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POSITION PAPER

COVID-19 vaccination in patients receiving allergen immunotherapy (AIT) or biologicals—EAACI recommendations

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Abbreviations: 13-PCV, 13-valent conjugate pneumococcal vaccine; 23-PPV, 23-valent pneumococcal polysaccharide vaccine; Ab, antibody; ACE2, angiotensin-converting enzyme 2; AdV, adenovirus; AIRD, autoimmune rheumatic disease; AIT, allergen immunotherapy; AIV, anti-infectious vaccine; APC, antigen-presenting cell; ARDS, acute respiratory distress syndrome; B, B lymphocyte; Bθ, basophil; bAb, binding antibody; BAFF, B-cell-activating factor; Bmem, memory B cells; Breg, B regulatory cell; CCL-3, chemokine (C-C motif) ligand 3, CNS, central nervous system; COVID-19, coronavirus disease 2019; CRP, C-reactive protein; CRS, cytokine release syndrome; CSU, chronic spontaneous urticaria; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CXCL-8, chemokine (C-X-C motif) ligand 8; DC, dendritic cell; Eθ, eosinophil; EAACI, the European Academy of Allergy and Clinical Immunology; FcεRI, high-affinity IgE receptor; FDA, U.S. Food and Drug Administration; GC, germinal centre; GM-CSF, granulocyte-macrophage colony-stimulating factor; HIV, human immunodeficiency virus; IBD, inflammatory bowel disease; ICI, immune checkpoint inhibition; ICU, intensive care unit; Ig, immunoglobulin; IL/ILR, interleukin/interleukin receptor; ILC, innate lymphoid cell; INF, interferon; iTreg, induced regulatory T cell(s); LLPC, long-lived high-affinity plasma cell; LNP, lipid nanoparticle; mAb, monoclonal antibody; MERS-CoV, Middle East respiratory syndrome coronavirus; MHC, major histocompatibility complex; modRNA, nucleoside-modified messenger RNA; mRNA, messenger RNA; MS, multiple sclerosis; Mφ, macrophage; nAb, neutralizing antibodies; NCP, nucleocapsid protein; NET, extracellular neutrophil trap; NK, natural killer cell; NKT, natural killer T cells; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; non-T2, non-type 2 immune response; nTreg, natural regulatory T cells; OR, odds ratio; PBMC, peripheral blood mononuclear cells; PC, plasma cell; PD-1 / PD-L1, programmed cell death protein 1/programmed death-ligand 1; pDC, plasmacytoid dendritic cell; RA, rheumatoid arthritis; rAd26, human recombinant adenovirus type 26 vectors; RBD, receptor-binding domain; rRBD-AddaVax, recombinant RBD protein adjuvanted with squalene-based oil-in-water nano-emulsion (AddaVax); ROC, Research and Outreach Committee; RSV, respiratory syncytial virus; S protein, spike protein; S-2P, subunit 2 of spike protein; SARS-CoV, severe acute respiratory syndrome coronavirus; SNPs, single nucleotide polymorphisms; T, T lymphocyte; T1/2/3, type 1/2/3 immune response; Tc, cytotoxic lymphocyte; Tdap, tetanus toxoid, reduced diphtheria toxoid, acellular pertussis vaccine; Tfh, follicle T helper cell; TFR, T follicular regulatory cell; TGF, transforming growth factor; Th, T helper cell; Tmem, memory T cells; TNF, tumour necrosis factor; Treg, regulatory T cells; TSLP, thymic stromal lymphopoietin; TT, tetanus toxoid; VLP, viral-like particles.

Mohamed H Shamji and Ioana Agache joint last authorship.

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Abstract

Immune modulation is a key therapeutic approach for allergic diseases, asthma and autoimmunity. It can be achieved in an antigen-specific manner via allergen immunotherapy (AIT) or in an endotype-driven approach using biologicals that target the major pathways of the type 2 (T2) immune response: immunoglobulin (Ig)E, interleukin (IL)-5 and IL-4/IL-13 or non-type 2 response: anti-cytokine antibodies and B-cell depletion via anti-CD20. Coronavirus disease 2019 (COVID-19) vaccination provides an excellent opportunity to tackle the global pandemics and is currently being applied in an accelerated rhythm worldwide. The vaccine exerts its effects through immune modulation, induces and amplifies the response against the severe acute respiratory syndrome coronavirus (SARS-CoV-2). Thus, as there may be a discernible interference between these treatment modalities, recommendations on how they should be applied in sequence are expected.

The European Academy of Allergy and Clinical Immunology (EAACI) assembled an expert panel under its Research and Outreach Committee (ROC). This expert panel evaluated the evidence and have formulated recommendations on the administration of COVID-19 vaccine in patients with allergic diseases and asthma receiving AIT or biologicals. The panel also formulated recommendations for COVID-19 vaccine in association with biologicals targeting the type 1 or type 3 immune response. In formulating recommendations, the panel evaluated the mechanisms of COVID-19 infection, of COVID-19 vaccine, of AIT and of biologicals and considered the data published for other anti-infectious vaccines administered concurrently with AIT or biologicals.

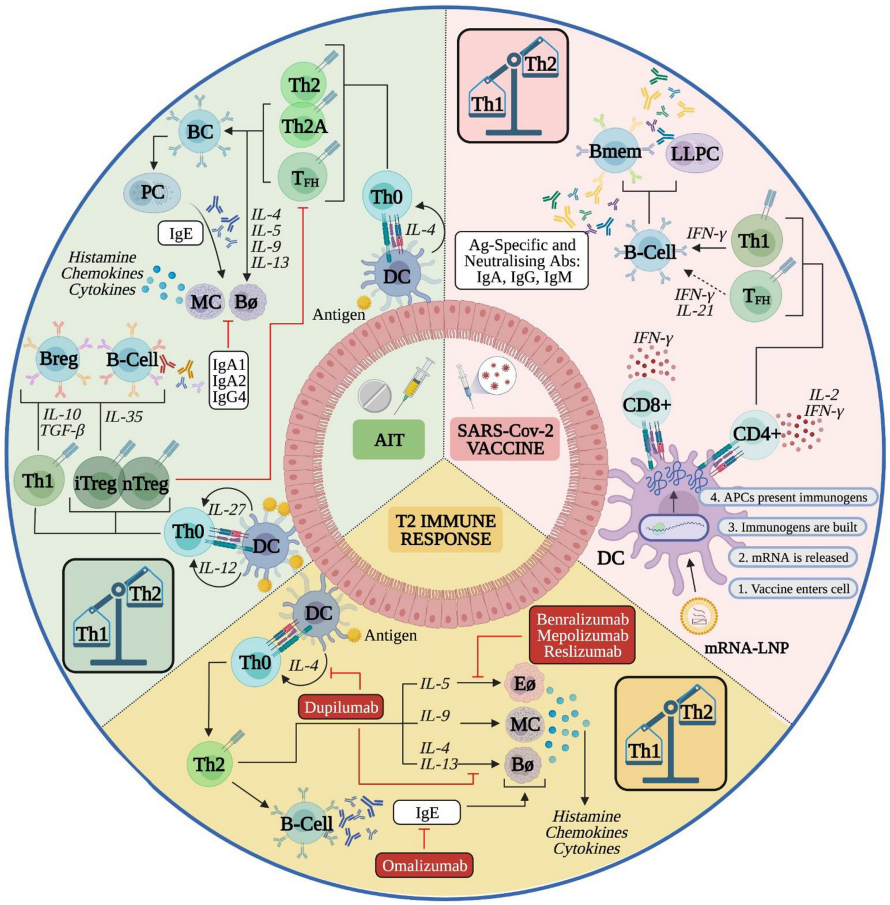
KEYWORDS
allergen, allergy, biologicals, Covid-19, immunotherapy, mRNA vaccines

1 | INTRODUCTION

1.1 | Immune responses to COVID-19 infection

The immune system protects the host against pathogens while maintaining tolerance against self- and innocuous non-self-antigens. Type 1 immune responses (T1) are mounted against intracellular like *Mycobacterium tuberculosis* or viruses. Innate lymphoid cells (ILC1), helper lymphocytes (Th) type 1, natural killer cells (NK), natural killer T cells (NKT) and cytotoxic lymphocytes (Tc) type 1 cells recognize and kill infected cells and their content, while macrophages (Mφ) and neutrophils ingest the dead cells and kill the pathogens. Different groups of immune cells orchestrate type 2 (T2) and type 3 (T3) immune responses. T2 immunity protects against large protozoan pathogens (helminths), toxins and venoms. It is characterized by ILC2, Th2 and Tc2 cells and involves IgE and effector cells like basophils, eosinophils and mast cells.[1] T3 immune responses fight against extracellular bacteria or fungi and are characterized by ILC3, neutrophils and Th17 cells, with IL-17 being the main effector cytokine and neutrophils being the primary effector cells.[2] Deviation of these immune responses may lead to immune deficiencies, autoimmunity, cancer and allergies.

