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Supplementary information

Vaccination and immunotherapies in neuroimmunological diseases

In the format provided by the authors and unedited

Supplementary table 1 | Key vaccine factors and immunological response

Vaccines	Adjuvanted	Vaccine type	Serum antibody response	Mucosal antibody response	Cellular response	Route of administration	Duration of Protection (in healthy adults)	Duration of Protection (in immuno-compromised)	
BCG (tuberculosis)	No	live attenuated	yes	unclear	T-cell mediated immunity	i.c.	NA (efficacy against TB varies from 0% to 80%)	ND	[1,2]
Cholera	no	inactivated whole-cell (O1 monovalent and O1/O139 bivalent) (Dukoral®, Shanchol®)	yes	yes		oral	6 months – 2 years (protective efficacy 50% over 3 years)	Vaccination safe in HIV	[3-5]
Cholera	no	live attenuated	yes	yes		oral	5 years	contraindicate	[5,6]
Dengue	no	live attenuated, chimeric yellow fever-dengue strain (Dengvaxia®)	yes		yes	i.m.		contraindicated	[7,8]
Diphtheria toxoid	Yes/no	Toxoid	yes	unclear		i.m.	10 years		[9-11]
Ebola	no	(rDNA, replication-incompetent) recombinant Adenovirus / Vaccinia Virus encoding glycoprotein of Ebola virus	yes		yes	i.m.	unknown	ND	
Ebola	no	recombinant vesicular stomatitis virus encoding ebolavirus surface glycoprotein (rVSVΔG-ZEBOV-GP, live)	yes		yes	i.m.	unknown	ND	
Hepatitis A	yes	Inactivated	yes	no	memory B cell and T cells	i.m.	> 35 years	Lower AB response in HIV	[12-15]
Hepatitis A		live attenuated vaccine (based on H2 or LA-1 HAV strains and manufactured as well as mainly used in China or India)	yes		memory B cell and T cells	i.m.	> 15 years		[16,17]
Hepatitis B (HBsAg)	no	Protein	yes	yes	induction of memory B and T cells	i.m.	> 10 years	hampered in HIV, chronic renal disease	[18-20]
Hib PS		polysaccharide	yes	yes		i.m.	10 years		[21]
Hib glycoconjugate		polysaccharide –protein	yes	yes		i.m.	10 years		[22]
Human papilloma virus HPV	yes	Virus-like particles	yes	yes		i.m.	~ 8 years		[23]
Influenza, seasonal	Yes/no	inactivated	yes	unclear	CD4+ and CD8+ T-cell immunity	i.m.	< 1 year		[24-26]
Influenza, seasonal	no	Subunit	yes	unclear	CD4+ and CD8+ T-cell immunity	i.m.	< 1 year		

Vaccines	Adjuvanted	Vaccine type	Serum antibody response	Mucosal antibody response	Cellular response	Route of administration	Duration of Protection (in healthy adults)	Duration of Protection (in immuno-compromised)	
Influenza, seasonal	no	Live attenuated	yes	yes	+ ($CD8^+$) CD4+ and CD8+ T-cell immunity	i.n.	< 1 year		
Influenza, pandemic (H1N1)	yes	inactivated, subunit	yes		CD4+ and CD8+ T-cell immunity	i.m.	unclear		
Japanese encephalitis	yes	Inactivated, vero-cell based (SA 14-14-2 viral strain)*	yes	no	yes	i.m.	10 years after first booster		27,28
Measles	no	Live attenuated	yes	yes	$CD8^+$	i.m.	Long-lasting		29-32
Meningococcal PS	no	polysaccharide	yes	no		i.m.	1-2 years		33,34
Meningococcal conjugates	No (Menveo, Menactra), yes (Menjugate, Meningitec)	PS-protein conjugated to Corynebacterium diphtheriae CRM protein (Menjugate®, Menveo®, Menactra®)	yes	no		i.m.	5 years		35
Meningococcal conjugates	Yes (NeisVac-C), no (Nimenrix, MenQuadfi)	PS-protein conjugated to tetanus toxoid carrier protein (NeisVac C®, Nimenrix®, MenQuadfi®)	yes	no	B-Cell Memory	i.m.	Long-lasting (after priming)		36
Meningococcal B*	yes	Protein (recombinant protein & outer membrane vesicles Bexsero®; recombinant lipidated protein Trumenba®)	yes	no	yes	i.m.	> 4 years		37,38
Mumps	no	Live attenuated	yes		yes	i.m.			32
Pertussis, whole cell	yes	Inactivated	yes		yes	i.m.			39,40
Pertussis, acellular	yes	Protein	yes	no	$CD4^+$	i.m.	< 10 years		40,41
Pneumococcal PS	no	PS	yes	yes		i.m.	5 years	~ 3 years	42
Pneumococcal conjugates	yes	PS-protein (d-carrier protein, tetanus toxoid, or diphtheria toxoid protein)	yes	yes		i.m.	n.d.	n.d.	42,43
Polio Sabin	no	Live attenuated	yes	yes		oral	10 years		44
Polio Salk	no	Inactivated	yes	yes		i.m.	10 years		
Rabies	no	Inactivated	yes			i.m.	5 years		
Rotavirus	no	Live attenuated (Rotarix®); live reassortant human-bovine (RotaTec®)	not relevant	yes		oral	1-3 years		
Rubella	No	Live attenuated	yes	yes		i.m.	> 10 years		
Tetanus toxoid	Yes/no	Toxoid	yes		IgA +	i.m.	> 10 years		45
Tic-borne encephalitis (TBE)	yes	Inactivated	yes		yes	i.m.	5 years	Shorter in elderly subjects	
Typhoid	no	Live attenuated (Vi-negative strain)	yes	yes	yes	oral	3-5 years		
Typhoid PS	no	PS (+/- conjugated)	yes	no	yes	i.m.	3-5 years		

