerosis (MS); nuclear factor erythroid 2-related factor 2 (Nrf2); nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB); 13-valent pneumococcal conjugate vaccine (PCV13); 23-valent pneumococcal polysaccharide vaccine (PPSV23); relapsing-remitting multiple sclerosis (RRMS); rituximab (RTX); sphingosine-1-phosphate (S1P); tetanus toxoid (TT).

1781) The HI assay reports the inverse of the dilution (the titer) at which a patient's antibody-containing serum is no longer able to inhibit the viral hemagglutination property. For inactivated influenza vaccine, an HI titer of ≥ 40 is considered protective. (Zacour et al., 2016) Cellular immune responses to vaccines are less well-studied, and measurement methods are highly variable. Irrespective of vaccine type, immune responses to vaccination are generally more robust in women, in whom MS has a predilection. (Flanagan et al., 2017)

Vaccine safety in MS was a subject of debate throughout the 1990s and 2000s, as seasonal influenza, measles/mumps/rubella (MMR), Hepatitis B (HBV), H1N1 influenza, and human papillomavirus (HPV) vaccines were all implicated and subsequently refuted as being linked to MS development or worsening. (Mailand and Frederiksen, 2017; Stratton et al., 2012; Moriabadi et al., 2001; Miller et al., 1997; Scheller et al., 2015; Auriel et al., 2012; Confavreux et al., 2001; Langer-Gould et al., 2014) Vaccine efficacy in MS has been less controversial, as studies of untreated MS patients have not shown differences in responses compared to healthy controls (HC). (Moriabadi et al., 2001) Regulatory bodies now recommend vaccinating people with MS on a normal schedule, with some caveats regarding live attenuated vaccines. (14; Lebrun and Vukusic, 2019; Epstein et al., 2018)

The various immunomodulatory and immunosuppressive effects of different DMTs add complexity regarding vaccinations. Live vaccines are generally contraindicated in MS patients on immunosuppressive treatments. Mechanistically, DMTs that impact the adaptive immune system may decrease the efficacy of vaccines by impairing the development of long-term memory. (Loebermann et al., 2012) This review evaluates the current evidence regarding the impact of DMTs for MS on vaccine responses in humans.

2. Methods

A PubMed search was performed on May 1, 2020 for English language articles that were published between January 1, 1995 and May 1, 2020 using the MeSH terms *multiple sclerosis* and *vaccine* with each individual DMT. Articles not focusing on vaccine response in the setting of DMT use, such as basic pathophysiologic reviews, author commentaries, reports of vaccines used as MS therapy, and animal studies were excluded. Additional references were obtained from a Google search of each individual DMT and *immunization* and *vaccination* (May 2–3, 2020), secondary review of the articles discovered in these searches, searches of ClinicalTrials.gov (May 1, 2020) and CDC.gov (May 3, 2020), and review of manufacturer prescribing information for each DMT. Bias was qualitatively assessed for each study and funding sources are noted in Table 2. Levels of evidence for each study are assigned based on the Oxford centre for Evidence-Based Medicine 2011 Levels of Evidence. (18)

3. Discussion

Table 2 provides a summary of all published studies of vaccine responses in people using FDA-approved DMTs for MS.

3.1. Beta-interferon effects on responses to vaccines

A prospective, non-randomized, open label study compared responses to an inactivated influenza vaccine in 86 relapsing MS patients taking interferon beta-1a 44 mcg three times weekly and 77 untreated relapsing MS patients. (Schwid et al., 2005) There was no difference in the proportion of patients in each group with seroprotective HI titers (93.0% beta-interferon group vs. 90.9% untreated group), or the proportions mounting 2-fold (75.6% vs. 75.3%) and 4-fold (50.0% vs. 58.4%) increase in HI titers. This study offers Level 3 evidence that MS patients taking high-dose, high-frequency beta-interferon mount an appropriate immune response to the influenza vaccine.