The secretion of interferons (IFNs) is one of the most potent antiviral components of the innate immune response. IFNs exert their antiviral effects by blocking virus attachment, entry, movement, protein production and genome amplification, virus assembly and exit. IFNs activate other innate and adaptive immune responses. However, in the case of COVID-19, these responses appear to be weakened or dysregulated.[3] SARS-CoV and middle east respiratory syndrome coronavirus (MERS-CoV) viruses can inhibit IFN signalling at various levels.[4] A decreased antiviral response through the inhibition of the IFN pathway, along with an ongoing pro-inflammatory response, presumably increased by viral load, can lead to excessive inflammation and worsening of the disease. In the SARS-CoV-2 animal model, a delayed-type I IFN response resulted in the accumulation of inflammatory monocytes and Mφ, leading to elevated



GRAPHICAL ABSTRACT

Immune modulatory responses of COVID-19 vaccination, allergen immunotherapy and Biologicals T2 responses.

cytokines and chemokines in the lungs, vascular leakage and an impaired T-cell response.[5]

Monocytes, Mφ and dendritic cells (DCs) play a key role in antiviral response by interlinking innate and adaptive immunity. Peripheral activation and accumulation of the activated pro-inflammatory agent monocytes and Mφ in the lungs have become the hallmark of symptomatic SARS-CoV-2 infection.[6] Coronaviruses can induce NOD-, LRR- and pyrin domain-containing protein 3 (NLRP3) inflammasome activation in monocytes and Mφ, producing high amounts of pro-inflammatory mediators such as IL-6, granulocyte-macrophage colony-stimulating factor (GM-CSF), IL-1beta(β), tumour necrosis factor (TNF), C-X-C Motif Chemokine Ligand 8 (CXCL-8) or C-C Motif Chemokine Ligand 3 (CCL-3). In addition to this, coronaviruses also increase cell death, induce cytokine storm, or cytokine release syndrome (CRS).[6] Neutrophils are the dominant cells infiltrating the lung in severe SARS-CoV-2 infection.[7] During systemic inflammation, neutrophil activation occurs, which may be associated with the release of extracellular neutrophil traps (NETs) which allows the entrapment of pathogens. On the contrary, NET formation is associated with lung diseases, especially acute respiratory distress syndrome (ARDS). In severe SARS-CoV-2 infection, the uncontrolled progressive inflammation likely induces intense crosstalk between NET-releasing neutrophils and Mφ IL-1β secretion, which may lead to further complications.[8] $CD8^+$ T cells directly neutralize infected cells, and $CD4^+$ T cells help B cells initiate a humoral response against the pathogen. T cells play an essential role in developing virus-specific memory $CD8^+$ and $CD4^+$ T cells.[9-11] SARS-CoV-2-specific $CD8^+$ and $CD4^+$ T cells have recently been identified in ~70% and 100% of patients following SARS-CoV-2 infection, respectively. Delayed development of adaptive responses along with prolonged virus clearance has been reported in cases of severe SARS-CoV-2 infection.[12] The mechanisms related to lymphocytopenia are still unknown in SARS-CoV-2 infection. Moreover, as with SARS-CoV-2, alteration in antigen-presenting cells (APC) function followed by impairment of T cell stimulation may lead to the ineffective and delayed formation of virus-specific T cells.[13-15] Data on NK cell count in COVID-19 patients are variable. Functional depletion of NK cells and $CD8^+$ T cells has been described in relation to severe SARS-CoV-2 infection.[16] The number of the regulatory T cells (Treg) is reduced during SARS-CoV-2 infection.[17] The intense cytokine response can induce apoptosis of T cells.[18]

Infection with human SARS-CoV-2 activates the immune mechanisms of B and Th cells, with production of neutralizing antibodies (nAb), that binds specifically to surface structures on the virus, preventing them from interacting with the host cells. Moreover, nAb can

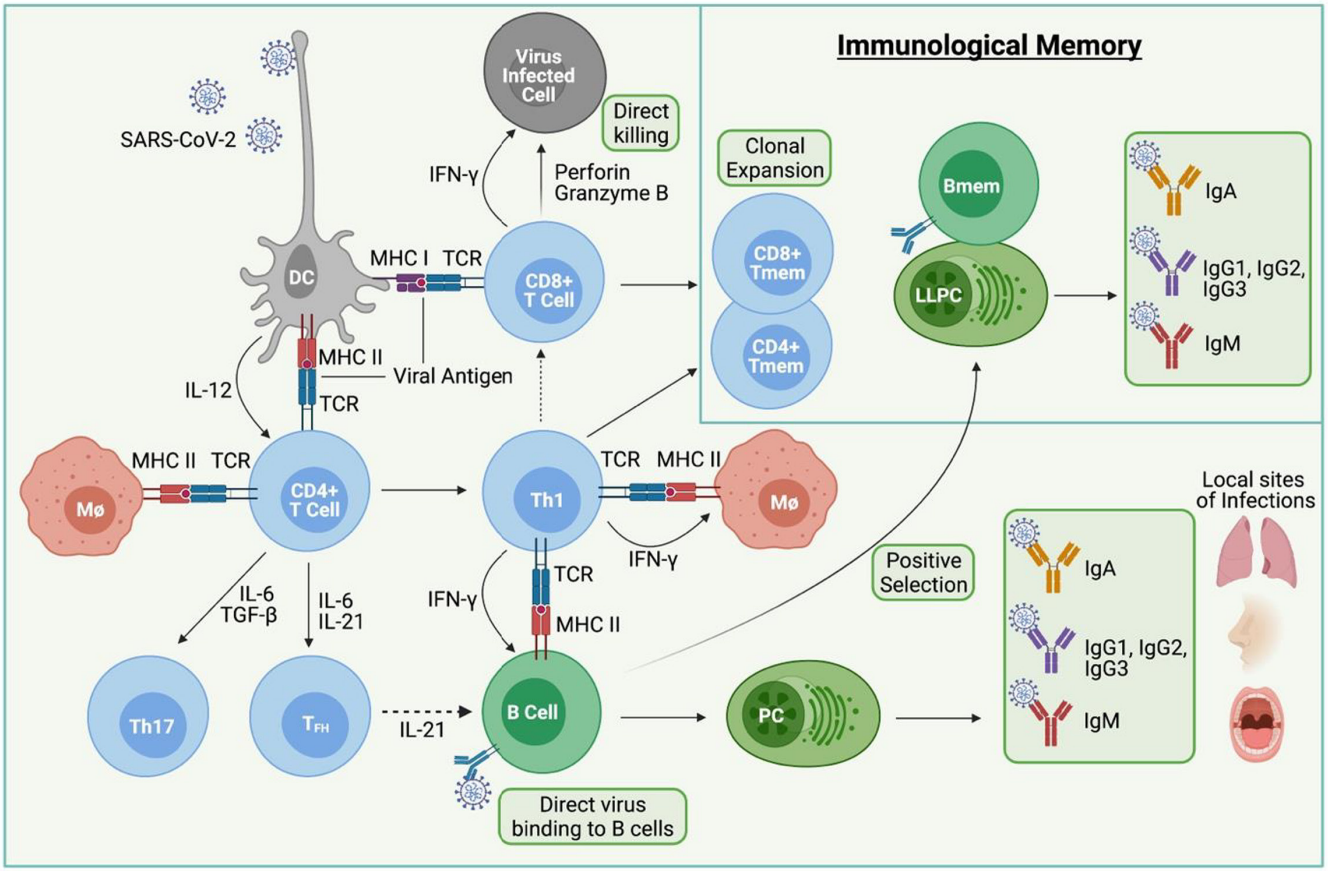


FIGURE 1 Immune response to SARS-CoV-2

either interfere with the virus infectivity or binding antibodies (BAbs), which bind specifically to the virus, but do not interfere with it infectivity. Most of the SARS-CoV-2 neutralizing antibodies target the glycoprotein S (or spike (S) protein) receptor-binding domain (RBD), which engages the host receptor angiotensin-converting enzyme 2 (ACE2) for viral entry.[19] The antibody response occurs 4–8 days after the onset of COVID-19 symptoms by IgM.[20] Early humoral response is dominated by IgA antibodies,[21] and plasmablasts were detected shortly after the onset of symptoms and peaked in the third week of illness. Neutralizing IgA serum titrants decreased notably after 1 month of the onset of symptoms but remained detectable in saliva up to 49 to 73 days post-symptoms.[22] The development of mucosal IgA can prevent re-infection with SARS-CoV-2, while circulating IgA can contribute to the systemic neutralization of SARS-CoV-2 and the reduction of inflammation during active infection.[23] SARS-CoV-2 IgG nAb specific to the S protein decrease after 5–8 weeks but are still detectable up to 8 months after infection.[24] For this reason, passive transfer of human serum obtained during convalescence was suggested as a therapeutic approach.[25] However, low affinity or suboptimal levels of IgG may increase viral entry through IgG binding to the Fcγ receptor (FcγR) expressed on immune cells. This mechanism may induce the release of inflammatory cytokines and contribute to the CRS associated with severe COVID-19.[26] The potential contribution of the B cell population to COVID-19 pathology has not yet been fully elucidated. The main challenges with B cell responses to SARS-CoV-2 is the duration of the antibody response (IgG) after the infection and the ability of SARS-CoV-2-specific memory B cells to expand or replenish the plasma cell compartment after re-infection[27] (Figure 1). In COVID-19 patients, S protein-specific memory B cells were more frequent at 6 months than at 1 month after symptom onset and the IgG to the S protein was relatively stable over 6 months.[28] While serum IgG to RBD and nucleocapsid protein (NCP) was identified in all COVID-19 patients, antibody levels began declining at 20 days post-symptom onset. RBD- and NCP-specific memory B cells (Bmem) predominantly expressed IgM^+or $IgG1^+$ and continued to increase up to 150 days.[29]

DC present SARS-CoV-2-derived antigenic peptides on MHC II to $CD4^+$ T cells, in the presence of IL-12. $CD4^+$ T cells differentiate into either Th17 in the presence of IL-6 and TGF-β, T_{FH} in the presence of IL-6 and IL-21 or into Th1 cells. Moreover, Mφ can also present SARS-CoV-2-derived antigenic peptides on MHC II to activate $CD4^+$ T cells and Th1 cells. DC also present SARS-CoV-2-derived antigenic peptides on MHC I to $CD8^+$ T cells, which in turn become activated and release IFN-γ and elicit direct killing of virus-infected cells via perforin and granzyme B. $CD4^+$ T cells and $CD8^+$ T cells undergo clonal expansion into $CD4^+$ T mem and $CD8^+$ Tmem, constituting immunological memory. T_{FH} cells release IL-21, which induces class switching in B cells to virus-specific IgA, IgG_1, IgG_2, IgG_3 and IgM. Furthermore, SARS-CoV-2 virus can directly bind to B cells. High-affinity B cells differentiate into PC, which secrete antibodies. Moreover, positively selected high-affinity B cells differentiate

into Bmem and LLPC secreting IgA, IgG_1, IgG_2, IgG_3 and IgM, also constituting of immunological memory. The local sites of infection for SARS-CoV-2 are the lung and the nasal and oral mucosa. Bmem, memory B cells; DC, dendritic cell; IFN-γ, interferon-γ; Ig, immunoglobulin; IL, interleukin; LLPC, long-lived high-affinity plasma cell; MHC, major histocompatibility complex; Mφ, macrophage; PC, plasma cell; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T_{FH}, T follicular helper cell; TGF-β, transforming growth factor β; Th1, T helper type 1 cell; Th17, T helper 17 cell; Tmem, memory T cells. Figure 1 created with BioRender.com.