Vaccines	Adjuvanted	Vaccine type	Serum antibody response	Mucosal antibody response	Cellular response	Route of administration	Duration of Protection (in healthy adults)	Duration of Protection (in immuno-compromised)	
Varicella (chickenpox)	no	Live attenuated	yes		$CD4^+$	i.m.	life-long		
Varicella (zoster)	no	Live attenuated	yes		$CD4^+$	i.m.	> 4 years		
Varicella (zoster)	yes	Inactivated (shingrix®)	yes		yes	i.m.	> 4 years		
Yellow fever	no	Live attenuated	yes		yes	s.c.	life-long		[46]
SARS-Cov-2*	no	modRNA (e.g. BNT162b2)	yes	yes	Th1-based CD4+ and CD8+ response	i.m.	unclear		[47-50]
	no	modRNA in lipid nanoparticle dispersion (e.g. mRNA-1273)	yes	yes	Th1-based CD4+ and CD8+ responses	i.m.	unclear		[51-53]
	no	Non-replicating viral vector (e.g. ChAdOx1-s, Ad26.COV2-S)	yes	yes	Th1-based CD4+ and CD8+ responses	i.m.	unclear		[54-61]

Abbreviations: i.c., intracutaneously; i.m., intra muscular; s.c., subcutaneous; i.n., intranasal; modRNA, nucleoside-modified messenger RNA; NA, not applicable; PS, polysaccharide; VLP, virus-like particle

* Other vaccine types available in different countries. Note: This table may not be exhaustive and includes currently licenced vaccines in various countries. Additional information based on [62-72].

Supplementary table 2 | Adjuvants used in different licenced vaccines

Type	Adjuvant (components)	Examples of vaccine	Aspects in immunosuppression
Oil-in-water emulsions	Exact molecular mechanisms unknown - antigen dose sparing effect - enhances diversity of induced antibodies - indirect stimulation of immune response (activation of APCs via stimulation of TNF-alpha, IL-1B, CCL)[73]; localized and short impact on immune system[74]		
	MF59 (Squalene; polysorbate 80; sorbitan trioleate)	Seasonal influenza, pandemic influenza, avian influenza	induces the release of extracellular ATP as endogenous stress signal[75] resulting in activation of innate immune pathways; adjuvant effects may be retained in CD4-deficient conditions[76]
	AS03 (Squalene; alpha-tocopherol polysorbate 80)	pandemic influenza, avian influenza	effective in organ transplant recipients[26,77]; not effective to overcome immunosuppression on rituximab therapy[78]; enhanced IgG memory B-cell response in HIV[79]; no increased short-term risk in MS[80]
	AF03 (squalene; polyoxyethylene cetostearyl ether; mannitol)	pandemic influenza[81] not marketed	[82]
Aluminium salt	Exact molecular mechanisms unknown - possible depot mechanism (unclear) - enhanced uptake by APCs - Direct stimulation of innate immune receptors (interaction with surface membrane lipids of dendritic cells)[83-85]		
	Crystalline aluminium oxyhydroxide (aluminium hydroxide)	Japan B encephalitis, meningococcus C[86], tetanus/diphtheria/pertussis, HAV	Adjuvant effect not hampered by IL-1beta inhibition[86]
	Aluminium phosphate	Tetanus/diphtheria, pertussis, and poliomyelitis; Haemophilus influenzae	
	Aluminium potassium phosphate (alum)	Tetanus, diphtheria, pertussis, influenza	
	Aluminium hydroxyphosphate sufate	HPV (Gardasil®), HAV (Vaqta®)	[87]
Toll-like receptor agonists	Trigger of innate immune response; activation of TLRs results in secretion of IL-10, TNF-α, and IL-6 of type 1 interferon response		
	AS01 (MPL; liposome, QS-21), TLR4 agonist	Herpes zoster subunit[88-90]	
	RC529 (chemical mimetic of MPL), TLR4 agonist	HBV (Supervax®) combined with alum[91]	
	AS04 (MPL; aluminium hydroxide), TLR4 agonist	HPV (Cervarix®); Hepatitis B (Fendrix®)[92]	
Virosomes	Liposomes with surface exposed vaccine antigens, uptake in APCs, cell activation, boost antibody response, deliver immune activators directly to the B cells [73,93-95]		
	Unilamellar liposomes	Influenza (Inflexal V®), Hepatitis A (Epaxal®)[96-98] COVID-19 vaccine [99]	
	Matrix M (purified saponin nanoparticles from *Quillaja saponaria* Molina)	COVID-19 vaccine; Plasmodium vaccine, influenza vaccine (phase 3 studies)[100-102]	
Abbreviations: APC=antigen presenting cells; TNF-alpha=tumor necrosis factor-alpha; IL-1B=interleukin 1b; CCL=chemokine C-C ligands ; TLR= Toll-like receptor; MPL = monophosphoryl lipid; QS-21 = *Quillaja saponaria* Molina, fraction 21;			