Another study compared immune responses after seasonal influenza

vaccination in 82 teriflunomide-treated relapsing MS patients to 46 beta-interferon-treated relapsing MS patients. (Bar-Or et al., 2013) For all 3 influenza strains used, $> 90\%$ of those in the beta-interferon group had protective HI titers 28 days post-vaccination. Ratios of post-vaccination to pre-vaccination geometric mean titers (GMT) were all ≥ 3.4, indicating an effective immune response. This study was limited by lack of an untreated MS control group. Level 3 evidence.

A prospective observational study evaluated the effects of the inactivated influenza vaccine in 26 patients taking a variety of beta-interferon preparations, comparing anti-influenza IgM and IgG titers to those in 33 HC at multiple time-points post-vaccination. (Mehling et al., 2013) No significant difference between groups was found in the degree or duration of these humoral immune responses, with the exception of a significantly higher anti-influenza B IgG titer at days 14 and 28 in the beta-interferon group. Cellular immune responses were also compared by measuring the frequency of T cells secreting gamma-interferon in response to influenza antigen, with no differences between groups. Level 3 evidence.

A retrospective, non-randomized, observational study evaluated responses to the vaccine against 2009 H1N1 influenza (a neoantigen responsible for the "swine flu" pandemic) and the 2010 seasonal influenza vaccine in MS patients on a variety of DMTs. (Olberg et al., 2014) The beta-interferon group ($n = 36$ for 2009 and $n = 17$ for 2010) showed no significant differences from HC in the proportion reaching a protective HI titer in response to either the 2009 H1N1 vaccine (44.4% vs. 43.5%) or the 2010 seasonal influenza vaccine (88.2% vs. 71.2% [H1N1 influenza A strain] and 88.2% vs. 79.5% [H3N2 influenza A strain]). Protective antibody titers were measured several months post-vaccination, demonstrating durability. Study limitations include the small numbers of patients in each DMT subgroup and the use of questionnaires that may have led to recall bias. Level 3 evidence.

The same investigator group performed another observational study of 25 MS patients taking beta-interferons and compared influenza vaccine responses at multiple post-vaccination intervals to 62 HC. (Olberg et al., 2018) No differences in the proportion reaching a protective HI titer were observed between the two groups at any time, including at the peak antibody response time of 3 months (88.0% in the beta-interferon group vs. 94.6% in HC). Level 3 evidence.

Another observational study evaluating vaccine responses in 38 patients taking dimethyl fumarate included an arm of 33 relapsing-remitting MS (RRMS) patients taking beta-interferons. (Von Hehn et al., 2018) IgG titers were assessed pre- and post-vaccination with 3 vaccines to assess different types of immune responses: tetanus-diphtheria toxoid vaccine to assess T-cell dependent anamnestic humoral response, 23-valent pneumococcal polysaccharide vaccine (PPSV23) to assess T-cell independent humoral response, and quadrivalent meningococcal conjugate vaccine (MCV4) to assess neoantigen responses. Those with $a \geq 2$-fold rise in IgG levels after vaccination were considered responders. For anti-tetanus/diphtheria, there was no difference in the responder proportion (dimethyl fumarate group 68% vs. beta-interferon group 73%). Pneumococcal vaccination responses were not significantly different between the two groups, though there was considerable variability in GMT ratios across serotypes. Neoantigen responses to MCV4 were not different, with 53% of each group demonstrating a 2-fold rise in IgG. Post- to pre-vaccination GMT ratios were similar in the dimethyl fumarate and beta-interferon groups (4.1 vs 4.3, respectively). Level 3 evidence.

A prospective, multicenter, non-randomized study evaluated influenza vaccine responses in patients treated with a variety of DMTs. (Metze et al., 2019) Patients taking beta-interferons showed a significantly greater proportional vaccine response as measured by HI titer than other DMT groups taking glatiramer acetate, fingolimod, and natalizumab. Beta-interferon-treated patients reached seroprotective rates of $> 80\%$ for each strain, and reached protective HI titers to all 3 strains (73.3% of 45 patients) more frequently than those treated with glatiramer acetate (57.7% of 26 patients), fingolimod (33.3% of 6 patients),

and natalizumab (14.3% of 14 patients). This study was limited by lack of an untreated control group and low numbers, especially in the fingolimod and natalizumab groups. Level 3 evidence.