1.2 | Immune mechanisms of COVID-19 vaccination

The major mechanism of protection against viral infection triggered by the licensed vaccines relies on generating antigen-specific memory cells, which when re-exposed to the pathogen, will quickly create a T and B cell response that persists over time.[30] Persistent antibodies against viruses are generated at microanatomical sites of secondary lymphatic organs called germinal centres (GCs), where antigen-activated B cells generate antibodies with the high affinity for the pathogen.[31] Only the B cells reaching high affinity are positively selected and saved from apoptosis. This process produces long-lived high-affinity plasma cells (LLPC) and memory B cells (Bmem), which are the desired cell types induced by vaccination.

The efficacy of vaccination against SARS-CoV-2 may to a large extent depend on the induction of T-cell responses for several reasons. Among $CD4^+$ T cells, T follicular helper cells (T_{FH}) are key regulators of GCs affinity-matured antibody responses.[32,33] By delivering costimulatory molecules and cytokines to B cells, T_{FH} cells mediate GCs formation and select affinity-matured GCs B cells, which may further differentiate into LLPC or Bmem. T_{FH} cells may differentiate towards the Th1 or Th2 phenotype, which will affect the switching of antibodies produced by LLPC to Th1- or Th2-dependent antibody class.[34] Other subsets of $CD4^+$ T cells may serve various essential functions, including facilitating optimal CD8 T-cell responses. In addition, cytotoxic $CD8^+$ T cells responsible for the direct killing of pathogen-infected cells by releasing molecules such as granzyme and perforin provide an important 'safety net' that has to be created by vaccination in case protective antibodies do not completely control the viral infection.[35]

Specific immune reactions occur during vaccination, depending on the route, dose and type of vaccine and adjuvants. The work on 200 new potential vaccine preparations is underway around the globe. Researchers are currently testing 82 vaccines in clinical trials in humans, and 23 have reached the final phase. At least 77 preclinical vaccines are under active investigation in animal models. The vaccine platform used for specific COVID-19 vaccines include messenger RNA (mRNA)-based, recombinant viral vectors (viral vector non-replicating), inactivated vaccine virus, subunit (recombinant protein vaccines), viral-like particles (VLP) and live-attenuated, or recombinant viral vectors (viral vector replicating).

2 | COVID-19 VACCINATION AND THE KINETICS OF THE IMMUNE REACTION

2.1 | RNA-based vaccines

Two RNA-based COVID-19 vaccines have been the first to be approved globally, and these were produced by BioNTech/Pfizer and Moderna, respectively.[36] The BioNTech/Pfizer vaccine BNT162b2 is a lipid nanoparticle formulated nucleoside-modified messenger RNA (modRNA) encoding SARS-CoV-2 full-length S glycoprotein modified by 2 proline mutations to lock it in the prefusion conformation.[37–42] The Moderna vaccine mRNA-1273 is also a lipid nanoparticle-encapsulated mRNA-based vaccine that encodes the prefusion stabilized full-length spike protein of SARS-CoV-2.[43,44]

BNT162b1 and b2 (Comirnaty). The efficacy was evaluated in a multinational, placebo-controlled pivotal phase 2/3 trial with 43,548 participants aged 16 years old or older over the course of two months. Administration of 30-μg dose, 21 days apart compared with placebo, elicited 95% protection against COVID-19.[37,45] A case–control study compared 596,618 people who were newly vaccinated in Israel and matched them to unvaccinated controls according to demographic and clinical characteristics. The outcomes were collected from 20 December 2020 to 1 February 2021 in time periods: Days 14 to 20 after the first dose of vaccine or day seven or more after the second dose. Two doses of the vaccine reduced symptomatic cases by 94%, hospitalization by 87%, and severe COVID-19 by 92%. In Israel, the second dose of vaccine is given on Day 21, in line with the trials and the manufacturer's recommendation. The study also suggests the vaccine is effective against the B.1.1.7 (α) variant, which was first identified in the United Kingdom (U.K.). During the study period, this variant was isolated in Israel in up to 80% of cases.[46] Possible escape of an α variant from BNT162b2-mediated protection was investigated in a study using pseudoviruses bearing SARS-CoV-2 S protein variants of either Wuhan reference strain or the α (B.1.1.7) with sera of 16 participants from a previously reported trial. The immune sera were reported to have equivalent nAb titres to both variants, emphasizing that the α variant will unlikely compromise the efficacy of BNT162b2.[47] Micro-neutralization assays with sera obtained after Comirnaty vaccination in 36 healthcare workers showed significant fold change reduction in neutralizing titres in δ (B.1.617.2) compared with the original virus: γ (P.1) 2.3, β (B.1.351) 10.4, δ 2.1 and 2.6. The reduction of the α (B.1.1.7) variant was not significant.[48]

Vaccine doses are administered intramuscularly on Day 0 and 21. Concentrations of RBD-binding IgG and SARS-CoV-2-neutralizing titres were assessed at baseline, 7 and 21 days after the BNT162b1 priming dose, and 7 and 21 days after the boost dose (Days 29 and 43). Twenty-one days after the first dose, concentrations of RBD-binding IgG had increased in a dose-dependent manner, ranging from 265 to 1,672 units (U) ml^{-1}, with an increase (21 days after boost) up to in the range of 3,920–18,289 (U) ml^{-1}. SARS-CoV-2 nAb increased in a dose-dependent manner 21 days after the priming dose. Substantially higher serum-neutralizing titres were achieved seven days after the booster dose. On Day 43 (21 days after the boost),

the neutralizing and RBD-binding start decreasing. It should be mentioned that, the absolute mean titer of neutralizing Ab in a group over the age of 80 years remained lower than the < 60 years of age group. After the second vaccination, 31.3% of the elderly had no detectable neutralizing Ab.[49] The intensity of RBD-specific $CD4^+$ T cell responses correlated positively with both RBD-binding IgG and SARS-CoV-2-nAb titres. The intensity of RBD-specific $CD8^+$ T cell responses correlated positively with vaccine-induced $CD4^+$ T cell responses but did not significantly correlate with SARS-CoV-2 nAb titres. RBD-specific $CD4^+$ T cells secreted IFN-γ, IL-2 or both, but in most individuals, they did not secrete IL-4. Similarly, fractions of RBD-specific $CD8^+$ T cells secreted IFN-γ and IL-2. Five vaccinated participants were stimulated *ex vivo* with overlapping RBD peptides and produced the pro-inflammatory cytokines TNF, IL-1β and IL-12p70, but neither IL-4 nor IL-5. In summary, these findings indicate that BNT162b1 induces functional and pro-inflammatory $CD4^+$ and $CD8^+$ T cell responses with detection of IFN-γ, IL-2 and IL-12p70, but not IL-4 or IL-5, which reveals a favourable Th1 profile and the absence of a potentially deleterious type 2 immune response.[50] With this in mind, antigen-specific T cell responses were characterized in mice 12 and 28 days after BNT162b vaccine immunization. A strong IFN-γ producing $CD4^+$ and $CD8^+$ T cell responses, and a high fraction of $CD8^+$ T cells that produced IL-2 were observed. Moreover, 28 days after immunization with 1-μg BNT162b2, splenocytes revealed high levels of Th1 cytokine production (IL-2 or IFN-γ), along with undetectable levels of Th2 cytokines IL-4, IL-5 or IL-13. In addition, one immunization with BNT162b2 induced high dose level-dependent RBD- and S1-binding serum IgG titres. Furthermore, IgG elicited by BNT162b2 revealed a strong binding affinity for the recombinant RBD target antigen.[38]

mRNA-1273 (spikevax). The efficacy was investigated in phase 3 randomized placebo-controlled trial with 30,420 participants (15,210 participants in each group) across the United States (U.S.). Similar to BNT162b2 vaccine efficacy, the mRNA-1273 vaccine also elicited 94.1% protection against symptomatic COVID-19 when injected at 100-μg after the second dose on day 29.[43,51] Another preliminary study investigating the immune responses of mRNA-1273 vaccine against the α variant revealed similar reactions to BNT162b2 vaccine[52] and all individuals had responses to all virus variants (α, β, ε, γ, and δ).[53]

Vaccine doses are administered intramuscularly on Day 0 and 29. BAb specific to S-2P protein (anti-spike) together with serum nAb titres against SARS-CoV-2 were measured on Days 1, 29, 43, 57, 209 and 394.[54] The vaccine induced increases in the levels of anti-SARS-CoV-2-spike BAb by 28 days after the first vaccination. Their titre substantially increased by 14 days (day 43) after the second vaccination to peak levels of 189 mg/ml in younger participants and 153 mg/ml in older participants.[55,56] nAb increased from baseline by 28 days post-vaccination. Fourteen days following the booster (Day 43), their level significantly increased to a maximum of 1909 mg/ml at 100 mg mRNA-1273 in younger adults and 1686 mg/ml in older adults. Both antibodies remained elevated in all participants 3 months after the booster vaccination. Serum nAb continued to be detected in all the participants on Day 119.[57,58] Splenocytes from mice immunized with mRNA-1273 secreted more IFN-γ (a prototypic Th1 cytokine) than IL-4, IL-5 or IL-13 (classical Th2 cytokines), whereas restimulation with SARS-CoV-2 S(2P) protein with alum adjuvant induced a Th2-biased response.[59] Animals immunized with mRNA-1273 had lower concentrations of Th2-associated cytokines than animals in the PBS-immunized group. mRNA-1273 vaccination elicits S-specific $CD4^+$ T_{FH} and B cell responses.[60]

