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CURRENT OPINION

Recommendations for Vaccination in Children with Atopic Dermatitis Treated with Dupilumab: A Consensus Meeting, 2020

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Abstract
Dupilumab is the only biologic therapy currently approved in Europe and the United States for severe atopic dermatitis in patients 6 years of age or older. Off-label use is rationalized in younger children with severe atopic dermatitis. Decisions about vaccination for children on dupilumab are complex and depend on both the child's current treatment and the type of vaccination required. To achieve consensus on recommendations for vaccination of pediatric patients with atopic dermatitis treated with or planning to start dupilumab, a review of the literature and a modified-Delphi process was conducted by a working group of 5 panelists with expertise in dermatology, immunology, infectious diseases and vaccination. Here, we provide seven recommendations for vaccination of pediatric patients with atopic dermatitis treated with or planning to start dupilumab. These recommendations serve to guide physicians' decisions about vaccination in children with atopic dermatitis treated with dupilumab. Furthermore, we highlight an unmet need for research to determine how significantly dupilumab affects cellular and humoral immune responses to vaccination with live attenuated and inactivated vaccines.

1 Introduction

Increasing use of dupilumab for atopic dermatitis [1] in younger and younger children has stimulated new questions about immunization. Immunization is the process of acquiring protective immunity from the vaccine agent and should be distinguished from "vaccination," which is the act of administering a vaccine. The former may occur, or not, depending on the recipient's capacity to elicit an optimal immune response to the vaccine [2].

Key Points

Decisions about vaccination for children on dupilumab are complex and depend on both the child's current treatment and the type of vaccination required.

Pediatric patients with atopic dermatitis on treatment with dupilumab can safely receive inactivated vaccines, whereas live attenuated vaccines, including boosters, should be avoided or carefully considered on an individual basis and with the involvement of appropriate pediatric subspecialists until further evidence demonstrates their safety.

Atopic dermatitis (AD) affects predominantly young children, with most patients presenting within the first 5 years of life. The recent approval of dupilumab in children as young as 6 years of age and its off-label use in even younger children raise the dilemma of how to safely immunize pediatric patients on dupilumab [3].

Dupilumab is a human immunoglobulin (Ig)G4 monoclonal antibody that blocks the α-subunit shared by the types I and II receptor complexes for interleukin-4 (IL-4) and IL-13,

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decreasing signaling by these two cytokines [4, 5]. It is the only systemic treatment currently licensed to treat severe AD in children aged 6–11 years and moderate-severe AD in adolescents and adults by the US Food and Drug Administration [6, 7]. Its efficacy and safety profiles have been demonstrated in several studies and have been consistent among these age groups (see the electronic supplementary material) [1, 8–13].

Public health agencies such as the Centers for Disease Control (CDC) and Public Health Agency of Canada (PHAC) encourage physicians to ensure adequate vaccination of immunocompromised patients on a case-by-case basis to avoid vaccine-preventable infections [14, 15]. We followed a modified-Delphi process to reach consensus on recommendations for vaccination of pediatric patients with AD currently on or planning to start dupilumab.

2 Materials and Methods

2.1 Literature Search

A literature search was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines for systematic reviews to answer the research question "What is the safety of vaccinations in pediatric patients taking dupilumab for AD?" A research librarian and an MD, both independent of the consensus panel, ran search strategies in Medline and Embase. The last search was run on February 2, 2020. Two researchers (SMC and SD) independently screened titles and abstracts for relevance. If an article was relevant to the research question, the full text was reviewed to determine if it met eligibility criteria (see the electronic supplementary material). Disagreements between the two reviewers were resolved by discussion. Reference lists from relevant articles were reviewed to identify additional relevant studies. As no search results met the eligibility criteria, a second literature search was performed on February 2020 in Medline for articles on live attenuated and inactivated vaccines in pediatric AD patients and on pediatric patients receiving biologics, national and international guidelines on vaccination of immunocompromised pediatric patients, and dermatologic guidelines for children with AD (see the electronic supplementary material).

A detailed review of the search results along with the full references was sent to the panelists in advance of the meeting.

2.2 Expert Working Group

The working group included members with expertise in the fields of dermatology (SMC, MR, and MK), pediatric dermatology (MR), immunology (LMF and MK), and infectious diseases (CMC).

Two participants (SMC and MR) developed the seven initial statements that were circulated and revised based on feedback received (MK) before the consensus meeting.

2.3 Consensus Meeting

The consensus meeting was conducted using a modified-Delphi method in which a physical meeting took place on March 12, 2020. The study followed the Guidance on Conducting and Reporting Delphi Studies (CREDES) [16]. The meeting was chaired by one moderator [5] and had two rounds (see the electronic supplementary material). A detailed overview of the process can be found in the electronic supplementary material. An online poll created using Poll Everywhere (San Francisco, California) with a 5-point Likert scale to describe level of agreement (strongly disagree, disagree, neutral, agree, and strongly agree) was used. In the first round, the panel discussed and revised each statement after voting. A consensus of 75% or more agreement was the predetermined level to include a statement in the final recommendations. Standards for QUality Improvement Reporting Excellence (SQUIRE) guidelines were followed for developing the manuscript.