Supplementary table 3 | Disease-modifying treatment and vaccination

Disease-modifying treatment (Dosage)	Available since	Half-life[1]	Mode of action	Risks for infection	Possible mechanism of interaction with vaccines
Direct depletion/cytolysis					
Ocrelizumab First dose is split into 2 separate infusions of 300mg i.v. 2 weeks apart. The following doses of 600 mg i.v. will be given once every 6 months.	2017 US 2018 EU	26 days	CD20 B-cell depletion. Causes fast and nearly complete B- cell elimination from circulation but lesser in lymph node follicles, marginal zone of spleen, and peritoneal cavity[103]. Continuous immunosuppression	Serious infections: 1.3% ocrelizumab versus 2.9% in interferon beta- 1a-treated group (RR-MS) [104] Upper respiratory tract infections more common in ocrelizumab-treated group compared to placebo (PP-MS)[105]. Serious infections seen in treatment of rheumatoid arthritis patients (opportunistic infections, such mycobacterial infections, hepatitis B reactivation, histoplasmosis, pneumocystis pneumonia, VZV pneumonia or candida infections)[106] have not been observed in MS studies so far. PML (case report), case series of carry-over PML[107]	CD20 antibody dependent B-cell and CD20 pos. T-cells (subgroup) cytolysis Causes fast and nearly complete B-cell elimination from circulation but lesser in lymph node follicles, marginal zone of spleen, and peritoneal cavity. Potential reduction of IgG (hypogammaglobulinaemia)[104,108]
Rituximab Various schemes Start with two-1000 mg i.v. doses separated by 2 weeks Individual maintenance treatment with 1000mg i.v. every 6 months or depending on B-cell counts	1997 (NHL) 2006 (RA)	18 (8-20) days	Anti- CD20 B-cell depletion. Causes fast and nearly complete B- cell elimination from circulation but less so in lymph node follicles, marginal zone of spleen, and peritoneal cavity [103]. Continuous immunosuppression	61.4% mild- to- moderate infection- associated events (Phase I study, RR-MS) [109]. About 70% infections (Phase II, RR-MS) in both groups (Rituximab vs. placebo). No opportunistic infections [110]. No serious AEs (Phase II and III, PP-MS) [111]. Most common infection-associated adverse events (>10% in the rituximab group) found in a Cochrane review (RR-MS) were nasopharyngitis, upper respiratory tract infections, urinary tract infections and sinusitis. Among them, only urinary tract infections (14.5% versus 8.6%) and sinusitis (13.0% versus 8.6%) were more common in the rituximab group [112,113].	CD20 antibody dependent B-cell and CD-20 pos. T-cells (subgroup) cytolysis Causes fast and nearly complete B-cell elimination from circulation but less so in lymph node follicles, marginal zone of spleen, and peritoneal cavity. Potential reduction of IgG (hypogamma-globulinaemia)