Prospective cohorts of healthcare personnel, first responders, and other essential and frontline workers over 13 weeks in eight U.S. locations confirmed that authorized mRNA COVID-19 vaccines (BNT162b2 and mRNA-1273) are highly effective in real-world conditions.[61] The mRNA-1273 vaccine was still effective in preventing COVID-19 illness and severe disease at more than 5 months.[62] The U.S. Food and Drug Administration (FDA) has demonstrated in a retrospective analysis of 31,069 individuals receiving at least one dose of either mRNA-1273 or BNT162b2 vaccine an 88.7% protection against SARS-CoV-2 infection with onset at least 36 days after the first dose. Furthermore, vaccinated patients who were subsequently diagnosed with COVID-19 had significantly lower 14-day hospital admission rates than propensity-matched unvaccinated COVID-19 patients.[63]

2.2 | Recombinant vaccines

Gam-COVID-vac (Sputnik V) developed by the Gamaleya Research Institute of Epidemiology and Microbiology in Russia is the world's first registered vaccine based on human recombinant adenovirus (AdV) type 26 and 5 vectors (rAd26 and rAd5) and the world's first registered vaccine against SARS-CoV-2. The vaccine is administered intramuscularly in a prime-boost regimen: a 21-day interval between the first dose (rAd26) and the second dose (rAd5), both vectors carrying the gene for the full-length SARS-CoV-2 glycoprotein. The vaccine's efficacy is confirmed at 91.6% based on the analysis of data from 21,977 volunteers: the vaccine-induced strong humoral and cellular immune responses. RBD-specific IgG were detected in 98% samples and nAb in 95%. Cellular immune response was evaluated with the secretion of IFN-γ of peripheral blood mononuclear cells (PBMC) upon stimulation with SARS-CoV-2 glycoprotein S. By Day 28 after the first vaccination, all participants had significantly higher levels of IFN-γ secretion compared with the day of administration of the first dose.[64] In the analysis of 327 naive individuals after first dose of Gam-COVID-vac, 30% developed *ex vivo* IFN-γ ELISpot responses (significantly lower than AZD1222) and high frequency of CD107a expressing T cells along with Bmem cell responses.[65]

ChAdOx1 nCoV-19 (AZD1222) vaccine produced by University of Oxford/AstraZeneca contains DNA delivery within a non-replicating AdV system consists of a chimpanzee adenoviral vector ChAdOx1, containing the SARS-CoV-2 structural surface glycoprotein S antigen gene. The vaccine efficacy is 91%, respectively, based on data from blinded, randomized, controlled trials done across three countries, on 23,848 participants.[66] Anti-spike IgG antibodies

to SARS-CoV-2 S spike and RBD titres rose after the first vaccination, with a further increase after the second. Vaccination increased anti-S IgM and IgA titres with a peak response 28 days after priming. IgG_1 and IgG_3 responses were detectable on day 28 and remained at a similar level before boosting. naAb were induced following prime vaccinations and significantly increased after the booster dose. Anti-spike antibody function was explored to determine the ability of antibodies induced by vaccination to support antibody-dependent monocyte and neutrophil phagocytosis. Both functions were induced by the first vaccination and substantially increased by the second dose. Antibody-dependent complement deposition was also induced by prime vaccination and increased following booster doses. In a Chinese study, individuals with prior SARS-CoV-1 infection and one dose of ChAdOx1 had higher anti-SARS-CoV-2-spike RBD Ab levels than those without infection and either one or two doses of ChAdOx1, despite being older and having a longer interval between vaccination and Ab level measurement.[67] Single-dose of ChAdOx1 nCoV-19 induced low anti-spike Ab-dependent NK cell activation, boosted by the second dose given either on day 28 or day 56. Antigen-specific T-cell responses measured by IFN-γ were induced and peaked 14 days after the first dose.[68]

Ad.26.COV2.S (JNJ-78436725) manufactured by Janssen/Johnson & Johnson vaccine is also an AdV vaccine. It uses the replication-defective human type 26 adenovirus vector expressing SARS-CoV-2 virus S glycoprotein. Previously, the same vector (AdVac® technology) was used in the Ebola vaccine.[69] Participants received 1 or 2 intramuscular injections with 5 × 10e10 viral particles or 1 × 10e11 viral particles of Ad26.COV2.S. By Day eight following immunization, bAb against full-length S protein were observed in 65% of vaccine recipients and against the S RBD in 90% of vaccine recipients. Virus Ab was observed in 25% of vaccine recipients. By day 15, S-specific and RBD-specific bAb were observed in 100% of vaccine recipients and nAb were observed in 85% of vaccine recipients. bAb and nAb continued to increase on Days 29, 57 and 71. By Days 57 and 71, 100% of vaccine recipients showed nAb and S- and RBD-specific bAb. The boost dose on day 57 increased bAb titres by 2.56-fold and nAb titres by 4.62-fold. Detailed assessment of antibodies type showed that Ad26.COV2.S induced S- and RBD-specific IgA1, IgA2, IgG1, IgG2, IgG3, IgG4 and IgM subclasses: FcγR2a, FcγR2b, FcγR3a and FcγR3b binding. Antibody-dependent complement deposition, neutrophil/monocyte phagocytosis, NK cell activation and functional antiviral responses were observed together with the induction of central memory $CD27^+/CD45RA^-/CD4^+$ and $CD8^+$ T-cell responses. IFN-γ responses were observed in 65% of vaccine recipients by day 15 and in 84% of vaccine recipients by day 71.[70]

2.3 | Inactivated vaccines

The inactivated vaccine platform was the first technology used in a plethora of vaccination strategies developed since the beginning of the SARS-CoV-2 pandemic. Authorized vaccines of this type are the Chinese CoronaVac (Sinovac Biotech), BBIBP-CorV and WIBP-CorV; the Indian Covaxin; and the RussianCoviVac.[71-74] These vaccines elicit antibody response, which target not only the S protein of the SARS-CoV-2 virus but also other antigens such as virus N proteins.[75,76] In comparison with vaccines that target only the S protein of the SARS-CoV-2 virus, inactivated vaccines may benefit from the broader antigenic spectrum of the whole virus resulting in a more heterogenous immune response. This needs to be further confirmed in efficacy trials. Findings from CoronaVac revealed that antibody titres of nAb to live SARS-CoV-2 and RBD-specific IgG were induced after two doses on Days 0 and 14 and Days 0 and 28 in adults aged 18–59 years old. Data showed persistence of nAb titres beyond 28 days. Seroconversion of nAb was seen for 92% of participants receiving the 3 μg dose of vaccine, and in 98% receiving the 6 μg dose. nAb titres induced by the 3 μg dose were similar to those of the 6 μg dose, supporting the use of the 3 μg dose CoronaVac in phase 3 trials to assess protection against COVID-19. At 14 days after the second dose of vaccine, the levels of IFN-γ were measured. T-cell responses were low in participants that was administered the vaccine, which provided no clear evidence that the vaccine-induced T-cell responses.[77] Similar observations were made in the group of adults over 60 years of age.[71] CoronaVac was also well-tolerated and safe and induced humoral responses in children and adolescents aged 3-17 years in a double-blind, randomised, controlled, phase 1/2 clinical trial.[78]

2.4 | COVID-19 subunit vaccinations

Currently, most of the protein subunits vaccines have focussed on the virus' S protein subunits or the domain directly involved in RBD.[79] In contrast with traditional vaccines, subunit vaccines should have fewer side effects and higher safety at the injection site. These vaccines require adjuvant activities to exert an optimal effect because of the poor immunogenicity of the subunit's proteins. Adjuvants are included as vehicles to target antigen-presenting cells or to enhance the innate immune response. NVX-CoV2373 had an efficacy of 89.9% against the historical strain, 86.3% against α and 60% against β strain.[80]

Further vaccine development could aim at structural, non-structural and accessory proteins of SARS-CoV-2 which could potentially serve as targets of vaccine-induced immune responses. B cell and T cell epitopes are highly conserved between SARS-CoV-2 and SARS-CoV, indicating that a vaccine against such a conserved epitope may elicit cross-immune responses to mutant viruses. Among viral structures, S protein is the main protein used as a target in COVID-19 vaccines. In experimental models, recombinant S trimeric protein mimics the native S form inducing high nAb titres accompanied by high Th1 and low Th2 cell responses that reduce viral loads in lungs and confer clinical protection after the SARS-CoV-2 challenge. The authorized COVID-19 subunit vaccines include peptide preparation EpiVacCORONA and RBD-Dimer.[81]

Comparative safety and immunogenicity of different COVID-19 vaccines given as a third (booster) dose were performed. Different

COVID-19 vaccines as a third dose after two doses of ChAdOx1 nCov-19 or BNT162b2 were used (NVX-CoV2373, ChAdOx1 nCov-19, BNT162b2, VLA2001, Ad26.COV.2, mRNA 1273 or CVnCoV). All studied vaccines boosted Ab and neutralizing responses after ChAdOx1 initial course and all except one after BNT162b2, with no safety concerns.[82,83]

In summary, the levels of antibodies (binding Ab specific to S-2P protein and neutralizing Ab) were assessed on different days after the first dose of the vaccine (from Day 7 to 40) and at various time points after the booster dose, up to 3 months. The antibody levels were increased up to day 28. Limited data were available after Day 28 and showed antibody increase up to Day 40 after the first dose (Moderna, BioNTech/Pfizer). At the same time, Tmem and Bmem cells were generated. These T and B cell responses are crucial for the rapid initiation of the immune response. Further studies are needed to elucidate the role of Tmem and Bmem cell responses.