3 Results

The modified-Delphi process resulted in seven recommendations intended to guide vaccination in children with AD on dupilumab (Table 1).

Statement 1

Based on available data, dupilumab does not appear to affect the development of protective antibodies titers to inactivated vaccines.

Evidence Summary

The expert panel agreed dupilumab does not appear to affect the development of antibody titers in adults, according to a phase 2, randomized, placebo-controlled study (97 patients in each group) that assessed vaccine responses [17]. The T cell dependent humoral response to tetanus toxoid (Tt) vaccine (Adacel®) demonstrated that vaccination at week 12 of dupilumab therapy (300 mg weekly) did not interfere with IgG production. Most patients (83.3%) developed a protective response, achieving a fourfold increase in titer 1 month after vaccination (median Tt titers from 1.21 IU/mL to 13.91 IU/mL; $p < 0.0001$). Moreover, no differences were observed between IgG titers in the dupilumab-treated group compared to the placebo group at week 16. Dupilumab did not affect T

Table 1 Recommendations for vaccination in pediatric patients with atopic dermatitis treated with dupilumab based on our modified-Delphi process

Initial statements	Level of agreement (%)	Final statements/recommendations	Level of agreement
Dupilumab interferes with humoral or cellular immune responses to vaccines but does not appear to affect the development of protective titers	2 (40) neutral 3 (60) disagree	Based on available data, dupilumab does not appear to affect the development of protective antibodies titers to inactivated vaccines	100% strongly agree
Dupilumab should not be interrupted for inactivated vaccines	3 (60) strongly agree 2 (40) agree	Dupilumab treatment does not need to be interrupted for administration of inactivated vaccines	100% strongly agree
Seasonal and pandemic influenza vaccination should not be avoided while on dupilumab	2 (40) strongly agree 3 (60) agree	For patients on dupilumab treatment, seasonal inactivated influenza vaccination should continue as recommended	100% strongly agree
Live vaccinations should be given prior to dupilumab if possible	1 (20) strongly agree 4 (80) agree	Based on available data, live attenuated vaccines should be avoided while on dupilumab	100% strongly agree
Live attenuated vaccines should be avoided while on dupilumab	4 (80) agree 1 (20) neutral	When live attenuated vaccinations are required, they should be given at least 4 weeks prior to initiation of dupilumab treatment, if possible	100% strongly agree
Measurement of antibody levels after vaccination is necessary to ensure serologic protection	1 (20) agree 3 (60) neutral 1 (20) disagree	While on dupilumab, measurement of specific antibody levels can be considered to ensure serologic protection after vaccination on dupilumab therapy	100% strongly agree
There is no risk of atopic dermatitis exacerbation with immunization on dupilumab	1 (20) agree 4 (80) neutral	There is no evidence to suggest that immunization while on dupilumab causes an exacerbation of atopic dermatitis	100% strongly agree

cell independent responses to the serogroup C meningococcal polysaccharide from the MPSV4 vaccine (Menomune®), with titer levels comparable to placebo treatment (median titers from < 4 IU/mL week 12 to 1024 IU/mL week 16 in both groups) [17]. It is important to note that the Tdap vaccine (Adacel®; approved ≥ 4 years old) is a booster (a subsequent exposure to the vaccine antigen) that elicits a different immune response than the primary series (the first encounter with the vaccine antigen). The primary series triggers the beginning of the immune response, producing IgM and memory cells, whereas a booster produces a secondary immune response in which those previously developed memory T cells and B cells will recognize the vaccine antigen, resulting in a faster, larger, and more effective response, primarily producing IgG specific antibodies. This mechanism explains why immunosuppressive therapies hamper booster responses less than they inhibit primary immune responses. In contrast, Menomune® can be used for both primary immunization and booster. Unfortunately, the MPSV4 vaccination status of patients in this study was not documented, so we cannot distinguish if these patients' responses were primary or secondary.

AD patients are prone to infection in part due to overexpression of IL-4 and IL-13 [18, 19]. Specifically, IL-4 has been shown to impair antiviral immunity as it downregulates the type I immune response, thereby decreasing cell-mediated immunity (Fig. 1) [20, 21]. IL-4/13 blockade has numerous potential benefits for AD patients, including a decrease in skin infections, better antimicrobial immunity [22–27], and possible enhanced T helper (T_H)1 responses that are critical to antiviral immunity and vaccination responses [17, 28] (Table 2).