Disease-modifying treatment (Dosage)	Available since	Half-life[1]	Mode of action	Risks for infection	Possible mechanism of interaction with vaccines
Ofatumumab 20 mg s.c. every 4 weeks after treatment initiation with 20 mg s.c. day 1, day 7, day 14	2020 US 2021 EU	14 days	Depletion of CD20 + B-cells and depletion of CD20 + T-cells in blood and lymph-nodes like RTX/OCR but less depletion of marginal zone B-memory cells in spleen compared to RTX [114] Continuous immunosuppression	Increased risk of infections observed with other anti-CD20 B-cell depleting therapies Potential increased risk of infections including serious bacterial, fungal, and new or reactivated viral infections (some fatal) in patients treated with other anti-CD20 antibodies. Rate of infections similar to teriflunomide. The most common infections reported were upper respiratory tract and urinary tract infections [115].	CD20 antibody dependent B-cell and CD20 pos. T-cells (subgroup) cytolysis Causes fast and nearly complete B-cell elimination from circulation and lymph node follicles but with minor extent in marginal zone of spleen. Potential reduction of IgG (hypogammaglobulinaemia)[108]
Inebilizumab: Initial dose is two single 300 mg i.v. given 2 weeks apart. Subsequent doses (starting 6 months from the first dose) 300 mg i.v. every 6 months	2020 US EU pending	18 days	Precise mechanism of therapeutic effects in NMOSD is unknown but is presumed to involve binding to CD19 present on pre-B and mature B lymphocytes causing depletion through antibody-dependent cell-mediated cytotoxicity. Continuous immunosuppression.	An increased risk of infection was noted comparable to that observed with other B-cell-depleting therapies. Most common infections reported included urinary tract infection (20%), nasopharyngitis (13%), upper respiratory tract infection (8%), and influenza (7%). No confirmed cases of PML were identified in clinical trials. [116,117].	CD19 antibody dependent B-cell depletion. Cell surface binding to B lymphocytes results in antibody-dependent cellular cytolysis. Potential reduction of IgG (hypogammaglobulinaemia)[108]
Alemtuzumab 2 or more treatment courses separated by a year. Cumulative dose first course 60mg i.v., every following course 36 mg i.v. (12 mg each day of course)	2013 EU 2014 US	4-5 days	CD52 cell depletion Repopulation of lymphocytes, leading to long-term changes in adaptive immunity and rebalancing of the immune system [118]. Intermittent immunosuppressive	Infections more frequent compared to IFN-beta 1a treated patients: (majority mild to moderate). Upper respiratory tract and herpes infections were predominant. PML (case report). Listeria meningitis (case reports). Herpesvirus (incidence reduced by acyclovir prophylaxis (30 days after each treatment cycle) [119-124].	CD52 antibody dependent cellular cytolysis (T- and B-cells) Leukopenia and long lasting lymphopenia (T cells affected more than B cells)

Disease-modifying treatment (Dosage)	Available since	Half-life[1]	Mode of action	Risks for infection	Possible mechanism of interaction with vaccines
Cladribine Weight dependent dose: 2 treatment courses separated by a year with 2 treatment cycles in each course. During each cycle daily oral application for 4 or 5 days. The 2 cycles are separated by a month.	2017 EU 2019 US	5.4 h	Synthetic chlorinated deoxyadenosine (purine) analogue: Preferential accumulation of cladribine phosphates in cell types with a high intracellular ratio of deoxycytidine kinase to 5'-nucleotidases leading to sustained reduction of circulating T and B lymphocytes. Interferes with DNA synthesis and repair through incorporation into DNA and through inhibition of enzymes involved in DNA metabolism causing DNA strand breaks and ultimately cell death[125]. Induces apoptosis and depletion of B- and T-cells including non-proliferating cells [126] Intermittent immunosuppression, immune reconstitution	Incidence of infections was 48.3% with cladribine tablets and 42.5% with placebo, with 99.1% and 99.0% rated mild-to-moderate. Herpes zoster infections developed in 20 (2.3%) cladribine-treated patients; all cases were dermatomal. Overall no significant elevated risk of infection[127]. The incidence rates of infections and infestations showed no clear relation to total dose received, with the exception of the herpes zoster. Infection rate higher with increased doses compared to other groups (4.8%-1.1%, placebo 2.0%)[128]. No cases of progressive multifocal leukoencephalopathy (PML)[128].	Reduced proliferation of B-and T-lymphocytes Interference with lymphocyte proliferation Lymphopenia[129]
Reduced proliferation					
Teriflunomide 14 mg once daily p.o.	2012	19-20 days	Dihydro-orotate dehydrogenase inhibitor (reduced de novo pyrimidine synthesis in fast dividing immune cells/autoreactive cells), antiproliferative (Salvage pathway for de novo pyrimidine synthesis still working [130]. Does not affect dividing or resting cells [130,131]. Possibly immunosuppressive	No increased risk of infections. Single cases of appendicitis, bronchitis, pneumonia, Klebsiella sepsis, and UTI were reported. Neither PML nor other opportunistic infections related to the treatment [132]. Single cases of combined HCV/CMV-infection and one intestinal TBC were considered not treatment related[133].	Interference with lymphocyte proliferation Leukopenia (neutropenia)
Azathioprine Individual dosing 25-50 mg up to 3 times a day p.o., 2-4 mg/kg BW/d p.o. depending on leukocyte count (target 3500-4000/µl) and lymphocyte count (target 1000/µl) count	1957	26 to 80 min (3-5 h metabolites) biological effect: 24 h [134]	Purine analogue, antimetabolite (prodrug) Inhibition of purine nucleotide synthesis during RNA-/DNA-synthesis [135] Effect on Na(+)/H(+)-exchanger activity in dendritic cells [136]. Induces apoptosis in stimulated T cells [137]. Continuous immunosuppression	Increased risk of bacterial, viral, fungal, protozoal, and opportunistic infections, including reactivation of latent infections.	Reduced proliferation of B-and T-lymphocytes. Interfering with the maturation and function of dendritic cells (DCs)/antigen-presenting cells linking innate and adaptive immunity Leukopenia and lymphopenia