3 | IMMUNOLOGICAL MECHANISM OF ALLERGEN IMMUNOTHERAPY AND BIOLOGICALS

3.1 | Allergen immunotherapy

AIT is an intervention for allergic diseases and asthma-inducing tolerance to the sensitizing allergen eliciting the symptoms.[84] By continuous administration of high amount relevant allergen(s), a tolerogenic immune response is generated. Main mechanisms involve early effector cell desensitization and progressive onset of a regulatory B and T cell response followed by significant decreases in allergen-specific type 2 especially Th2 cells and type 2 ILCs in circulation and the affected tissue.[85-87] Effective AIT has been shown to reverse the Th2 dominance with increased IFN-γ production and reduction in Th2 cytokines.[88] Although AITinduced changes are antigen-specific, recent data support a positive effect in the overall rebalance of Th2-skewed innate immune system.[89,90] COVID-19 does not considerably increase in severity in allergic disease, such as rhinitis, urticaria and atopic dermatitis or even asthma, if controlled under background treatment.[91,92] The immunological mechanisms of AIT and COVID-19 vaccine do not seem to interfere as both primarily target the immune system in a specific, non-overlapping manner.

The effect of AIT on the effector cell desensitization, especially mast cell desensitization, is rather limited, antigen/allergen specific and occurs early during AIT.[93] However, mast cells are not considered to be relevant for antiviral immune response.

3.2 | Biologicals targeting the Type 2 immune response (anti-IgE, anti-IL-4R, IL-5, IL-13, TSLP)

Biologicals block specific immune pathways within the cascade of immunological events that result in chronic allergic inflammation and/or acute exacerbations. Their availability transformed the way severe allergic diseases are treated beyond systemic steroids or immunosuppressants. Despite their specificity for molecular targets, pathways of allergic inflammation may overlap with immunologic events that serve to cope with viral infections or are associated with vaccine response. Real-life relevance is sometimes difficult to predict due to redundancies within the human immune system. Upstream of allergen-specific responses, innate cells drive allergic inflammation in tissue and mucosal surfaces. Tezepelumab blocks the epithelial-derived cytokine thymic stromal lymphopoietin (TSLP) and thereby is considered to address upstream events in the tissue/mucosa. TSLP promotes epithelial inflammation and initiates type 2 DCs, activates ILC2s and adaptive type 2 T and B cells. Furthermore, TSLP is considered a central regulator of environmental triggers such as allergens, pollutants and viruses and is upregulated in the airways of asthmatics. The clinical relevance of TSLP blockade via the monoclonal antibody (mAb) Tezepelumab demonstrated clinical efficacy in treating adults with uncontrolled asthma.[94] During SARS-CoV-2 infection, TSLP levels in serum are not altered, neither over time nor in patients with severe disease.[95] Very recent findings demonstrate a suppressive effect of TSLP on recall responses of $CD8^+$ T cells in the context of infections.[96] Bone marrow-derived cells from $TSLP^{-/-}$ mice display an enhanced viral response in a neonatal rodent model of respiratory syncytial virus (RSV) infection.[97] Despite the lack of human data, blocking TSLP may have beneficial effects in suppressing viral infections, while no information is available on vaccine response under TSLP blockade. IL-4 and IL-13 receptors (R) share the IL-4Rα chain. Similar to TSLP, IL-13 reduces barrier function, facilitates virus entry and negatively affects rhinovirus induced immune responses. IL-4 is the critical cytokine that promotes the isotype switch towards IgE and is a key cytokine in B-cell function. It also acts on innate APCs and effector cell populations. IL-4 also plays a role in neutrophil function.[98] IL-4-producing $CD8^+$ T-cell subsets can dampen the development of effective Th1 immunity in several viral infections, including chronic human immunodeficiency virus (HIV)-1.[99] Inhibition of IL-13 expression may enhance antiviral immunity.[100] In the context of vaccine immune response, it has been shown that IL-4, IL-4Rα and IL-13 polymorphisms influence pneumococcal serotype-specific IgG antibody responses.[101] Haplotypes composed of IL-4 and IL-4Rα SNPs, showed a higher discriminative power in vaccine responsiveness compared with single nucleotide polymorphisms (SNPs) analyses,[101] which may affect the vaccine response with other preparations. Transient inhibition of IL-4 and or IL-13 at the vaccination site has been shown to induce sustained solid, high-quality $CD8^+$ T-cell immunity against a mucosal pathogen such as HIV-1 and IL-4/IL-13 receptors/antagonist have also been proposed as vaccine adjuvants.[102] Omalizumab reduces dendritic cell receptors high-affinity IgE receptor (FcεRI) by blocking free IgE, which is fundamental in allergic asthma, restoring the ability to produce IFN-α, which translates into a greater antiviral response.[103] Combined blockade of multiple Th2-associated cytokines (IL-13, IL-4 and IL-5) may be a better approach to overcome cytokine redundancy and gain full control of asthma symptoms, including exacerbations, lung function and quality of life, by simultaneous optimization of airway hyper-reactivity, eosinophil and IgE targeting.[104]

3.3 | Mechanisms of biologicals targeting the non-Type 2 pathway

Biologicals represent an essential cornerstone in the management of non-type 2 inflammatory diseases. Anti-cytokine antibodies are applied in patients with inflammatory bowel disease, rheumatic diseases or inflammatory skin diseases.[105] These antibodies modulate cytokine dysregulation being involved in disease onset and progression. In autoimmunity, B-cell depletion via anti-CD20 biological is used in not only organ specific but also systemic diseases for elimination of auto-reactive B cells and plasma cells.[106] Moreover, natalizumab is a humanized anti-α4 integrin monoclonal antibody impeding cell migration by interference of integrin binding to their endothelial receptors. This antibody is used to suppress central nervous system (CNS) inflammation in multiple sclerosis patients. Also in oncological patients, immune-modulating therapies are applied.[107] Small molecules result in immune-check-point inhibition leading to better tumour defence in a variety of cancers.[108] Besides substantial treatment efficacy, biologicals substantially influence the immune response to microorganisms, often resulting in the enhanced susceptibility to infections.

4 | COVID-19 VACCINATION IN PATIENTS RECEIVING AIT OR BIOLOGICALS

4.1 | Possible interference of COVID-19 vaccination and AIT

AIT is an effective treatment for allergic rhinitis with and without asthma and is associated with reduced clinical symptoms, the need for rescue medication and disease exacerbation. AIT induces long term clinical and immunological tolerance where clinical benefit is observed beyond the cessation of treatment administration.[109–111] Safety and efficacy are essential for an allergic patient undergoing AIT who intend to receive an anti-infectious vaccine (AIV). Current guidelines recommend that the administration of AIT and AIV should be separated by a minimum of a 7-day interval to avoid potential interfering reactions.[112,113] However, this is based on a pragmatic approach rather than on existing evidence from clinical studies. A retrospective analysis of 875 subjects showed that patients receiving AIT and AIV on the same day did not experience more systemic reactions than those receiving AIT alone.[114] Data on AIV impact on AIT suggest that booster vaccines can be effectively and safely administered in allergic patients receiving AIT.[115] From the mechanistic point of view, AIT and COVID-19 immune responses do not seem to interfere negatively (Table 1). AIT patients might even benefit by rebalancing the innate immune system and favouring protective responses (Table 2, Figures 2 and 3). No data on the effects of AIT on the COVID-19 vaccine-induced antibody production are available. Due to different antigen specificity, it can be speculated that there is no interference. The data on the inflammatory marker induction, for example C-reactive protein (CRP) protein, IL-1 and TNF-α, are very limited. Consequently, it is not possible to recommend the interval between AIT and COVID-19 vaccination based on objective measures. This should be considered on a case-by-case basis. Studies show that the COVID-19 vaccines elevate IFN-γ production but have no influence on IL-4 production. This might account for the synergistic effect of COVID-19 and AIT.

Recommendation 1: COVID-19 vaccines should be administered at the interval of 7 days from the subcutaneous allergy vaccines to unequivocally assign potential side effect of each one. Likewise, sublingual daily dose should be stopped 3 days before COVID-19 vaccine administration and restarted 7 days after.

Reslizumab, mepolizumab and benralizumab are anti-IL-5/IL-5R targeted biologicals. Dupilumab is an IL-4Rα subunit targeted biological treatment, which inhibits the action of the IL-4 and IL-13. Omalizumab is an anti-IgE biological treatment. Red inhibition lines indicate where these five biologicals elicit inhibitory actions within the T2 allergic response. Biological inhibition of the T2 immune response deviates to a Th1-driven cellular response. AIT, administered subcutaneously or sublingually, induces allergen-specific responses. AIT results in an increased allergen-load captured by DC, skewing naïve Th0 cell differentiation into iTreg, nTreg cells and Th1 cells in the setting of IL-27 and IL-12. iTreg, nTreg cells and Th1 cells release anti-inflammatory cytokines IL-10, IL-35 and TGF-β, which induce class switching in Breg and B cells to IgA_1, IgA_2 and IgG_4. IgA_1, IgA_2 and IgG_4 inhibit IgE-cross linking, preventing effector cell activation. iTreg and nTreg cells also inhibit T_{FH} and Th2 cellular responses. AIT therefore causes immunodeviation to a Th1 cellular response due to high allergen exposure. During SARS-CoV2 vaccination, mRNA-LNP (encoding SARS-CoV2-modified S protein) enters the cell and releases its mRNA. The host-APC then builds the encoded immunogens and presents them on MHC I to $CD8^+$ T cells, which subsequently secrete antiviral IFN-γ. DC also present the encoded immunogen antigen on MHC II to $CD4^+$ T cells, which secrete IFN-γ and IL-2, and differentiate into T_{FH} and Th1 cells. T_{FH} and Th1 cells release IFN-γ with antiviral activity and IL-21, promoting B-cell isotype class switching to SARS-CoV-2 S protein-specific and neutralizing antibodies; IgA, IgG_1, IgG_2, IgG_3 and IgM. B cells with high affinity are positively selected and further differentiate into LLPC and Bmem. The SARS-CoV-2 vaccination immune pathway is therefore mediated through a Th1 cellular response.