Differentiation and maturation of dendritic cells (DCs) are essential to vaccination because of their role in initiating the immune response by presenting vaccine antigens. The effect of dupilumab on DCs and vaccination is unknown, but it does suppress the T_H2 pathway (chemokines for DCs and T cells) and DC markers and genes [28]. The significance of this suppression is unclear, but it may return overactive DCs to a closer-to-physiologic state.

Statement 2

Dupilumab treatment does not need to be interrupted for administration of inactivated vaccines.

Evidence Summary

The expert panel agreed that inactivated vaccines can be administered while patients are on dupilumab based on the non-existent risk of vaccine-strain infection [29–32]. AD patients with dupilumab who received inactivated (Tdap and MPSV4) vaccination elicited a satisfactory humoral response [17], suggesting immunogenicity is not affected.

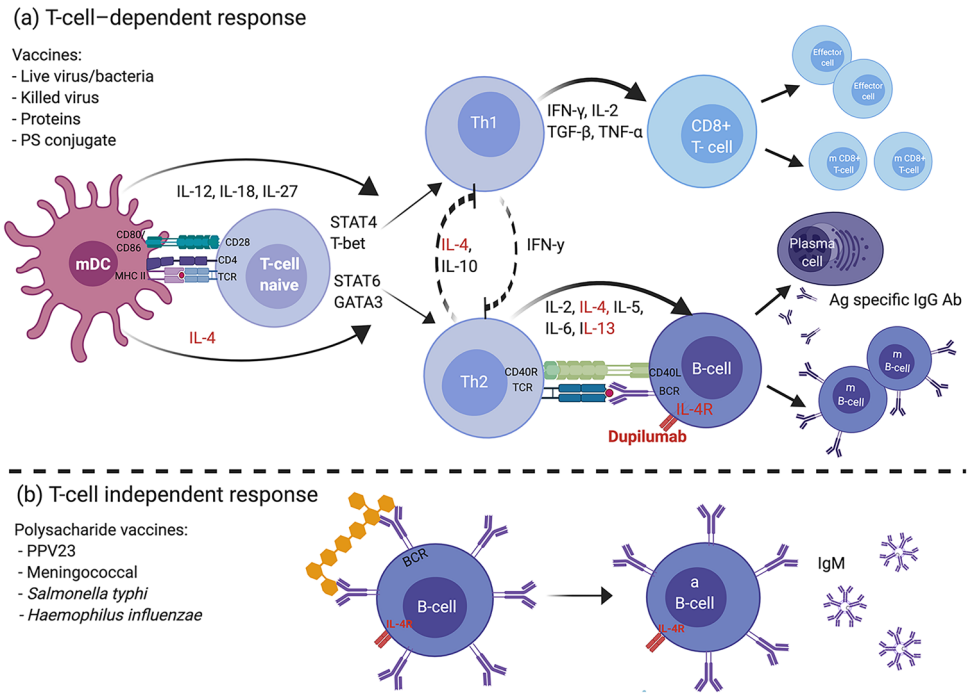

Fig. 1 Vaccine response and the potential impact of dupilumab. Dupilumab is a human (IgG4) monoclonal antibody anti-IL-4 receptor that blocks the α-subunit shared by IL-4R receptor type I and II, decreasing the signal induced by IL-4 and IL-13. **a** T cell-dependent response vaccines generate humoral and cellular responses with immune memory. After recognition of the antigen, APCs (B cells, macrophages, or DCs) present the processed antigen to naive T cells via peptide-MHC II. Co-stimulation between B7 ligands (CD80/CD86) and CD28 on the T cell is required. The type of pathogen determines the cytokine environment, which dictates the development of a specific T cell phenotype. IL-12, secreted by the DC in response to virus infection or intracellular bacteria, promotes polarization towards the T_H1 pathway, which secretes IFNγ and activates CD8 + CTLs and phagocytic cells and inhibits T_H2 development. In contrast, IL-4 initiates polarization to T_H2 pathways and inhibits T_H1 development. Via activation of STAT6 and GATA3, IL-4 promotes gene expression of IL-4, IL-5, and IL-13. APCs trigger a T_H2 cell response in the presence of thymic stromal lymphopoietin, IL-25, and IL-33 produced by epithelial cells. T_H2 responses drive B cell activation, requiring co-stimulatory signals through the CD40–CD40L (CD154) from the T_H cell and leading to differentiation into a plasma cell, isotype class switching, antibody secretion and clonal expansion of memory B cells. IL-4 acts as a B cell growth factor, and IL-6 assists in maturation of the antibody response. Theoretically, blocking IL-4 does not impair response to viral infection. **b** Polysaccharide vaccines elicit a T cell–independent response. The antigen directly interacts with B cells, producing antibodies limited to IgM without immunologic memory. Live bacteria: BCG. Live virus: influenza (intranasal), measles, mumps, oral polio, rotavirus, rubella, varicella zoster, yellow fever. Killed virus: inactivated poliovirus. PS conjugated: *Haemophilus influenzae* type B, meningococcal and pneumococcal conjugated. Protein: acellular pertussis, diphtheria, hepatitis B, human papillomavirus, influenza, tetanus. *Ab* antibody, *aB cell* activated B cell, *Ag* antigen, *APC* antigen presentation cell, *BCG* bacille Calmette-Guerin, *BCR* B cell receptor, *CTL* cytotoxic T lymphocytes, *DC* dendritic cell, *IFN* interferon, *Ig* immunoglobulin, *IL* interleukin, *m B cell* memory B cell, *m CD8 + T cell* memory T cell, *mDC* mature dendritic cell, *MHC* major histocompatibility complex, *PS* polysaccharide, T_H T helper, *TNF* tumor necrosis factor, *TCR* T cell receptor, *TGF* transforming growth factor. Created with BioRender.com