Disease-modifying treatment (Dosage)	Available since	Half-life[1]	Mode of action	Risks for infection	Possible mechanism of interaction with vaccines
Cyclophosphamide 10-15 mg/kg body weight, repeated every 4-8 weeks	1965	7 h	Alkylating metabolites cause single and double-strand breaches in fast reproductive cells with consecutive reduction of CD4+ helper-cells and increased number of CD8+ suppressor-cells [138]. Continuous immunosuppression	Increased risk of infection (classical immunosuppressive agent). Exclude latent infections or laboratory changes in cellular and humoral immune parameters before application[139]. Infection was the most common side-effect (28% of patients with various autoimmune diseases, mainly SLE) but rarely required in-patient treatment (9% of the patients). No relationship could be found between the occurrence of infection and the dose of CYC or of GCS[140].	Reduced proliferation of B-and T-lymphocytes Increase in CD8+-suppressor cells and a reduction in CD4+-helper cells
Mitoxantrone 5-12 mg/m^2 body surface area i.v., every 1-3 months	2000	9 days	Topoisomerase inhibitor: Suppresses macrophages, B cells and T cells, with a preferential effect on helper subsets [141,142]. Modulates astrocyte activity[143]. Continuous immunosuppression	Frequent UTIs and upper airway infections [144]. Cases of septicaemia, pneumonia and opportunistic infections. No heightened risk of viral infections[144].	Reduced proliferation of B-and T-lymphocytes Suppresses macrophages, B cells and T cells, with a preferential effect on helper subsets
Mycophenolate mofetil Off-label use in MS/NMOSD/MG 1-3 g/d p.o. in two doses	US 1995 EU 1996 (Kidney transplantation)	17.9±6.5 hours	reversible, non-competitive inhibitor of inosine-5'-monophosphate dehydrogenase; inhibition of *de novo* purine synthesis	opportunistic infections, reactivation of latent viral infections, (herpes virus infections, polyomaviruses (JC, BK))	selective inhibition of DNA replication in T- and B-cells
Anti-migratory effects					
Natalizumab 300mg once per month i.v. 2 x 150mg once per month s.c.	2006 s.c.: 2021 (EU)	16 days	Anti VLA-4, selective adhesion molecule inhibitor: Prevents immune cells (T, B, and NK cells) from crossing blood vessel walls to reach affected organs [145]. Induces lymphocyte apoptosis [146]. Continuous local immunosuppression.	Based on diminished immune surveillance in the CNS a broad spectrum of infections are possible [147,148]. Main issue: PML (JCV-infection, recently increased risk in pooled cohort) [149,150]. Pooled cohort: <1% (156 of 37 249) had PML. Anti-JCV antibody-negative patients (n=13 996): PML risk < 0.07 per 1000 patients. Anti-JCV antibody-positive patients (n=21 696): cumulative PML probability over 6 years was 2.7% with previous immunosuppressant use and 1.7% without. Without previous immunosuppressant use (n=18 616), annual PML risks per 1000 patients, ranged from 0.01 in year 1 to 0.6 in year 6 (JCV-Ab-index < 0.9), 0.1 in year 1 to 3.0 in year 6 (JCV-Ab-index > 0.90·to ≤1.5); 0.2 in year 1 to 10.0 in year 6 (JCV-Ab-index >1.5) [151,152].	Altered lymphocyte trafficking to CNS via blockade of alpha-4 subunit of the VLA-4 receptor