Bθ, basophil; Bmem, memory B-cell; Breg, regulatory B cell; Eθ, eosinophils; IFN-γ, interferon-γ; Ig, immunoglobulin; IL, interleukin; iTreg; induced regulatory T cells; LLPC, long-lived high-affinity plasma cells; MC, mast cell; MHC, major histocompatibility complex; mRNA-LNP, lipid nanoparticle; nTreg, natural regulatory T cells; S protein, spike protein; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T2; type 2 immunity; DC, dendritic cell; T_{FH}, T follicular helper cell; T_{FR}, T follicular regulatory cell; TGF-β, transforming growth factor β; Th0, naïve T cells; Th1, T helper type 1 cell; Th2, T helper type 2 cell; TNF-α, tumour necrosis factor α. Figure 2 created with BioRender.com.

SARS-CoV-2 vaccine has been demonstrated to induce T1 polarization. Therefore, through increasing T1 immunity, the COVID-19

TABLE 1 Immunological characteristics of AIT and COVID-19. Ab—antibody; B—B lymphocyte; Breg—regulatory B cell; COVID-19—coronavirus disease 2019; CRS—cytokine release syndrome; CTLA-4—cytotoxic T-lymphocyte-associated protein 4; GC—germinal centre; Ig—immunoglobulin; IL / ILR—interleukin / interleukin receptor; ILC—innate lymphoid cell; INF-γ—interferon γ; LLPC— long-lived high-affinity plasma cell; LNP—lipid nanoparticle; mRNA—messenger RNA; NK—natural killer cell; PD-1—programmed cell death protein 1; RBD—receptor-binding domain; rRBD-AddaVax—recombinant RBD protein adjuvanted with squalene-based oil-in-water nano-emulsion (AddaVax); S—spike; SARS-CoV—severe acute respiratory syndrome coronavirus; T—T lymphocyte; T1 / 2 / 3—type 1 / 2 / 3 immune response; Tc1/2—cytotoxic lymphocyte type 1 or 2; T_{FH}—follicle T helper cell; TGF-β—transforming growth factor β; Th1/2—T helper cell type 1 or 2; Treg—regulatory T cells; TSLP—thymic stromal lymphopoietin

	AIT	Biologicals targeting T2 inflammation	COVID−19	COVID−19 vaccine
Immunological changes	■ No impact on the whole immune system; no systemic immune deficiency ■ response targets allergen-specific T and B	■ No impact on the whole immune system (only on specific blocked pathways); no systemic immune deficiency reported ■ Response targets specific T2 pathways: IgE (Omalizumab), IL-4Rα (Dupilumab), IL-5 (Mepolizumab, Reslizumab), IL-5Rα (Benralizumab), Alarmins (anti-TSLP or anti-IL33 under development)	■ does not significantly increase the severity of allergic disease ■ the disruption of T1 and innate antiviral immunity plays a role in the pathogenesis and severity of COVID-19	■ The formation of LLPCs and Bmem ■ Induced a dose-dependent SARS-CoV-2-specific Ab response ■ Germinal Center-derived B-cell response induced by SARS-CoV-2 mRNA vaccines
T-cell responses	■ decreases allergen-specific T2 responses (Th2 cells and ILC2) in circulation and in the affected organs such mucosal tissues ■ induction of allergen-specific Treg ■ together with Breg cells T regs create a tolerogenic milieu: by the release of IL-10, TGF-β and by direct cell contact-mediated bymolecules like CTLA-4 and PD-1 ■ switch between T2 and T1	■ Decreases expansion and activation of memory Th2 responses (Omalizumab and Dupilumab) and effector responses by directly or indirectly blocking specific effector cytokines (all of them). ■ Induction of Treg cells (showed in vitro for Omalizumab)	■ CD4 and CD8 T cells decrease (lymphopenia in severe cases) ■ inhibition of IFN-γ signalling results in reduced antiviral response and ongoing pro-inflammatory response ■ excessive inflammation and worsening of the disease ■ decreased number of Treg cells ■ progressive increase in (Tfh) in non-severe COVID-19 ■ in severe disease a systemic severe inflammatory response occurs with a CRS—T1 and 3-driven ■ these inflammatory responses are potentially counteracted by anti-inflammatory cytokines, such as IL-10 and TGF-β, and potentially by T2 responses which facilitate recovery	■ Tfh cells are crucial regulators of GC and affinity-matured Ab responses ■ Other CD4 T-cell subsets might serve different important functions, including facilitating optimal CD8 T-cell responses ■ SARS-CoV-2 mRNA-LNP vaccines favour the functional polarization of total CD4 T cells towards Th1, while Tfh cells are characterized by the production of both Th1 (IFN-γ) and Th2 (IL-4) cytokines
$CD8^+$ T cells	■ No major change	■ Inhibition of tissue and mucosal infiltration of CD8 + T cells and Tc2 in particular.	■ total number of NK and CD8+ T cells markedly decreased in severe COVID (functional exhaustion of Tc)	■ No indication that the induction of $CD8^+$ T cells is required for successful protection against SARS-CoV-2 via vaccination
Th1—Th2 response		■ Specific blocking of Th2 responses.		■ Th1- and Th2-biased Tfh cells are both relevant in shaping a neutralizing response to SARS-CoV-2 ■ mRNA-LNP vaccines skewed Tfh cells towards a Th1 phenotype when using full-length S D furin as immunogen, or towards a mixed Th1/Th2 phenotype when RBD was the immunogen ■ rRBD-AddaVax induced Th2-biased T_{FH} cells

TABLE 2 COVID-19 vaccines and immunological effects[158]

Vaccine platform	Name; Manufacturer (Phase)	Administration route	Immunological mechanism	Ref
Approved or in Phase 3 clinical trials				
mRNA	1. BNT162b2 (Comirnaty); BioNTech/Pfizer (Phase 4) 2. mRNA −1273 (Spikevax); Moderna/ National Institute of Allergy and Infectious Disease (Phase 4) 3. CureVac COVID-19 (CVnCoV); CureVac AG (Phase 3) 4. ARCoV; Academy of Military Science (AMS), Walvax Biotechnology and Suzhou Abogen Biosciences (Phase 3). 5. ARCT-154 mRNA Vaccine; Arcturus Therapeutics, Inc. (Phase 3)161	im	Antigen-specific cytotoxic $CD8^+$ T cells (IFN-γ released) Antigen-specific $CD4^+$ T cells (Th1; Th2-not detected) Antigen-specific and neutralizing antibodies	[37,38,43,58]
Recombinant viral vectors (Viral vector non-replicating)	1. ChAdOx1 nCoV-19 (AZD1222); University of Oxford/AstraZeneca (approved, Phase 4) 2. Ad5-nCoV; CanSino Biological /Beijing Institute of Biotechnology (Phase 4) 3. Gam-COVID-Vac (Sputnik V); Gamaleya Research Institute of Epidemiology and Microbiology in Russia (Phase 3) 4. Ad26.COV2.S; Janssen Pharmaceutical (Janssen/Johnson &Johnson) (Phase 4)	im	Antigen-specific cytotoxic $CD8^+$ T cells (IFN-γ released) Antigen-specific $CD4^+$ T cells (Th1; Th2-not detected) Antigen-specific and neutralizing antibodies	[64,162,163,164]
Inactivated vaccine virus	1. CoronaVac (PiCoVacc); Sinovac (Phase 4) 2. Vero cell; Sinopharm/Wuhan Institute of Biological Products (Phase 3) 3. BBIBP-CorV, Sinopharm/Beijing Institute of Biological Products (Phase 4) 4. SARS-CoV-2 inactivated vaccine (Vero cells); Institute of Medical Biology/ Chinese Academy of Medical Sciences (Phase 3) 5. QazCovid-in®—COVID-19; Research Institute for Biological Safety Problems, Rep of Kazakhstan (Phase 3) 6. BBV15 A, B, C; Bharat Biotech (Phase 3) 7. VLA2001, Valneva, National Institute for Health Research, United Kingdom (Phase 3) 8. TURKOVAC; Ercives University and the Health Institutes of Turkey (TUSEB) (Phase 3)	im	?	[159,165,166,167,168]

(Continues)

TABLE 2 (Continued)

Vaccine platform	Name; Manufacturer (Phase)	Administration route	Immunological mechanism	Ref
Subunit (recombinant protein vaccines)	1. NVX-CoV2373 (full-length spike glycoprotein of the prototype strain plus Matrix M adjuvant); Novovax (Phase 3) 2. Recombinant SARS-CoV-2 vaccine (CHO Cell); Anhui Zhifei Longcom Biopharmaceutical/Institute of Microbiology, Chinese Academy of Sciences (Phase 3) 3. SCB-2019 + AS03 or CpG 1018 adjuvant plus Alum adjuvant (Native-like Trimeric subunit Spike Protein vaccine); Clover Biopharmaceuticals /GSK/ Dynavax (Phase 2/3 4. VAT00008: SARS-CoV-2 S protein with adjuvant; Sanofi Pasteur + GSK (Phase 3) 5. COVAX-19® Recombinant spike protein + adjuvant SPIKOGEN; Vaxine Pty Ltd./CinnaGen Co. (Phase 3) 6. EpiVacCorona; Federal Budgetary Research Institution State Research Center of Virology and Biotechnology "Vector" (Phase 3) 7. FINLAY-FR-2 anti-SARS-CoV-2 Vaccine (RBD chemically conjugated to tetanus toxoid plus adjuvant); Instituto Finlay de Vacunas (Phase 3) 8. RBD (baculovirus production expressed in Sf9 cells) Recombinant SARS-CoV-2 vaccine (Sf9 Cell); West China Hospital + Sichuan University (Phase 3) 9. CIGB-66 (RBD+aluminium hydroxide); Center for Genetic Engineering and Biotechnology (CIGB) Biological E. Limited (Phase 3) 10. Recombinant Sars-CoV-2 Spike protein, Aluminum adjuvanted (Nanocovax); Nanogen Pharmaceutical Biotechnology (Phase 3) 11. GBP510, a recombinant surface protein vaccine with adjuvant AS03 (aluminium hydroxide); SK Bioscience Co., Ltd. and CEPI (Phase 3) 12. Razi Cov Pars, recombinant spike protein; Razi Vaccine and Serum Research Institute (phase 3) 13. Recombinant SARS-CoV-2 Fusion Protein Vaccine (V-01); Livzon Pharmaceutical (Phase 3) 14. RBD protein recombinant SARS-CoV-2 vaccine (Noora Vaccine); Bagheiat-allah University of Medical Sciences/AmitisGen (Phase 3)	im	?	[160,169,170,171]
Less advanced COVID−19 vaccine candidates				
Viral-like Proteins (VLP)	1. Coronavirus-Like Particle COVID-19 (CoVLP); Medicago (Phase 2/3)	im	?	
Live-attenuated	1. COVI-VAC; Codagenix/Serum Institute of India-phase I_NCT04619628	im	?	
Recombinant viral vectors (Viral vector (Replicating)	1. Coronavirus-Like Particle COVID-19 (CoVLP); Medicago Inc. 2. RBD SARS-CoV-2 HBsAg VLP vaccine; Serum Institute of India +Accelagen Pty +SpyBiotech	im	?	