Statement 3

For patients on dupilumab treatment, seasonal inactivated influenza vaccination should continue as recommended.

Evidence Summary

Based on the high rates of seasonal influenza infection (influenza A and B) in children, as well as complications associated with this infection, seasonal inactivated influenza vaccination is recommended in pediatric patients with chronic diseases, including pediatric AD patients on dupilumab. The type of seasonal flu vaccine is region-specific and may mount a slightly different immune response and may have varied vaccine efficacy in dupilumab-treated patients. The PHAC and CDC recommend routine annual influenza immunization with an inactivated influenza vaccine (IIV) that is safe and immunogenic in immunocompromised children older than 6 months [14, 15, 33, 34]. The live attenuated influenza vaccine, given intranasally, is contraindicated in patients with compromised immune systems, including immunosuppression caused by medications [14]. The World Health Organization (WHO)-recommended quadrivalent influenza vaccine for the Northern Hemisphere in the 2020–2021 season, the antigenic strains are influenza A (H3N2 and H1N1) and the two influenza B viruses

Table 2 IL-4 and IL-13 summary. Adapted from Delves et al. [78], Bao and Reinhardt [79], and Kelly-Welch et al. [80]

	IL-4	IL-13
Gene	Chromosome 5	Chromosome 5
Source	T_H2, mast cells, basophils, eosinophils, NK, NKT, γδ T cell,	T_H2 and mast cells
Target	T cell, B cell, macrophage	B cell, macrophage
Function	Induces differentiation of T_H0 cell to T_H2, creating a positive feedback loop, producing more IL-4 Regulation of B cell function and class switching to IgG_1 and IgE[a] Proliferation of activated B, T, and mast cells Upregulates IgM, CD23 and MHC class II on B cells DC differentiation Differentiation, maturation, and functionality of DC in vitro Increases macrophage phagocytosis Inhibition of cell-mediated immunity	Regulation of several stages of B cell maturation and proliferation Switching to IgG_1 and IgE Inhibits activation and cytokine secretion by macrophages Induces VCAM-1 Modulates smooth cell muscle contraction and mucus secretion in the airway epithelium Inhibits cell-mediated immunity
Receptor	Type I receptor (IL-4Rα/γc)[b] Type II receptor (IL-4Rα/IL-13Rα1)	Type II receptor (IL-4Rα/IL-13Rα1) IL-13Rα2[c]
Downstream signaling pathways	JAK1 JAK3 STAT6	JAK1 TYK2 STAT6

DC dendritic cell, *Ig* immunoglobulin, *IL* interleukin, *JAK* Janus kinase, *MHC* major histocompatibility complex, *NK* natural killer, *NKT* natural killer T cell, T_H T helper, *VCAM-1* vascular cell adhesion molecule 1

[a]IL-4 induces class switching to IgG_1 and IgE

[b]Type I and II receptor are expressed on hematopoietic cells. Type II is expressed on non-hematopoietic cells as well

[c]IL-13Rα2: decoy receptor without signaling function

(Yamagata or Victoria) [35]. Studies in vaccinated pediatric oncology patients, pediatric solid organ transplant recipients, and pediatric patients receiving biologics for inflammatory bowel disease or rheumatologic conditions have documented satisfactory humoral immune responses [36–40].

Statement 4

Based on available data, live attenuated vaccines should be avoided while on dupilumab. However, such vaccines can be considered on a case-to-case basis weighing the risk of infection versus the risks of vaccination.

Evidence Summary

The expert panel emphasizes that there is insufficient data on the safety and efficacy of live attenuated vaccines in patients on biologics including dupilumab and recognizes the urgent need for further research to determine whether dupilumab affects the immune response against live attenuated vaccines and how safe these vaccines would be in children on active therapy.