Disease-modifying treatment (Dosage)	Available since	Half-life[1]	Mode of action	Risks for infection	Possible mechanism of interaction with vaccines
Fingolimod 0.5 mg once/d p.o.	2010	6 to 9 days (9-10 days)	S1P1 modulator: Prevention of lymphocyte egress (mainly CCR7+CD4+ naive and central memory T cells) from lymph nodes [153]. Reversibly redistributes lymphocytes into lymphoid tissue, while preserving lymphocyte function Prevents naive and central memory T cells from circulating to non-lymphoid tissues such as the CNS Causes lymphoid cell retention in secondary lymphoid tissue Can exert neuroprotective effects by crossing the blood–brain barrier and binding to neuronal and glial cells [154]. Alters the balance of NK-cell subsets [155]. Could modulate remyelination [156]. Increases astrocyte migration [157]. Continuous immunosuppression	No elevated risk of serious infectious adverse effects, including severe HSV infections [158]. Incidence of VZV infections ranges from 7 to 11 per 1,000 patient-years (versus 6 in 1,000 patient-years in the placebo group) [159] Reports of single cases of cryptococcal brain and skin infections and PML cases [reviewed [147]]	Binding to S1P receptors prevents lymphocytes to exit lymph nodes Lymphocyte trapping in lymph node Lymphocyte redistribution
Ozanimod 0.92 mg once/d p.o.	2020	19 h	Selective S1P-receptor 1 and 5 modulator: Regulation of lymphocyte migration, regulation of survival, migration and differentiation of oligodendrocytes [160-162]. Reversibly redistributes lymphocytes into lymphoid tissue, while preserving lymphocyte function. Prevents naive and central memory T cells from circulating to non-lymphoid tissues such as the CNS. Causes lymphoid cell retention in secondary lymphoid tissue. Ozanimod induced dose-dependent reductions in circulating B- and T-cell counts and differential effects on naive and memory CD4+ and CD8+ T cells and CD19+ B cells. [163,164]. Can exert neuroprotective effects by crossing the blood–brain barrier and binding to neuronal and glial cells [165]. Continuous immunosuppression.	Infectious risk might be elevated due to reduction of peripheral lymphocyte count.	Binding to S1-P receptor preventing lymphocytes from exiting lymph nodes Lymphocyte trapping in lymph node Lymphocyte redistribution

Disease-modifying treatment (Dosage)	Available since	Half-life[1]	Mode of action	Risks for infection	Possible mechanism of interaction with vaccines
Ponesimod 20 mg once /d p.o.	03/2021 US 06/2021 EU	21.7 - 34 h	S1P1-modulator ($S1PR_1$ > $S1PR_5$)	Infectious risk might be elevated due to reduction of peripheral lymphocyte count. No significant difference to teriflunomide treatment (nasopharyngitis, upper respiratory tract infection, herpetic infections) [166]	Binding to S1-P receptor preventing lymphocytes from exiting lymph nodes (naïve T cells and helper T cells > memory and cytotoxic T cells; partial sparing of regulatory T cells) Lymphocyte trapping in lymph node Lymphocyte redistribution[167]
Siponimod 2 mg once daily p.o. consider dose reduction in dependence of genetic status	2019 US 2020 EU	56.6 h	Predominantly $S1PR_1$and $S1PR_5$ modulator	Increased risk of infections. Monitoring for infections before treatment initiation and during treatment mandatory. Herpetic infections rate increased (treatment 4.6% vs. placebo 3.0%, Herpes zoster rate 2.5 vs. 0.7%). Single cases of cryptococcal meningitis. No PML-case so far, but single cases under other S1P receptor-modulators.	Binding to S1P receptors preventing lymphocytes to exit lymph nodes Lymphocyte trapping in lymph node Lymphocyte redistribution Avoid live vaccines for weeks after stopping treatment. Vaccination may be less effective if administered during treatment. Discontinuation one week prior and until 4 weeks after a planned vaccination is recommended.
Pleiotropic effects					
Interferon-beta: Interferon beta 1a i.m. (once a week) Interferon beta 1a s.c. (TIW) Interferon beta 1 b s.c. (every other day) Peg-Interferon beta 1 a s.c. or i.m. (once in 2 weeks)	1996 2002 1993 2014	10 h 50-60 h up to 5 h 78±15 h (steady state)	Immunomodulatory, pleiotropic immune effects: Inhibition of T-cell proliferation Increased T-suppressor cell activity Inhibition of pro-inflammatory cytokines (TNF-α, IFN-γ) Induction of immunomodulatory cytokines IL-10 and TGF-β Suppression of expression of HLA class II and adhesion molecules Blockade of metal-matrix proteinases/ chemokines Activating transcription of antiviral, antimicrobial, antiproliferative, and immunomodulatory genes Regulates the expression of a complex set of pro- as well as anti-inflammatory genes [168,169] Continuous/pulsatile type 1 interferon receptor stimulation and downregulation Not immunosuppressive; anti-inflammatory; antiviral	Type 1 interferons protect mammals against viral infections [170]. Involvement of the interferon type I signaling defense against viral infections [171]. No increased risk for infections. Treatment-associated leukopenia. Occasional local infections or abscess formation at injection site [172-176].	Interaction with MHC II receptor Inhibition of antigen presentation Decreased INF-gamma production Leukopenia (lymphopenia in particular)