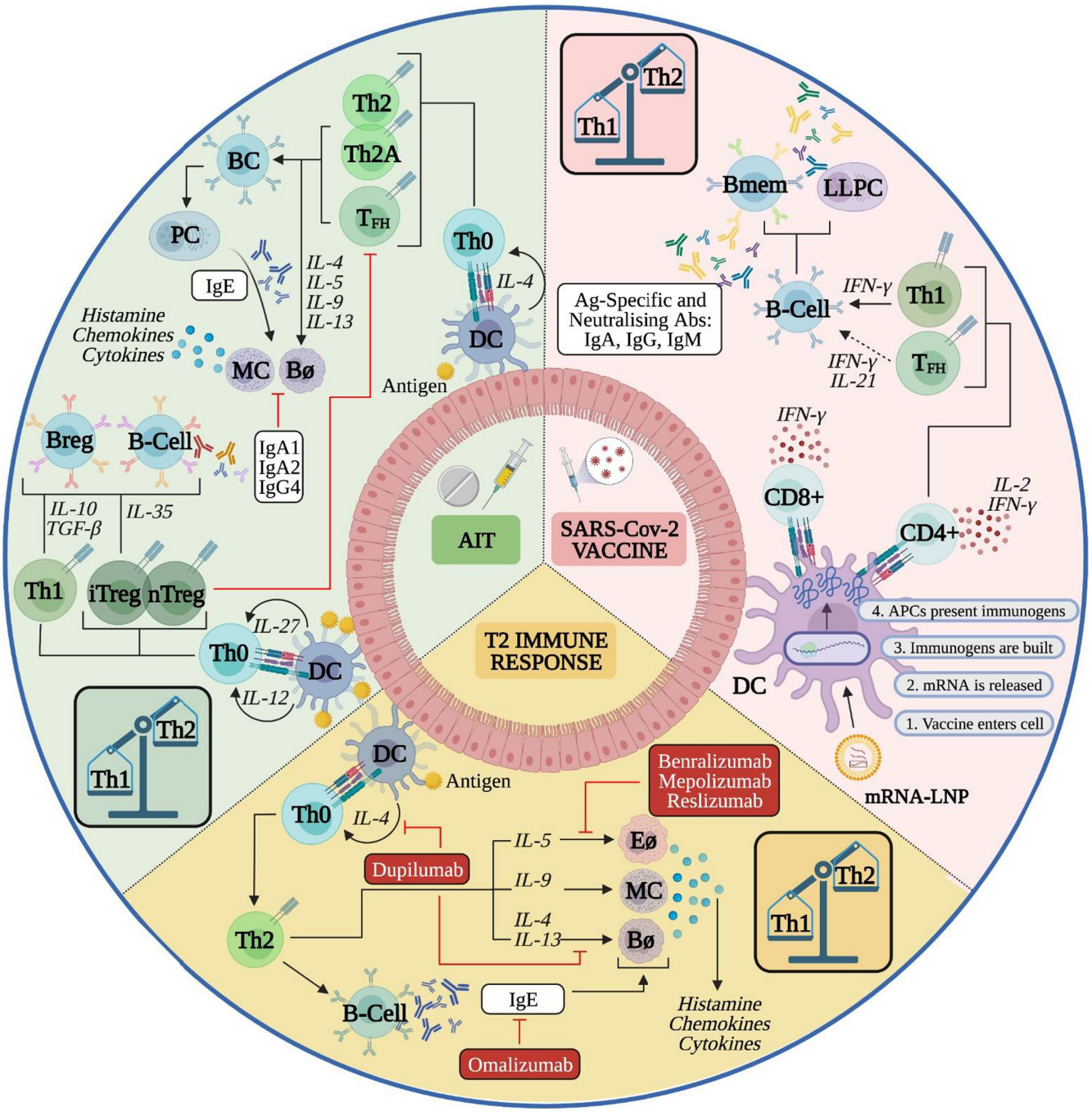


FIGURE 2 Immune modulatory responses of COVID-19 vaccination, allergen immunotherapy and Biologicals T2 responses

vaccine may decrease the effect of biologicals targeted against T1 inflammation. Moreover, T1 polarization may provide an additive effect to AIT and biologicals which target T2 immunity. It can be postulated that the suppression of T2 immunity and induction of Treg cells observed during AIT may increase the risk of early inflammatory adverse reactions by a short interval. Moreover, the reduction in T2 immunity may potentially suppress IFN-γ, which was released by $CD4^+$ and $CD8^+$ after vaccination and decrease the risk of anaphylaxis. AIT, allergen immunotherapy; IFN-γ, interferon-γ; T1, type 1 immunity; T2, type 2 immunity; Treg, T regulatory cells. Figure 3 created with BioRender.com.

4.2 | Possible interference of COVID-19 vaccine and biological therapies targeting the T2 immune response

Five mAbs are currently approved for severe type 2 asthma: omalizumab, mepolizumab, benralizumab, reslizumab and dupilumab.[116] The use of these mAbs during the COVID-19 pandemic is considered safe, as they do not increase the rate of viral transmission.[117,118] Conversely, international guidelines recommend the withdrawal of these drugs in case of active SARS-CoV-2 infection because of reports of delayed and diminished anti-SARS-CoV-2

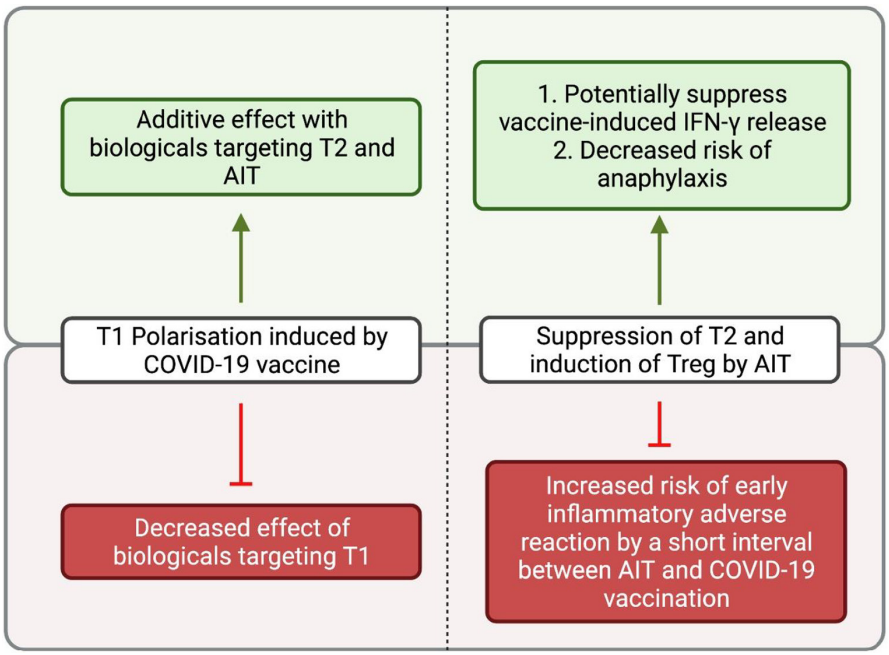


FIGURE 3 Potential impact of the COVID-19 vaccination on the efficacy and safety of AIT and biological treatment and vice versa

Ab production in asthmatic patients who became infected while receiving mAbs.[119,120] In a series of 4 cases, asthmatic patients on mepolizumab experienced COVID-19 of varying severity.[121] However, the production of anti-SARS-CoV-2 antibodies was not investigated. The inhibition of type 2 response in severe and critical COVID-19 cases may cause an aggravation of the disease and hamper recovery. Therefore, EAACI recommends that such biologicals should be discontinued until the COVID-19 infection is cleared. Due to their long *in vivo* half-life in the range of a few weeks, it remains unclear to which extent such an action would impact acute management and what the risk of losing disease control and comorbidity, later on, could be. Interestingly, the up-regulation of IgE, IL-5, IL-13 and eosinophils have been reported in severe COVID-19.[95] Although eosinopenia is not an exclusive feature of severe COVID-19, a reduced number of eosinophils has been associated with worse outcomes of COVID-19, while their restoration precedes recovery.[119,122] Moreover, eosinophils may play a role in virus recognition, presentation and clearance.[123] Thus, IL-5 targeting biologicals mepolizumab and reslizumab and the IL-5 receptor targeting mAb benralizumab could affect the antiviral response. This hypothesis has not been supported by *in vivo* data.[124-127] However, the increased pulmonary presence of eosinophils and acute eosinophilic pneumonia in post-mortem findings after SARS-CoV-2 indicate that IL-5-induced reduction in eosinophils might be beneficial in the pathological response in the lung. Vaccines for the previous SARS-CoV have been associated with an immunopathology eosinophilic lung infiltrate. This point should be considered in the development of a vaccine strategy for COVID-19.[128]

