Table 1. Mode of action, effect on the immune system, SARS-CoV-2 infection risk, vaccine response and the strength of evidence for the different treatments in MS

Class DMT	Mode of action[3]	Effect on immune system[3]	SARS-CoV-2 symptomatic infection, hospitalization and death risk	SoE SARS-CoV-2 risk[43]*	SARS-CoV-2 vaccine response	Breakthrough infection	SoE vaccine response[43]*
Interferon-beta	Immunomodulatory, pleiotropic	Lymphopenia	Possible symptomatic infection and hospitalization protective effect[8,15]	Moderate	>90% seroconversion. >80% SARS-CoV-2-specific cellular responses. [39,44,45]	-	Humoral resp: Moderate Cellular resp: Very low
Glatiramer acetate	Immunomodulatory	Rare leukocytosis or mild leukopenia	Possible symptomatic infection protective effect[15]	Very low	>90% seroconversion. >80% SARS-CoV-2-specific cellular responses. [39,44,45]	-	Humoral resp: Moderate Cellular resp: Very low
Teriflunomide	Dihydro-orotate dehydrogenase inhibitor (reduced de novo pyrimidine synthesis),anti-proliferative	Neutropenia	-	Low	>90% seroconversion. >80% SARS-CoV-2-specific cellular responses. [39,44,45]	-	Humoral resp: Moderate Cellular resp: Very low
Dimethyl fumarate	Pleotropic, Nrf2 activation, downregulation of NF-Kβ	Lymphopenia	-	Low	>90% seroconversion. >80% SARS-CoV-2-specific cellular responses. [39,44,45]	-	Humoral resp: Moderate Cellular resp: Very low
Natalizumab	Anti-α4-integrin antibody	Diminished immune surveillance in the CNS	Possible increase of symptomatic infection[15]	Very low	>90% seroconversion. >80% SARS-CoV-2-specific cellular responses. [39,44,45]	-	Humoral resp: Moderate Cellular resp: Very low
S1PRM	Sphingosine 1-phosphate receptor functional antagonist	Peripheral lymphopenia	-	Low	<50% seroconversion in Fingolimod, >80% in siponimod, ponesimod and ozanimod.[46–48] <20% SARS-CoV-2-specific cellular responses.[39] Lymphopenia and longer treatment duration may decrease antibody production.[41,48,49]	Increased risk of symptomatic infection. Mostly mild cases.[50,51]	Humoral resp: High Cellular resp: Low Risk factors for vaccine response: Very low Breakthrough infection: Very low
Cladribine	Synthetic purine nucleoside analogue that inhibits DNA synthesis selectively, mainly in circulating T cells and B cells	Depletion: immature B cells (6-9 months), memory B cells (>1 year), CD4 (40-50%), CD8 (30-40%), NK (50%)	-	Very low	>90% seroconversion in most studies.[45] Probably preserved cellular response (inconclusive evidence).[39]	-	Humoral resp: Low Cellular resp: Very low
Alemtuzumab	Monoclonal anti-CD52 antibody	Depletion: immature B cells (3-6m), memory B cells (>1 year), CD4 (70-90%), CD8 (70-90%), NK (40%), Monocytes (1-2 months), Neutrophiles	-	Very low	>90% seroconversion.[39] >80% SARS-CoV-2-specific cellular responses. [39]	-	Humoral resp: Very low Cellular resp: Very low

Anti-CD20s	Anti-CD20 antibody	Depletion: Immature B cells, memory B cells, CD4 (40-50%), CD8 (30-40%), NK (50%)	Possible increase of symptomatic infection, [15]hospitalization[7,9,17] and mortality[9]	Moderate	<50% seroconversion. [26,41,46] >80% SARS-CoV-2-specific cellular responses even in seronegative cases.[26] Increase of antibody response with time elapsed since last infusion, B-cell count and shorter treatment duration. [26,39]	Increased risk of symptomatic infection and hospitalization. Mostly mild cases.[51]	Humoral resp: High Cellular resp: Moderate Risk factors for vaccine response: Low Breakthrough infection: Very low

* Strength of Evidence according to the GRADE approach, the baseline rating was moderate due to the observational nature of the studies. Upgrading occurred when the results aligned with quantitative analyses in individual studies. Downgrading was conducted in cases of a low count of studies with measurable relative effects, inconsistency, the risk of missing results, or imprecision.[43]

Empty cells marked with "-" indicate that no effect or association was observed for the specific category. Seroconversion is defined as the percentage of individuals who develop anti-SARS-CoV-2 spike antibodies following SARS-CoV-2 vaccination. SARS-CoV-2-specific cellular responses as the percentatge of individuals with detectable cellular response against SARS-CoV-2 measured by interferon-gamma release assays or intracellular cytokine staining exceeding the detectable limit.

Abbreviations: SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2; SoE: Strength of Evidence; MS: multiple sclerosis; S1PRM: sphingosine 1-phosphate receptor modulators; DMT: disease modifying therapy; Nrf2: nuclear factor (erythroid-derived 2)-like 2 ; NF-Kβ: nuclear factor kappa beta; DNA: Deoxyribonucleic acid; CD52: cluster of differentiation 52; CD20: cluster of differentiation 20; CNS: Central Nervous System; CD4: cluster of differentiation 4; CD8: cluster of differentiation 8; NK: Natural Killers