Together, these studies convincingly demonstrate adequate immune responses to a variety of vaccine mechanisms in MS patients treated with beta-interferons.

3.2. Glatiramer acetate effects on responses to vaccines

Some of the already-discussed studies of vaccine immune responses in people receiving beta-interferons also included people receiving glatiramer acetate. In the observational study of immune responses to the 2009 H1N1 pandemic influenza vaccine and the 2010 seasonal influenza vaccine discussed above, (Olberg et al., 2014) 37 MS patients taking glatiramer acetate had substantially lower rates of protection post-vaccination with the 2009 H1N1 "swine flu" vaccine (21.6%; GMT 153) compared to 216 HC (43.5%; GMT 170). Reduced rates of seroprotection were also observed for two different antigens in the 2010 seasonal influenza vaccine (58.3% and 41.7% in the 12 patients in the glatiramer acetate group vs. 71.2% and 79.5% in 73 HC). Level 3 evidence.

In a follow-up study of immune responses to the 2012/2013 seasonal influenza vaccine, (Olberg et al., 2018) most of the 23 MS patients treated with glatiramer acetate responded to the H1N1 influenza antigen (91.3% seroprotection at 3 months), similar to the 56 HC (94.6%), 14 untreated MS patients (92.9%), and 25 beta-interferon treated patients (88.0%). Responses to the H3N2 influenza antigen were low for all groups. Although the glatiramer acetate group responded less well than the beta-interferon and HC groups, this difference was not significant. Level 3 evidence.

In the 2019 prospective, multicenter, non-randomized study of several different DMTs discussed above, (Metze et al., 2019) 26 patients taking glatiramer acetate were included. The glatiramer acetate group demonstrated post-vaccination seroprotection rates to the 3 influenza antigens of 88.5%, 73.1%, and 80.8%, close to rates of the 45 people in the beta-interferon group (84.4%, 91.1%, and 88.9%). Level 3 evidence.

Although immune responses to influenza vaccines were observed in glatiramer acetate-treated patients in these studies, the results suggest that responses were reduced compared to HC and to those treated with beta-interferons. These studies regarding inactivated vaccination responses may not be generalizable to other vaccine types (such as live attenuated, nucleic acid, recombinant vector, or subunit vaccines), for which immune responses have not been reported in people on glatiramer acetate.

3.3. Teriflunomide effects on responses to vaccines

A study already mentioned in the beta-interferon section investigated the effect of teriflunomide on influenza vaccination responses in MS patients. (Bar-Or et al., 2013) This non-blinded, non-randomized, multicenter, multinational, parallel-group study included 128 patients in 3 groups: teriflunomide 7 mg (*n* = 41), teriflunomide 14 mg daily (*n* = 41), and beta-interferons (*n* = 46, the reference population). More than 90% of all patients in all groups achieved seroprotection (HI titer ≥ 40) for the H1N1 and influenza B antigens. Seroprotection was lower in the H3N2 teriflunomide 14 mg group (76.9%), compared to 90% in the 7 mg per day teriflunomide and beta-interferon groups. GMT ratios were reduced in the teriflunomide groups (2.3–3.1) compared to the beta-interferon group (3.4–4.7). A limitation of this study is that it was not powered for comparisons of immune responses in the teriflunomide and beta-interferon groups. Level 3 evidence.

A prospective, randomized, double-blind, parallel-group, placebo-controlled study compared antibody responses to rabies vaccine (neoantigen) and delayed type hypersensitivity (recall) to Candida albicans, Trichophyton, and tuberculin in 23 healthy people assigned to 14 mg/day teriflunomide with 23 healthy individuals assigned to placebo. (Bar-Or et al., 2015) GMTs for rabies antibodies were lower with teriflunomide than with placebo, but all subjects assigned to teriflunomide achieved seroprotective antibody levels. Teriflunomide had no adverse impact on the cellular memory response to recall antigens. Level 2 evidence.