Limited data are available regarding AIV administration while receiving anti-T2 mAbs. Evidence for the safety of the biologicals and vaccine responses is available for omalizumab, dupilumab and benralizumab, with no proof yet of a negative impact of the respective biological on the vaccine response.[129,130] Omalizumab has been linked to positively affect plasmacytoid dendritic cells (pDCs) dependent IFN type I production in asthmatics and chronic spontaneous urticaria (CSU) patients.[131] It may even restore reduced type I IFN production in patients with allergic diseases, thereby supporting antiviral immune responses. Omalizumab has been used in several AIT trials as co-medication to reduce IgE-mediated side effects. Current data from AIT trials do not suggest that omalizumab impacts allergen-specific IgG responses and T-cell responses outside of the AIT related immunomodulation. In addition, on a case report basis, omalizumab was applied successfully to treat COVID-19-driven urticaria.[132]

A preclinical study showed that omalizumab does not affect the ability of T and B cells to mount protective responses after vaccination with tetanus toxoid (Novartis, data on file). Moreover, published trials of omalizumab did not consider the recent AIV administration course as an exclusion criterium. Therefore, several AIV (diphtheria, inactivated hepatitis B, tetanus toxoid, influenza or pneumococcal vaccines) were administered within the trial period, without specific reports of adverse events.[133] Nevertheless, this is not sufficient to guarantee that omalizumab does not impair the production of protective antibodies after AIV. There are only limited data available on vaccination safety under omalizumab: A recent small retrospective study reported the safety of yellow fever vaccination under omalizumab treatment for CSU.[134] Omalizumab reduces FcεRI expression on DCs and, very significantly, restores the capacity of pDCs to produce high levels of type I IFN-α,[135,136] which has been associated with the reduction in asthma exacerbations triggered by viral infections.[137,138] Omalizumab also restores *in vitro* the capacity of atopic pDCs to polarize Treg cells, contributing to proper antiviral immune responses.[139] In a double-blind, placebo-controlled study involving 87 and 91 patients with atopic dermatitis treated with dupilumab

TABLE 3 Summary of studies on patients under treatment with allergen immunotherapy (AIT) / biologicals receiving anti-infectious vaccines

Treatment	Vaccine	Underlying disease	Patients number	Conclusion
AIT (*Garner-Spitzer, 2018*) [101]	Booster of tick-borne encephalitis	Allergic rhinoconjunctivitis and asthma	119 (49 allergic, 21 allergic on AIT and 49 non-allergic)	No effect of AIT on antibody response
Omalizumab (*Criado PR, 2019*) [119]	Yellow fever	chronic spontaneous urticaria (CSU)	28	No cases of mild yellow fever
Omalizumab (*Turner P, 2020*) [122]	Live-attenuated influenza	Moderate- severe asthma	478	Well tolerated
Dupilumab (*Blauvelt A, 2019*) [129]	-Tdap (tetanus toxoid, reduced diphteriua toxoid, acellular pertussis vaccine) - meningococcal polysaccharide vaccine	Atopic dermatitis	87 treated by dupilumab / 91 with placebo	Satisfactory and equal IgG response with or without dupilumab 4 weeks after injection

and placebo, respectively, study participants received subcutaneous Tdap (tetanus toxoid, reduced diphtheria toxoid and acellular pertussis vaccine) or meningococcal polysaccharide vaccine after 12 weeks of treatment. At Week 16, the proportion of patients showing satisfactory IgG responses against both infectious agents and the median titles of the protective Abs were similar in both groups[129] (Table 3).

Recommendation 2: A 7-day interval between administration of a biological targeting the T2 immune response and COVID-19 vaccine is recommended to unequivocally assign potential side effects of each other.

4.3 | Possible interference of COVID-19 vaccination and biologicals targeting non-Type 2 inflammation

Applying biologicals in non-type 2 (non-T2) inflammatory diseases may interfere significantly both with the antiviral and the vaccine responses. Therapeutics affecting cell trafficking (e.g. natalizumab) may reduce local viral clearance. Anti-cytokine antibodies (anti-TNF-α, anti-IL1β and anti-IL-6) can suppress antiviral cellular responses and secondary humoral responses. On the contrary, autoimmune inflammatory conditions may negatively impact vaccine responses and treatment may theoretically restore and promote a more robust vaccine response. Although patients with immune-mediated inflammatory conditions seem to develop less commonly COVID-19, severity and mortality are increased compared with the general population once they acquire it, especially if the disease is not controlled with background therapy.[140]

Depletion of B cells via the anti-CD20 biologicals such as rituximab, obinutuzumab, ocrelizumab and ofatumumab or biosimilars are anticipated to impact COVID-19 vaccine responses as they efficiently suppress early IgM, IgG and IgA responses. Following B cell depletion therapy, vaccine response is dependent on the number of B cells still 'available'; thus, Ab titration assessment might be indicated. Patients on these treatments have per se a higher risk to develop severe or fatal COVID-19 due to concomitant risk factors and or additional systemic immune suppression. An increased risk of hospital and intensive care unit (ICU) admission following COVID-19 infection has been reported for rituximab and ocrelizumab (odds ratio: (OR) 2.37) and recent usage of methylprednisolone (<1 month; OR 5.24), but not for other disease-modifying drugs used for multiple sclerosis.[141]

A recent systematic review on the impact of COVID-19 on demyelinating diseases highlighted the complexity of estimating risks associated with immunomodulatory treatment in these patient groups regarding the severity of COVID-19 infection. It reported higher mortality in rituximab treated patients (4%) vs the overall multiple sclerosis (MS) population (1.8%).[142] Data from the post-marketing safety, real-world data and clinical trials on ocrelizumab reported comparable mortality rates compared with the normal population, and the non-ocrelizumab treated MS population.[143] The

VELOCE study investigated the impact of ocrelizumab on responses to a 23-valent pneumococcal polysaccharide vaccine (23-PPV; not received within >5 years), the 13-valent conjugate pneumococcal vaccine (13-PCV), tetanus toxoid (TT) containing vaccines (not applied for >2 years) and influenza vaccine (no vaccination in the last two seasons) in MS patients receiving either IFN-β or no additional therapy. Positive response rate to TT vaccine was observed in 24% of the patients receiving ocrelizumab and in 55% of those receiving placebo at 8 weeks. Furthermore, seroprotection rates against 5 influenza strains ranged from 55.6% to 80% in the ocrelizumab group, compared to 75% to 97% in the placebo group. In the pneumococcal vaccines, there was a reduced response to serotypes from 23-PPV (75% vs 100% pos response to >5 serotypes) reported but not for the 13-PCV.[144]

In the context of inflammatory diseases, TNF-α suppresses B and T cell function, which can be restored by anti-TNF-α treatment.[145-147] Undesired effects of this treatment on vaccine responses are not anticipated. Nevertheless, reduced pathogen-related responses and an increased risk for specific pathogens to cause severe disease have been reported under anti-TNF-α treatment due to its pleiotropic effect on immune responses to pathogens (e.g. *Mycobacterium tuberculosis*). Patients with inflammatory bowel disease (IBD) and rheumatoid arthritis (RA) receiving anti-TNF-α antibodies experience reduced response/seroconversion rates to influenza vaccines and hepatitis B vaccine compared with other treatment regimens in this cohort. However, a significant percentage of patients on this treatment can mount protective vaccine titres.[148-150] Data on certolizumab suggest that pneumococcal and influenza vaccine responses were not impaired when applied during therapy initiation.[151] A systematic review on biologicals on vaccine responses in the context of autoimmune inflammatory rheumatic diseases concluded that vaccine responses to influenza and pneumococcal vaccine are adequate under anti-TNF-α drugs, tocilizumab (anti-IL-6) and belimumab (anti-B-cell activating factor (BAFF); data only for the pneumococcal vaccine).[152] Accurate vaccine treatment responses have also been reported under treatment with ustekinumab in Crohn's disease patients[153] and secukinumab in patients with psoriatic arthritis[154] or ankylosing spondylitis.[155]

Immune checkpoint inhibition (ICI) via anti-programmed cell death protein 1 (PD-1)/anti-programmed death-ligand 1 (PD-L1) and or cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) reduces immune-regulatory responses to benefit better anti-neoplastic responses. Thus, viral responses could even be enhanced. COVID-19 morbidity and mortality are considered comparable in oncological patients on ICI than matched patient groups who are not on this treatment.[156] Vaccine response data are scarce. A recent systematic review reported a normal humoral response and an increased seroconversion under ICI. The majority of investigations focused on influenza vaccines. Notably, the rate of immune-related adverse events was elevated.[157] CTLA-4 targeting therapy via abatacept in autoimmune rheumatic disease (AIRD) was associated with a mildly reduced vaccine response in a systematic review based on controversial data with low evidence.

In summary, non-T2 diseases encompass a paramount of immune dysregulation and treatment approaches with biologicals. Most of the biological-based therapies either affect vaccine responses only mildly or not significantly. Robust evidence for a reduced vaccine response is reported for B cell depleting therapies.

Recommendation 3: A 7-day interval between administration of biological targeting the non-Type 2 immune response and COVID-19 vaccination is recommended to unequivocally assign potential side effect of each other.

5 | CONCLUSIONS

EAACI recommendations are based on the mechanistic evaluation as well as clinical experience and evidence involving other anti-infective vaccines.

The current assessment does not suggest any relevant interference compromising neither the safety nor the efficacy of AIT, biologicals or COVID-19 vaccines.

Further evidence from disease registries and other real-world data bases must be accumulated in order to refine current recommendations.

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CONFLICT OF INTEREST

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APPENDIX

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