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Original Article

A systematic review and expert Delphi Consensus recommendation on the use of vaccines in patients receiving dupilumab: A position paper of the American College of Allergy, Asthma and Immunology

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ABSTRACT

Background: Dupilumab is a monoclonal antibody that targets the interleukin (IL)-4 receptor alpha subunit, thus blocking the effects of IL-4 and IL-13, and has shown efficacy in treating various conditions including asthma, atopic dermatitis, eosinophilic esophagitis, and others. Because of its immune modulatory effects, clinical trials that studied dupilumab did not allow patients to receive live vaccines during the clinical trials because of an abundance of caution, and thus package inserts recommend that patients who are being treated with dupilumab should avoid live vaccines. Because dupilumab is now approved for use in patients from 6 months of age for the treatment of atopic dermatitis, this reported contraindication is now posing a clinical dilemma for patients and clinicians.

Objective: To perform a systematic review of literature on the safety and efficacy of vaccinations in patients who are receiving dupilumab and to provide expert guidance on the use of vaccines in patients who are receiving dupilumab.

Methods: A systematic review of the literature was performed, and an expert Delphi Panel was assembled.

Results: The available literature on patients who received vaccinations while using dupilumab overall suggests that live vaccines are safe and that the vaccine efficacy, in general, is not affected by dupilumab. The expert Delphi panel agreed that the use of vaccines in patients receiving dupilumab was likely safe and effective.

Conclusion: Vaccines (including live vaccines) can be administered to patients receiving dupilumab in a shared decision-making capacity.

Introduction

Dupilumab, an interleukin (IL)-4 receptor alpha antagonist that blocks the effects of IL-4 and IL-13, is currently approved for the treatment of atopic dermatitis, asthma, chronic rhinosinusitis with nasal polyposis, eosinophilic esophagitis, and prurigo nodularis in the United States[1]; and for atopic dermatitis, asthma, and chronic rhinosinusitis with nasal polyposis in Canada.[2] Because of its potential immune modulatory effects, the pivotal phase 3 trials for dupilumab did not allow for the administration of live vaccines to patients who received dupilumab.[3,4] Furthermore, treatment with a live attenuated vaccine within 12 weeks before the baseline visit was an explicit exclusion criteria for the phase 3 studies in atopic dermatitis. Because of this exclusion of live vaccination in the clinical studies of dupilumab, there are no controlled, prospective data to confirm the efficacy of vaccines or to evaluate concerns over safety or risk for dupilumab recipients in this setting. As such, the current package insert for dupilumab in the United States the following: "Consider completing all age-appropriate vaccinations as recommended by current immunization guidelines before initiating treatment with dupilumab. Avoid use of live vaccines in patients treated with dupilumab. It is unknown if administration of live vaccines during treatment with dupilumab will impact the safety or effectiveness of these vaccines."[1]

Because the initial dupilumab regulatory approval was only for use in adults, the clinical predicament of live vaccination in patients receiving dupilumab was a minor issue in the United States and Canada, because varicella was the only live vaccine routinely given to adults, and there is an alternative nonlive shingles vaccine available (Shingrix, GlaxoSmith Kline). However, with the subsequent approval of dupilumab for use in patients from the age of 6 months,[1] there is a dilemma of having to withhold or alter the dosing schedules of live vaccines for patients who can potentially benefit from receiving dupilumab. This has now become a critical clinical issue that needs attention and evidence-based guidance.

To date, there has been 1 consensus recommendation by a small panel of Canadian physicians on this topic, none with specialty training in allergy and immunology.[5] In this consensus statement, the authors concluded (with unanimous agreement) that "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 vs the risks of vaccination." Furthermore, the panel unanimously agreed that any live vaccine should be given 4 weeks before starting dupilumab, that dupilumab does not need to be interrupted for inactivated vaccines, and that inactivated influenza vaccine should be continued as recommended while using dupilumab. They also suggested measuring the specific antibody titers of the vaccine to ensure protection while using dupilumab, although dupilumab has not been shown to interrupt titer development to inactivated vaccines.

To provide evidence-based guidance regarding dupilumab and vaccination, we systematically reviewed all the studies that addressed vaccine efficacy and safety during dupilumab exposure and subsequently developed recommendations using an expert Delphi panel.

Methods

Search Strategy

Ten databases (MEDLINE, EMBASE, CENTRAL, CINAHL, PsycINFO, PubMed, Scopus, Web of Science citation searching, ClinicalTrials.gov, and Google Scholar) were used for the literature search from inception to January 2022. We used the following keywords: Dupilumab, vaccine, T-cell, immune response, co-administration, efficacy, Atopic Dermatitis, Asthma*.

Inclusion and Exclusion Criteria

Because we anticipated only a few studies that directly studied this question, we included any human subject study, in any language, that described live or nonlive vaccination of human subjects of any age who were also receiving dupilumab injections. Nonhuman studies were excluded. Studies that did not report outcomes of antibody titer(s), release of a cytokine indicative of an immune response, or detailed absence or presence of rates of infection to the infectious agent were also excluded.