Furthermore, given the lack of safety data on live attenuated vaccine administration in AD patients on dupilumab, the expert panel advises to consider the immunization process and to cautiously extrapolate data from other biologics until new evidence becomes available, with the caveat that the effect on the immune system depends on the type of immunomodulatory agent (Table 3).

In general, live attenuated vaccines require an appropriate T cell-dependent response for virus clearance and to develop an effective specific-antibody response (Fig. 1) [41–43]. Whereas in children, primary measles, mumps, rubella (MMR) vaccination predominantly elicits a T_H1 response, in adults, a T_H2 response predominates in receiving their booster of monovalent measles vaccine [44, 45]. In measles infection, the T_H1 pathway is the initial immune response, shifting towards T_H2 and T_H17 cells weeks later [46–50]. In theory, dupilumab's mechanism of action should not affect immune responses to MMR, but may influence the delayed T_H2 response and therefore the vaccine immunogenicity and safety.

Regarding measles, mumps, rubella, and varicella (MMR-V) booster vaccination during dupilumab therapy, which is of utmost interest to the panel as some AD pediatric patients would be in the age range when they may require a booster, safety data are insufficient to make a positive recommendation [51]. Nonetheless, the panel recommends an individualized assessment considering the benefit of MMR-V immunization against the risk of infection in patients already taking dupilumab. Specific antibody titers to assess immunity can assist decision making and are discussed in Statement 6.

The Pediatric Rheumatology European Association (PReS) vaccination working party [52] recommend

Table 3 Studies of LAVs in a pediatric population on immunosuppressive therapy

Year	Authors	Study design	Vaccine (*n*)	*n*	Age (range)	Disease	Biologics (*n*)	Safety	Outcome
2020	Uziel et al. [53]	Retrospective study. 13 pediatric rheumatology centers in 10 countries	MMR-V booster	234	5 ± 2.7 y	211 JIA 11 JDM 5 Scle 5 isolated IU 1 NOMID 1 MKD 1 FMF	MTX m (124) MTX + biologics (62): INX (1) ETN (33) ADA (22) TCZ (1) CAM (5) MTX + DMARDs (9): CsA (7) Salazopirin (1) LEF (1) Biologics (39): INX (1) ETN (16) ADA (6) TCZ (4) ANK (6) CAM (6)	No vaccine-related infection of measles, rubella, mumps, or varicella was reported. Mild adverse effects were reported	MMR-V booster vaccines were safe
2018	Jeyaratnam et al. [56]	Multicenter survey (85 physicians from 23 countries)	1st dose: YF (4); MMR-V (1); Var (1) Booster: MMR (7); Var (3); oral polio (1)	17	9 (1–58 y)	7 JIA 5 CAPS 4 MKD 1 FMF	Anti-IL-1 (10) Anti-IL-6 (7)	SAE: 2 pts (needing hospitalization)	Study reflects the reluctance of physicians to administer LAVs to patients using biologicals. LAVs cannot be considered entirely safe in patients using IL-1 or IL-6 blockade
2018	Speth et al. [57]	Prospective study	Var 1st dose (6): 3 LIIS 3 HIIS 1st + 2nd dose (9): 4 LIIS (6 wks apart) 5 HIIS (3 mo apart) Booster (9): 2 LIIS 7 HIIS	23	LIIS: 8.3 (1.8-17.8 y) HIIS: 9.7 (2.7-17.8 y)	LIIS: 8 JIA 1 SS HIIS: 11 JIA 2 JDM 1 MPA	MTX m (1); MMF m (1); LEF m (1); ETN m (3) LEF + biologics: + ABA (1) + ANK + Cs (1) + ETN + Cs (1) + TCZ (1) MTX + biologics: ADA (1) ANK + Cs (1) TCZ (1)	No vaccine-induced varicella disease symptoms. No other AEs within 4 wk after vaccination	Var vaccination is safe in children 5 out of the 6 pts naïve to Var vaccination had only one dose due to an increase in Var-IgG-level

Table 3 (continued)