Overall, these studies indicate modest negative effects of teriflunomide 14 mg/day on immune response to influenza and rabies vaccinations.

3.4. Effects of fumarates (dimethyl fumarate, diroximel fumarate) on responses to vaccines

3.4.1. Dimethyl fumarate

A single open-label, multicenter, non-randomized study evaluated the effects of dimethyl fumarate treatment on vaccination responses. (Von Hehn et al., 2018) 38 patients on dimethyl fumarate 240 mg twice daily were compared to 33 patients treated with beta-interferon after vaccination with 3 vaccines to assess different types of immune responses. This study is discussed in detail in the section on beta-interferons above and provided Level 3 evidence that dimethyl fumarate treatment did not reduce T-cell dependent and humoral immune responses.

3.4.2. Diroximel fumarate

No relevant studies were found.

3.5. Effects of sphingosine-1-phosphate receptor modulators on vaccine responses

3.5.1. Fingolimod

A small prospective study of immune responses to the seasonal influenza vaccine was performed in 14 fingolimod-treated MS patients and 18 HC. (Mehling et al., 2011) Influenza antigen-specific production of IgM and IgG, and the frequency of gamma-interferon secreting cells after immunization, were not significantly altered by fingolimod treatment compared to HC. However, the two groups were not well matched, with HC being younger (mean age 37, range 19–46) than the MS patients (mean age 44, range 31–60), and HC were 33% female compared with 57% female in the MS group. Level 4 evidence.

A blinded, randomized, multicenter, placebo-controlled study of response to seasonal influenza vaccine and tetanus toxoid (TT) booster was performed in 138 relapsing MS patients on either fingolimod 0.5 mg/day (*n* = 95) or placebo (*n* = 43). (Kappos et al., 2015) At 3 weeks post-vaccination, responder rates (proportion achieving seroprotective HI titers or a 4-fold increase in antibody titers against at least one influenza strain) for fingolimod vs. placebo, respectively, were 54% vs. 85%. At 6 weeks, responder rates were 43% vs. 75%. For TT, responder rates were 40% vs. 61% at 3 weeks and 38% vs. 49% at 6 weeks. Although many fingolimod-treated MS patients were able to mount protective immune responses, this study provided Level 2 evidence that response rates were reduced in patients on fingolimod compared with placebo-treated patients.

Fifteen patients on fingolimod were among the 90 MS patients and 62 HC included in a prospective study to measure antibody responses to the 2012/2013 influenza A H1N1 and H3N2 vaccine viruses. (Olberg et al., 2018) The fingolimod group developed reduced rates of seroprotection to H1N1 compared with controls or MS patients on beta-interferons and glatiramer acetate. At 3 months, 6 months, and 12 months, seroprotection rates were 71.4%, 58.3%, and 22.2% in the fingolimod group vs. 94.6%, 94%, and 70.4% in HC. The response to H3N2 was even poorer in those on fingolimod, with 21.4% protected at 3 months, 8.3% protected at 6 months, and 0% at 12 months post-vaccination compared with 69.6%, 58%, and 57.4% for HC. Level 3 evidence.

A non-randomized, prospective, non-controlled study of MS patients who underwent seasonal influenza vaccination discussed in earlier sections of this review included 6 people on fingolimod. (Metze et al., 2019) A lower proportion of fingolimod-treated patients achieved protection to H3N2 and influenza B compared to those on beta-interferons or glatiramer acetate. Interpretation of these results is limited by the very small size of the fingolimod subgroup. Level 4 evidence.

Taken together, these studies indicate that concurrent fingolimod reduces immune response to influenza vaccinations.