Disease-modifying treatment (Dosage)	Available since	Half-life[1]	Mode of action	Risks for infection	Possible mechanism of interaction with vaccines
Glatirameroids: 20 mg (once a day) 40 mg (3 times a week) s.c.	1996	NA	Immunomodulatory, pleiotropic immune effects: Th1 to Th2 cytokine shift [177]. Increases regulatory CD8+ cells. Activation of FOXP3 leads to shift from CD4+CD25- T-cells to regulatory CD4+CD25+T-cells [178] [179]. No immunosuppression	HSV infections and vaginal candidiasis were 2% more frequent in patients treated with glatiramer acetate than in placebo-treated patients, whereas other infections, such as abscesses, cellulitis, boils, shingles or pyelonephritis, were rarer with glatiramer acetate treatment than with placebo. No opportunistic infections have been described.	Th1 to Th 2 cytokine shift Inhibition of MHC II receptor Rare leukocytosis or mild leukopenia
Dimethyl fumarate 240 mg twice daily p.o.	2013	1 h (MoMF)	Pleiotropic: NRF2 activation [180]; Downregulation of NFκB (transcription factors) [181]; Protects against oxidative stress-induced cellular injury in neurons and astrocytes[182] Attenuating the activity of pro-inflammatory TH1 and TH17 cells by scavenging toxic oxygen metabolites[180,181]	DMF does not exacerbate the risk of infection in patients with MS [183] PML cases (MS- and psoriasis patients treated with DMF or fumaric acid esters, partly under combination therapy) [Reviewed [147]]	Enhancement of endogenous mechanisms to counteract oxidative stress Reduction of oxidative stress Potential leukopenia (lymphopenia)
Diroximel fumarate 462 mg twice/d p.o.	2019 US 2021 EU	1 h	See dimethyl fumarate	See dimethyl fumarate; PML risk	See dimethyl fumarate
Tocilizumab 8mg/kg bodyweight i.v. every 4 weeks	2007 US 2009 EU (treatment of RA)	8-14 days in steady state	IL-6 receptor blockade preventing interleukin-6 attaching to its receptors, Continuous immunosuppression	risk of serious bacterial infection, skin and soft tissue infections, and diverticulitis was higher (TCZ vs. TNFi) In NMOSD upper respiratory tract infection and urinary tract infection were reported less often with TCZ compared to AZA [184].	IL-6 inhibition may interfere with the normal immune response to new antigens (reduced B-cell differentiation with reduced immunoglobulin production)
Satralizumab 120mg s.c. every 4 weeks after loading dose of 120 mg week 0, 2 and 4	US 2020 EU 2021	30 days	inhibition of IL-6 receptor signalling by humanized anti-interleukin-6 (IL-6) receptor monoclonal recycling antibody Continuous immunosuppression	Rates of infection did not differ between satralizumab and placebo groups [185,186] In general an increased risk of infections has been observed in patients treated with IL-6 receptor antagonists. Most common infections nasopharyngitis and cellulitis.	IL-6 inhibition may interfere with the normal immune response to new antigens (reduced B-cell differentiation with reduced immunoglobulin production)

Disease-modifying treatment (Dosage)	Available since	Half-life[1]	Mode of action	Risks for infection	Possible mechanism of interaction with vaccines
Eculizumab: Induction dose 900 mg weekly i.v. for 4 weeks, maintenance dose 1200mg i.v. every two weeks	2007 PNH 2017 MG 2019 NMO	11.3 ± 3.4 days	Inhibition of terminal complement protein C5: preventing cleavage into pro-inflammatory protein C5a and protein C5b	MoA associated increased risk of meningococcal infections. Vaccination reduces, but does not eliminate, the risk of meningococcal infections Increased risk of infection with Neisseria and capsulated germs/ bacteria. Awareness of Gonorrhoea. Upper respiratory tract infections and headaches were more common in the eculizumab group, serious infections 8% with eculizumab vs. 15% under placebo[187].	Protective rSBA titres varied for meningococcal serogroups and over time reflecting an early decline to even non-protective rSBA titres. These data highlight the importance of serologic analyses under chronic CI. Currently, re-vaccination with a tetravalent meningococcal conjugate vaccine every 3 years is recommended on chronic CI. However, re-vaccination on CI might further rely on serologic analyses, implying even early booster vaccinations similar to adults with (functional) asplenia[188].
Glucocorticosteroids Pulses with 500-2000 mg (methyl-prednisolone equivalent) i.v. on 3-5 consecutive days	1948	161±32 min MP: plasma 1-3 h biol. 18-36 h Dexamethasone: plasma 3.5 h biol. 36-72 h	Pleiotropic effects. Suppression of inflammation via induction of apoptosis and inhibition of immune-cell migration, reduction of pro-inflammatory cytokines [189-191] Dose dependent immunosuppressive	Repeated pulse therapy, even at very high doses, does not increase the propensity to develop bacterial or fungal infections, but severe viral infections, such as varicella zoster virus (VZV) or herpes simplex virus (HSV), can develop [192] Long-term continuous glucocorticosteroid administration, which is not typically used in the treatment of MS, is associated with bacterial, viral, fungal, and parasitic infections [193].	Dose- and regime- dependent immunosuppressive to various degree Transient leukocytosis (increased neutrophils in particular) Lymphopenia