Year	Authors	Study design	Vaccine (*n*)	*n*	Age (range)	Disease	Biologics (*n*)	Safety	Outcome
2017	Groot et al. [58]	Prospective study	Var (1st and 2nd doses)	67	G1: 28 pts—5 (2–15 y) received 1 dose 21 pts—3.5 (2–17 y) received 2 doses CG: 8.5 (3–18 y) received one dose	G1: 39 JIA 5 JDM 5 JScle CG: 18 HP	MTX m (25) MTX + Cs (18) Biologics (3): ADA—received only the 1st dose Received 2 doses: ETN—responded to 2nd dose ABA—unresponsive	Pt on ABA developed chicken pox	Biologics affected the immunogenicity of the vaccine in contrast to immunosuppressive drugs
2015	Toplak and Avcin [59]	Prospective study	Var (1st and 2nd doses)	6	4.7 (2.5–7 y)	JIA	ETN (3) INX (1) TCZ (2)	SAE: 0 Mild Var infection (4 mo after the 2nd dose)—1 Pt [81] with low protective levels of Ab	Variable humoral response to vaccination, which did not always provide adequate protection 5 pts (83%) had protective Ab levels 6 wk after the 2nd dose
2013	Heijstek et al. [55]	RCT	MMR booster	131	Vg: 6.3 (5.9–6.7 y) CG: 6.5 (6.2–6.9 y)	Vg: 63 CG: 68 (no vaccination)	ETN (5) ADA (1)* ANK (3) 2 pts took oral Cs concomitantly	SAE: 0 None showed disease caused by attenuated viruses	Biologics did not affect humoral responses when stopped 5 half-lives before administration MMR booster induced high seroprotection rates in all pts At 12 mo after vaccination, Ab concentrations were significantly higher
2009	Borte et al. [54]	Prospective study	MMR booster	15	6–17 y	15 JIA: G1: 5 G2a: 5 G2b: 5 CG: 20 HP	G2b: low-dose MTX in combination with anti-TNF	No mumps, measles, and rubella infections were seen 6 mo after the booster	MMR booster was effective as virus specific IgG levels were not affected

Ab antibody, *ABA* abatacept, *ADA* adalimumab, *AE* adverse event, *ANK* anakinra, *CAM* canakinumab, *CAPS* cryopyrin-associated periodic syndrome, *CG* control group, *Cs* corticosteroids, *CsA* cyclosporine, *DMARDs* disease modifying antirheumatic drugs, *ETN* etanercept, *FMF* familial Mediterranean fever, *G* group, *HIIS* high-intensity immunosuppression including biological therapy, *HP* healthy persons, *Ig* immunoglobulin, *IL* interleukin, *INX* infliximab, *IU* idiopathic uveitis, *JDM* juvenile dermatomyositis, *JIA* juvenile idiopathic arthritis, *JScle* juvenile scleroderma, *LAVs* live attenuated vaccines, *LEF* leflunomide, *LIIS* low-intensity immunosuppression including biological therapy, *m* monotherapy, *MKD* mevalonate kinase deficiency, *MMF* mycophenolate mofetil, *MMR* measles, mumps, and rubella, *MMR-V* measles, mumps, rubella, and varicella, *mo* months, *MPA* microscopic polyangiitis, *MTX* methotrexate, *NOMID* neonatal onset multiinflammatory disease, *pt(s)* patient(s), *RCT* randomized controlled trial, *SAE* serious adverse event, *Scle* scleroderma, *SS* Sjögren syndrome, *TCZ* tocilizumab, *Var* varicella, *Vg* vaccinated group, *wk* weeks, *y* years, *YF* yellow fever.

*Were stopped before vaccination at 5 times their half-lives

administering an MMR-V booster in children based on a recent retrospective study in pediatric rheumatology that found no severe adverse events or vaccine-related infections in 39 children on biologics (six adalimumab, six anakinra, six canakinumab, 16 etanercept, one infliximab, four tocilizumab) and 62 children on methotrexate with biologics (22 adalimumab, five canakinumab, 33 etanercept, one infliximab, one tocilizumab) who received booster vaccines [53].

However, the results of case series of vaccination of pediatric rheumatologic patients on various biologics show mixed responses. For instance, the MMR/MMR-V booster vaccine was safe and immunogenic in five children who received it simultaneously with etanercept (0.4 mg/kg body weight twice weekly) in combination with low-dose methotrexate (10 mg/m^2 body surface per week) [54], and another study showed high and durable seroprotection to MMR booster when biologics (one adalimumab; three anakinra; five etanercept) were discontinued for five half-lives before vaccination [55]. In a study of patients on IL-1 or IL-6 blockade, seven patients received MMR booster and only one developed bacterial pneumonia after an MMR booster while on treatment with anti-IL-1 (canakinumab), prednisone (5 mg/day), and methotrexate [56], likely related to overall immunosuppression rather than the MMR booster.