3.5.2. Siponimod

Responses to seasonal influenza and PPSV23 vaccines were assessed in 120 healthy persons treated with siponimod 2 mg/day or placebo. (Ufer et al., 2017) The randomized, prospective study enrolled 30 people per group into 3 siponimod treatment groups and a placebo group. Treatment groups were "preceding siponimod" (stopping 7 days prior to immunization), "concomitant" (non-interrupted siponimod), and "interrupted siponimod" (treatment interrupted 10 days prior to and for 14 days after immunization). The durations of stopping or interrupting siponimod were based on the known time of 7–10 days for circulating lymphocytes to return after drug discontinuation. Each person received seasonal influenza and PPSV23 vaccines, with blood samples obtained at baseline and multiple times after immunization. Seroprotection rate ≥70%, GMT increase of ≥2.5 vs. baseline, and IgG response rate of ≥40% were examined. At 28 days, each group exceeded the 70% response threshold and a GMT increase ≥2.5-fold for both influenza A antigens compared with baseline. For one of the two influenza B viruses, the seroprotection response threshold of ≥ 70% was not met for the interrupted and concomitant siponimod groups. Over 90% in each group responded to PPSV23 with >2-fold increase in IgG on day 28 vs. baseline. Compared to the placebo group, the proportions of people with titer increased ≥ 4-fold at day 28 were decreased in the concomitant and interrupted siponimod groups for H1N1, H3N2, and one of the influenza B viruses. GMTs over time were lower for the concomitant siponimod group for both influenza A strains and one of the influenza B strains compared to the other 3 groups. This study provides Level 2 evidence of a lower response to influenza vaccines in those on siponimod at time of vaccination. Stopping siponimod at least 7 days prior to administration of a vaccine and resuming siponimod (after up-titration) 2 or more weeks later is a potential strategy to improve vaccine response.

3.5.3. Ozanimod

No relevant studies were found.

3.6. Oral cladribine effects on responses to vaccines

No relevant studies have been reported in MS patients on oral cladribine. A vaccine study is being planned by the manufacturer.

3.7. Natalizumab effects on responses to vaccines

An early study of 17 natalizumab-treated MS patients (14 female) and 10 HC (5 female) examined antibody response to seasonal influenza vaccination. (Vågberg et al., 2012) Mean antibody titers to influenza A and B were not different between the two groups, with a non-significant trend towards lower titers to influenza A for the natalizumab group. This study was likely underpowered, and the study groups were not well matched. Level 4 evidence.

A randomized, controlled, open-label study of 60 people with relapsing MS was done to study the response to a recall antigen (TT) and the neoantigen Keyhole limpet hemocyanin (KLH). (Kaufman et al., 2014) Patients were randomized 1:1 to control or natalizumab groups. The control group received immunizations shortly after randomization and delayed starting natalizumab until after day 56, whereas those randomized to natalizumab were treated with natalizumab beginning 6

months prior to immunizations. A lower proportion of those in the natalizumab group responded to TT and to KLH at day 56. Although the differences were not statistically significant, the study may have been underpowered. Level 3 evidence.

A previously mentioned real-world study of 113 MS patients and 216 HC examined response to the 2009 H1N1 pandemic "swine flu" vaccine. (Olberg et al., 2014) Seventeen of the MS patients in that study were on natalizumab. Only 4 of the 17 (23.5%) achieved seroprotective HI titers after immunization, compared to 94 of 216 controls (43.5%) and 16 of 36 (44.4%) of those on beta-interferon. Level 3 evidence.

The same group of investigators performed a prospective study of responses to the seasonal influenza vaccination in 2012/2013 in 90 MS patients on four different immunomodulatory therapies and 62 HC at baseline and 3, 6, and 12 months post-immunization. (Olberg et al., 2018) The proportion of those few patients on natalizumab ($n = 11$ at 3 months, $n = 8$ at 6 months, and $n = 9$ at 12 months) that had adequate response to the immunization was consistently 10% or more lower than HC and MS patients on beta-interferons. Level 3 evidence.