Disease-modifying treatment (Dosage)	Available since	Half-life[1]	Mode of action	Risks for infection	Possible mechanism of interaction with vaccines
IVIg Treatment initiation with 2g/kg body weight i.v. divided on 5 days, repeat courses of 0,4g/kg body weight i.v. every 4 -6 weeks	1981/ 1990	21-31 days	Various effects: Inhibition of complement-system, impact on B-cells and autoantibodies, influence on macrophages and T-cells, modulation of cytokine-networks [194,195]. Modulation of immune reactions at the level of T-cells, B-cells, and macrophages Interference with antibody production and degradation Modulation of complement cascade, Effects on cytokine network [196]. Effects on B-cells, antibodies, and on the complement system. Influence on T-cells Influence on cell migration[197].	Transmission of possibly unknown infectious agents cannot be ruled out when using drugs deriving from biological material/human donors. Existing inactivation and elimination procedures might be of restricted value for non- or uncoated viruses[198]. Potential antiviral effects[199].	Stimulation and support of requested and inhibition of unwanted immune processes
PE/IA 5-8 treatment cycles (relapse treatment)	1999 [200,201]	IgG Re-distribution: 1-3 %/h [202]	Rapid removal of pathological mediators (autoantibodies, immune complexes, complement, and cytokines) from the circulation [203] Intermittent immunosuppressive	Invasive therapy, exposes the patient to the risk of infection, primarily through the central venous catheter but also via elimination of immunoglobulins or complement components [204]. Catheter-associated complications range from 0.5% to 3.3% in patients with chronic hepatitis C, Guillain–Barré syndrome or other neurological diseases [205-207]. No plasmapheresis-associated infections were detected in 2,502 plasmapheresis sessions in a cohort of 335 patients (among which over 90% had neurological diseases) [208]. Transmission of viral infections becomes more frequent if plasmapheresis requires the use of fresh frozen plasma rather than albumin[209-211]	Immunoglobulin deficiency Reduction of antibody, complement and cytokine levels

Disease-modifying treatment (Dosage)	Available since	Half-life[1]	Mode of action	Risks for infection	Possible mechanism of interaction with vaccines

[1] according to various databases

Abbreviations

AE: adverse event; ALT: alanine-aminotransferase; BD: bis in die; BP: blood pressure; CD: cluster of differentiation; CIS: clinical isolated syndrome; CYC: cyclophosphamide; Dexa: Dexamethasone; DMARD: disease-modifying anti-rheumatic drug; DNA: deoxyribonucleic acid; DTH: delayed-type hypersensitivity; ECG: electrocardiogram; FBC: full blood count; FOXP3: forkhead-box-protein P3; GCS: Glucocorticosteroids; GI: gastro-intestinal; HC: healthy controls; HIV; human immunodeficiency virus; HLA: human leukocyte-antigen; IA: immune adsorption; i.a.: inter alia, IBD: inflammatory bowel disease; IFN : Interferon; IgG: Immunoglobulin G, IL: Interleukin; ITP: immune thrombocytopenia; IVIg: intravenous immunoglobulins; JCV: John-Cunningham-Virus; LFT: liver function test; LVEF: left ventricular ejection-fraction; mABs: monoclonal antibodies; µg: microgram; mg: milligram; MoA: mode of action; MHC: major histocompatibility complex; MG: Myasthenia Gravis; MMF: mycophenolate mofetil; MP: Methylprednisolone; MS: multiple sclerosis; NA: not available; NABs: neutralizing anti-bodies; NFκB: nuclear factor kappa B; NHL: non-Hodgkin-lymphoma; NK: natural killer; NMO: neuromyelitis optica; NRF2: NF-E2 related factor 2; OCR: ocrelizumab; OCT: optical coherence tomography; PCV: pneumococcal conjugate vaccine; PE: plasma exchange; pEP: primary endpoint; PML: progressive multifocal leukoencephalopathy; PNH : paroxysmal nocturnal Haemoglobinuria; PON: ponesimod; PPMS: primary progressive multiple sclerosis; PPSV: pneumococcal polysaccharide vaccine; PSV: polysaccharide pneumococcal vaccine; RA: rheumatoid arthritis; R-CHOP: rituximab combined with cyclophosphamide, doxorubicin, vincristine, prednisolone; RMS: relapsing multiple sclerosis; RNA: ribonucleic acid; RRMS: relapsing-remitting multiple sclerosis, RTX: rituximab; S1P1: selective Sphingosin-1-phosphate-receptor-1; SLE: Systemic lupus erythematosus; SOT: solid organ transplantation; SPMS: secondary-progressive multiple sclerosis; TB: tuberculosis; TCZ: tocilizumab; TFT; thyroid function test; TGF-β: transforming growth factor- beta; Th: T-helper; TIW: three times a week; TNF-α: tumor-necrosis factor-alpha; TNFi: tumor-necrosis factor-inhibitors; U&E: urea and electrolytes; ULN: upper limit of normal; VLA: very late antigen; VZV: varicella zoster virus

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