With regards to the varicella vaccine, studies have also found diverse immune responses [57]. Three children treated with methotrexate combined with biologics (adalimumab, etanercept, abatacept) did not develop antibodies against varicella after vaccination [58]. After a second dose of the vaccine, the patient on etanercept had an increase in varicella IgG titers, but no response was seen in the patient on abatacept who developed varicella infection 1 year after vaccination [58]. Another study of six children with rheumatologic diagnoses on biologics (one infliximab, three etanercept, two tocilizumab) who received two doses of varicella vaccine, showed that the patient on infliximab did not develop antibodies after two doses, while three patients on etanercept had low titers (one of whom developed mild varicella infection 4 months after vaccination). Two children on tocilizumab had an increase in antibody concentration, but their levels significantly declined at 11 and 27 months after vaccination [59]. Other studies in children on anti-IL-1 ($n=14$ patients) or IL-6 therapy ($n=3$ patients) reported two serious adverse events (SAEs); one of three patients who received a varicella booster had varicella infection on anti-IL-1 (anakinra) and disease-modifying antirheumatic drugs (DMARDs) (prednisone 0.12 mg/kg/day, methotrexate, leflunomide, and thalidomide), and another developed bacterial pneumonia after an MMR booster while on anti-IL-1 (canakinumab), prednisone (5 mg/day), and methotrexate [56]. Ultimately, although more evidence is needed, pediatric rheumatologists advocate that live attenuated booster vaccinations (MMR-V) can be considered individually as some studies have reassured safety, and no detrimental effect on immunogenicity has been described for glucocorticosteroids (low doses) and methotrexate. Indeed, rheumatic patients on biologics may need an additional booster due to a rapid loss of antibody levels despite having reached adequate immunogenicity, but less than drug-free patients. Most studies showing this loss in antibody concentrations were on patients using tumor necrosis factor-α (TNFα) blockers [60, 61].

Statement 5

When live attenuated vaccines are required, they should be given at least 4 weeks prior to initiation of dupilumab treatment, if possible. However, such vaccines can be considered on a case-to-case basis weighing the risk of infection versus the risks of vaccination.

Evidence Summary

The expert panel agreed that live attenuated vaccines should be given 4 weeks before starting dupilumab based on the Infectious Diseases Society of America (IDSA) recommendations for the timing of vaccinations in immunocompromised hosts [30]. These clinical guidelines recommend administering live attenuated vaccines at least 4 weeks prior to initiation of immunosuppressive medications [30]. It is important to note that dupilumab is considered immunomodulatory rather than immunosuppressive by the IDSA. Despite differences in mechanism and impact on immune system function, given the paucity of data, adherence to the IDSA guidelines is suggested. Canadian dermatology guidelines for adult patients on biologic therapy emphasize the importance of considering vaccine-induced viremia and the pharmacokinetic profile of the treatment to determine the best timing of vaccination [31]. Other societies take into account the incubation period instead of the post-vaccinal viremia [62].

For patients already on immunosuppressive therapy, the CDC recommends withholding live attenuated vaccine for 3 months after immunosuppressive therapies, including interleukins, colony-stimulating factors, and TNFα inhibitors, have been stopped [15]. Other guidelines recommend stopping biologic agents more than three half-lives before live attenuated vaccine administration [63–65]. Regarding dupilumab, pharmacokinetic studies showed that dupilumab concentrations decreased below the lower limit of detection 10 weeks after a last dose of 300 mg [6]. Nevertheless, there is insufficient data on its half-life to make an accurate safe timing recommendation [7, 66].

Some guidelines specifically suggest avoiding live attenuated vaccine within 2 weeks of initiation of immunosuppressive therapy [30]. The European League Against Rheumatism

(EULAR) [29] recommends withholding live attenuated vaccine in pediatric patients on high-dose DMARDs (methotrexate > 15 mg/m^2 per week; cyclosporine > 2.5 mg/kg per day; sulfasalazine > 40 mg/kg per day up to 2 g/day; azathioprine > 1 to 3 mg/kg; cyclophosphamide > 0.5 to 2.0 mg/kg per day orally; leflunomide > 0.25 to 0.5 mg/kg per day; 6-mercaptopurine > 1.5 mg/kg per day), high-dose glucocorticosteroids (≥ 2 mg/kg or a total dosage of ≥ 20 mg/day for ≥ 2 weeks or < 2 mg/kg/day if chronically administered) or biological agents (anti-TNFα, rituximab, anti-IL-6, and anti-CD11a) [29]. However, EULAR also advises carefully weighing the risk of wild-type infection against the risk of infection with an attenuated agent with vaccination [29, 52]. Similarly, the American Academy of Dermatology [67] recommends a detailed and cautious assessment when considering live attenuated vaccine in children with psoriasis treated with anti-TNFα and ustekinumab [68], while it advises discontinuing psoriasis biologics (anti-TNFα, anti-IL17, and IL-12/IL-23 inhibitors) before live attenuated vaccine in adults [64].

Statement 6

While on dupilumab, measurement of specific antibody levels can be considered to ensure serologic protection after vaccination on dupilumab therapy.

Evidence Summary

Assessment of serologic immune response is recommended by other authors based on studies in children and adult patients on immunosuppressive medications that showed a diminished immunologic response to influenza and pneumococcal [69], hepatitis B [70], and Pneumovax-23 vaccines [70].