In the previously-discussed 2019 non-randomized, prospective, study of 102 MS patients who underwent seasonal influenza vaccination, 14 were on natalizumab. (Metze et al., 2019) For H3N2 and the influenza B antigen, only 28.6% and 57.1%, respectively, of those on natalizumab achieved sufficient response, compared to 91.1% and 88.9% for the 45 people taking beta-interferon. Level 3 evidence.

Overall, these studies provide evidence that an inadequate response to some immunizations occurs in a sizeable proportion of people being treated with natalizumab.

3.8. Effects of anti-CD20 B cell depleting agents on responses to vaccines

3.8.1. Ocrelizumab

The VELOCE study (NCT02545868) investigated the effect of ocrelizumab treatment on responses to specific vaccine types. (Stokmaier et al., 2018) Relapsing MS patients were randomized 2:1 into Group A ($n = 68$), receiving a single dose of ocrelizumab 600 mg; or Control Group B ($n = 34$), on no DMT or taking interferon-beta 1a 44 mcg three times weekly. T-cell–dependent recall response was assessed with TT booster, PPSV23 was used to examine a mainly B-cell–dependent response, and the 13-valent pneumococcal conjugate vaccine (PCV13) was used to evaluate the response to a booster of PPSV23. Response to the seasonal influenza vaccine tested response to an inactivated vaccine, and immunization with KLH tested the humoral response to a previously unknown antigen. The ocrelizumab group had a poorer humoral response to vaccinations. 23.9% of the ocrelizumab group vs. 54.5% of the control group had responded (4-fold increase in antigen-specific IgG from baseline or development of protective antibody levels) to TT booster at 8 weeks post-vaccination. Positive response to ≥5 serotypes in PPSV23 at 4 weeks was 71.6% in the ocrelizumab and 100% in the control group. The PCV13 booster did not enhance the response to 12 serotypes in common with PPSV23 in the ocrelizumab group, whereas it did for the control group. The humoral response to KLH was greatly decreased in the ocrelizumab group vs. the control group. After immunization with KLH, the GMTs for IgM and IgG for the control group were almost 2000 and 60,000, respectively, but were less than 500 for IgM and IgG in those treated with ocrelizumab. Seroprotective titers at 4 weeks against five influenza strains (season 2015/2016 and 2016/2017) ranged from 55.6% to 80.0% in the ocrelizumab group, compared to 75.0% to 97.0% in the control group. Level 2 evidence.

3.8.2. Rituximab

Responses to vaccination were studied in non-MS populations treated with the B cell depleting chimeric monoclonal antibody, rituximab. In one study of 103 rheumatoid arthritis patients, patients were randomized 2:1 to take rituximab 1000 mg IV twice two weeks apart in addition to methotrexate (10–25 mg po weekly) vs. methotrexate alone.

Patients in each treatment group were examined for response to TT, PPSV23, and KLH, and for DTH to Candida albicans. (Bingham et al., 2010) Responses to TT vaccine were similar, with 39.1% of rituximab/ methotrexate vs. 42.3% of methotrexate alone patients achieving a 4-fold or greater rise in titer. DTH responses to the C. albicans skin test were similarly positive in 77.4% of rituximab/methotrexate patients and 70% of those on methotrexate alone. However, rituximab/methotrexate patients had reduced response to PPSV23: 57% of patients had a 2-fold rise in titer in response to >1 serotype, compared with 82% of patients treated with methotrexate alone. Only 47% of patients on rituximab/methotrexate had detectable anti-KLH IgG, compared to 93% of those on methotrexate alone. Level 2 evidence.

These two studies indicate that responses to neoantigens and T cell–independent antigens are greatly reduced by B cell depletion with anti-CD20 monoclonal antibody treatments. Recall responses to the T cell–dependent TT antigen and DTH responses were less affected by B cell depletion, with some differences noted in response to TT between the two studies which used different B-cell depleting agents. Both studies were done in the first year after B cell depletion; responses might change after longer treatment duration.