Since the degree of impairment of vaccine responses by dupilumab is unknown, the expert panel suggests assessing for seroconversion as available at local laboratories with specific antibodies 4–6 weeks after vaccination to ensure patients have achieved an adequate response. Seroconversion for diphtheria, tetanus, hepatitis A and B, measles, mumps, rubella, and varicella are widely available whereas pneumococcal may not be. Vaccines that do not elicit protective titers should be re-administered and post-vaccination titers repeated to ensure adequate immune responses. Laboratory tests assessing humoral and cellular immunity, including lymphocyte immunophenotyping by flow cytometry and serum immunoglobulins, are recommended if vaccination fails.

Statement 7

There is no evidence to suggest that immunization while on dupilumab causes an exacerbation of AD.

Evidence Summary

Immunizations in AD patients are safe and there is no evidence that immunization aggravates AD [71]. Furthermore, AD patients have a normal immune response to live attenuated vaccine and influenza vaccines [72, 73]. Vaccination at week 12 (with Tdap and MPSV4) of dupilumab therapy was not associated with AD exacerbation in adult patients receiving a weekly dupilumab (higher than standard dosing) [17].

In general, AD patients should be vaccinated according to the national vaccination plan, but they should not be vaccinated during an acute AD flare. In the scenario of an acute AD flare, starting treatment to achieve disease control should be prioritized over vaccination. Good clinical AD control for 2 weeks before receiving vaccinations is optimal to avoid skin complications related to vaccination [74].

4 Discussion

To our knowledge, this is the first consensus statement addressing the questions of safety and effectiveness of vaccination in children on dupilumab for AD. The strengths of this consensus include its adherence to a modified-Delphi methodology and a face-to-face interaction with multidisciplinary discussion and expert opinion. This consensus resulted in statements that offer an approach to vaccination for healthcare providers caring for children with AD on dupilumab.

The MMR-V booster was extensively discussed, as it is recommended at an age (4–6 years old) commonly affected by AD. Research in children with rheumatic diseases treated with other biologics has suggested booster vaccinations to be generally safe, though caution with live attenuated vaccine and anti-TNF and anti-IL-1/6 agents seems prudent based on severe but rare reports of adverse events. However, prospective studies to prove the safety and efficacy of booster live attenuated vaccines in dupilumab-treated children in the long term are required to provide an evidence-based risk–benefit assessment. If there is a situation where a live attenuated vaccine is needed, such as a measles outbreak in the community and children without protective measles antibody titers who would go to school, the expert panel recommends an individualized assessment weighing the risk of infection in conjunction with a clinical immunologist and an infectious disease specialist. Parents should be made aware of the risks taken regarding vaccination and the dangers of infection. Theoretically, based on the effect of dupilumab on the T_H2 pathway, blocking IL-4 probably would not impair the response to viral infection and to live attenuated vaccine; therefore, the immune response to live attenuated vaccines that elicit T_H1-dependent immunity should not be

affected. However, there is insufficient evidence to provide a formal recommendation.

Unfortunately, our work has several limitations, including the small number of panelists involved in this process and the use of a cut-off of 75% agreement for consensus. We would highlight that all statements did reach 100% agreement despite the a priori 75% level established. From an evidence perspective, there are no data on vaccination of pediatric AD patients from dupilumab clinical trials, as vaccinations were not permitted in trial subjects. Second, evidence of vaccine responses in pediatric AD patients on immunosuppressive treatment is also sparse. Most evidence on vaccinations in immunocompromised patients comes from children with rheumatologic conditions using psoriasis biologics with different mechanisms of action than dupilumab. Third, existing international guidelines on immunizations are primarily based on expert opinion and a moderate to low level of evidence. Though international AD guidelines and national publications providing clinical guidance on the management of adult and pediatric AD exist [75, 76], few have addressed vaccination while on immunosuppressive agents [74, 77]. The American Academy of Dermatology guidelines from 2014 advises considering administering a booster to AD children on long-term systemic steroids [77], whereas the European guidelines from 2018 recommend consulting a specialist before live attenuated vaccine is administered on children on immunosuppressive therapy [74]. Moreover, only two guidelines have been published since the approval of dupilumab [74, 76] (see the electronic supplementary material), but there was no recommendation in this regard. Finally, this consensus meeting happened before coronavirus disease 2019 (COVID-19) vaccines became available, which were not included in our literature review and recommendations statements.

5 Conclusion

This modified-Delphi consensus process identified critical questions for future studies. First, does dupilumab interfere with vaccination responses/development of immunity? Second, how do we address the lack of clinical studies addressing safety, immunogenicity, and clinical efficacy of primary vaccinations and boosters in children with AD on dupilumab, in particular, for the MMR-V booster vaccine, to keep our patients safe? Finally, is there an impact of long-term dupilumab therapy on protective antibodies developed pre-dupilumab therapy and are supplementary boosters required? In the absence of an evidence base to guide clinical decision making, our consensus discussions and statements are a starting point/food for thought for clinicians struggling with these decisions.

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Declarations

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