3.9. Alemtuzumab effects on responses to vaccines

Twenty-four people with MS taking alemtuzumab for median 18 months (range 1.5 to 86 months) took part in an investigation of the effects of alemtuzumab on vaccination responses. (McCarthy et al., 2013) To test T-cell-dependent antigen recall responses, IgG levels were measured before and 4 weeks after vaccinations with diphtheria and tetanus in 22 MS patients taking alemtuzumab, and in 21 patients taking alemtuzumab before and 4 weeks after inactivated polio 1, 2, and 3. Pre-vaccination, all had protection to diphtheria and TT that was maintained after alemtuzumab. Protection improved from 95% to 100% for polio 1 and from 77% to 95% for polio 3 after vaccination. At the time of vaccination, the median CD8 T-cell count was low and median CD4 T-cell and CD19 B-cell counts were normal. PPSV23 was used to test responses to T-cell–independent antigens. Of the 21 MS patients who were immunized, the proportion achieving seroconversion for serotypes 3 and 8 exceeded that of literature controls. Similarly, the proportion protected against Haemophilus influenzae type b and meningococcal group C (neoantigen) increased from 74% and 13%, respectively, to 100% and 91% post-vaccination, equivalent to published seroconversion rates for controls. The investigators noted that vaccination within 6 months of treatment resulted in a smaller proportion of responders. This study provides Level 3 evidence that response to prior vaccinations is maintained following alemtuzumab treatment, but suggests that vaccinations be delayed until at least at 6 months after alemtuzumab treatment.

3.10. Effects of corticosteroids on responses to vaccines

Several studies in non-MS patient populations (e.g. asthma, rheumatoid arthritis, systemic lupus erythematosus) have provided Level 3 evidence of minimal impact of chronic oral corticosteroids on vaccine responses. (Briggs et al., 1980; Lahood et al., 1993; Elkayam et al., 2002, 38) However, the doses of corticosteroids in these studies were all lower than those typically used for MS relapses. In their 2013 guidelines, the Infectious Diseases Society of America recognized the lack of data on vaccine efficacy in people treated with high doses of corticosteroids (≥ 20 mg prednisone equivalents for ≥ 14 days). (Rubin et al., 2013) It is generally recommended to avoid administering live vaccines during treatment with and until at least 4 weeks after discontinuing high-dose corticosteroids. (Lebrun and Vukusic, 2019; Rubin et al., 2013)

3.11. Potential effects of MS disease-modifying therapies on responses to a SARS-CoV-2 vaccine

Currently, many candidate SARS-CoV-2 vaccines of different types, including inactivated virus vaccines, subunit vaccines, non-replicating viral vector vaccines, and nucleic acid vaccines, are undergoing evaluation in clinical trials. (40) Of note, effects of MS DMTs on immune responses to viral vector and nucleic acid vaccine types have not yet been reported. Also, few studies have addressed effects of DMTs on cellular immune responses to vaccinations. The duration of treatment with certain DMTs may also have an effect. This review addresses effects of MS DMTs on immune responses to existing vaccines as a guide to potential effects on a vaccine against SARS-CoV-2. However, the dearth of high-quality clinical data limits the strength of recommendations that can be made for an individual DMT. Given the key role of B cells in antibody development, anti-CD20 B cell-depleting therapies such as ocrelizumab are expected to limit the humoral responses to a SARS-CoV-2 vaccine. Vaccination data reviewed here provide some guidance, but the effects of DMTs on a SARS-CoV-2 vaccine will ultimately require prospective evaluation of humoral and cellular immune responses in people treated with specific DMTs.

4. Conclusions

This review addresses effects of MS DMTs on immune responses to existing vaccines. Existing studies indicate that, with the exception of beta-interferons, many MS DMTs blunt humoral immune responses to a variety of vaccine types. The opinion of the authors is that decision-making regarding DMTs should weigh the DMT efficacy against MS for the individual patient versus expected response to any vaccinations that may be needed in the future, including a SARS-CoV-2 vaccine.

Declaration of Competing Interest

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