Study Selection and Data Extraction

Four authors (D.K.C., M.J.G., T.A., and J.A.L.) screened titles and abstracts and the full texts independently and in duplicate. Two authors (M.J.G and T.A.) extracted the following data independently and in duplicate, when available: (1) summary of included studies, study design, population studied, demographic, sample size, inclusion and exclusion criteria, and study arms; (2) continuous data on

vaccine immune response; and (3) dichotomous data on safety. A risk of bias assessment was performed for the selected manuscripts according to the JBI (https://jbi.global/) Risk of Bias Checklist. The certainty of evidence was assessed using the Grading of Recommendations, Assessment, Development, and Evaluation.[6-8]

Development of Expert Consensus

A modified Delphi panel was organized to evaluate the current evidence and to provide consensus regarding a recommended course of action for live and nonlive vaccination in the context of concurrent dupilumab use. A total of 28 specialist participants were selected by the lead authors (J.A.L and M.J.G.) to participate in the modified Delphi panel, chosen based on their eminence and publication track record in allergy health policy, their expertise in adverse reactions to vaccines, and their specialty training in allergy/immunology or cytokine biology and the development of the immune response to a vaccines. This methodology and threshold consensus procedure has been described previously,[9,10] but briefly, agreement and consensus with a recommended course of action regarding vaccination with concurrent dupilumab use was voted on using a REDCap survey (Research Electronic Data Capture, Nashville, Tennessee)[11] that was sent to the 28 voting panel members. Members, after reviewing the systematically reviewed evidence, were asked to rate their level of agreement with 3 questions regarding the efficacy and safety of live and nonlive vaccination while using dupilumab (1 = strongly disagree, 2 = moderately disagree, 3 = neither agree nor disagree, 4 = moderately agree, 5 = strongly agree). Members also had the opportunity to provide free-text comments for each statement. Strongly disagree and moderately disagree were grouped together as disagree and moderately agree and strongly agree were grouped together as agree. Consensus was defined as agreement or disagreement for statements equal to or exceeding 75%. If consensus for a statement was not achieved after the first Delphi round, 2 subsequent Delphi rounds were conducted to achieve consensus by including deidentified survey results from the previous rounds. If after the third round consensus was not achieved, the statement was categorized as consensus not achieved. One author (T.E.D.) was the Delphi methodologist and did not vote in the Delphi rounds. This study was approved with exemption from ongoing review by the University of Tennessee Health Science Center.

Results

Summary of Study Selection and General Characteristics of Included Studies

A total of 412 studies were identified. After duplicate removal, 249 studies were screened further, and 27 articles were identified as eligible for full-text assessment. After further review and based on the inclusion and exclusion criteria, we included a total of 9 studies in our systematic review[12-20] (Fig 1). A meta-analysis was not performed because of the paucity of data for pooling and the heterogeneity of the study populations and designs; instead, a narrative synthesis was performed. Half of the selected studies were conducted in the United States. The study designs included 5 cohort studies (population-based cohort, observational trial, and prospective and retrospective cohort), 1 randomized controlled trial (RCT), 2 retrospective case-control studies, and 1 case series. Moreover, 6 of the 9 studies involved patients with atopic dermatitis, 2 involved patients with asthma, and 1 involved patients with both conditions. The age of the study participants ranged from 8 months to 64 years old. Moreover, 7 of the 9 studies evaluated the effect of dupilumab with COVID-19 vaccinations (mostly messenger RNA [mRNA] vaccines). One study evaluated protein and polysaccharide vaccinations (tetanus toxoid with reduced diphtheria toxoid and acellular pertussis vaccine and quadrivalent meningococcal polysaccharide vaccine). Two studies evaluated live vaccine (yellow fever vaccine [YFV; YF-17D], measles/mumps/rubella vaccine [MMR], and varicella zoster vaccine [VZV]) administration among recipients of dupilumab. Table 1[12-20] shows the summary and baseline characteristics of the included studies and population.

Does Administering a Live Vaccine to Patients Concurrently Receiving Dupilumab Pose a Risk for Disseminated Viral Infection or Inhibit Development of Humoral Antibody Response?

Although the administration of a live vaccine concurrently with dupilumab use is largely unstudied, there are no preclinical data that suggest this practice is associated with any risk for disseminated infection from the vaccinating agent, any safety data that would suggest harm to human vaccine recipients, or any known reduction in immune response. Live vaccination was contraindicated during the phase 1 to 3 studies of dupilumab and as such, this contraindication became part of the package insert. Presently, there are no data to suggest that this practice is dangerous or ineffective.

The literature search identified no prospective RCTs or controlled prospective trials that evaluated this question as a powered primary endpoint. Two uncontrolled observational cohort studies were identified and thus a meta-analysis was not possible and data are narratively synthesized. Wechsler et al,[12] as part of a secondary analysis of nested data within the TRAVERSE study (dupilumab treatment in patients with moderate-severe asthma) examined the outcomes of vaccination with the YFV. During this study, there was a yellow fever outbreak in Brazil, which hosted study sites. A total of 37 TRAVERSE subjects living within the endemic region discontinued dupilumab treatment and were administered the YF-17D live attenuated YFV at a minimum of 7 days after discontinuation and a mean interval of 22.3 days after their last dupilumab dose (although the interval after vaccination to restart of dupilumab use was unknown). Safety and tolerability data, dupilumab serum concentrations, and humoral immune response (via plaque reduction neutralization titers before and after vaccination) were collected. All 37 patients achieved a therapeutic YF-17D antibody level and the magnitude of response seemed to be unrelated to the prevaccination dupilumab concentrations. There were no instances of vaccine-related adverse events or vaccine hypersensitivity and no adverse events in 36 of 37 patients; only 1 patient reported myalgia, malaise (both known YFV adverse events), and dizziness that lasted 2 weeks. Within a mean follow-up period of 186.6 days after vaccination, there were no instances of breakthrough yellow fever infection. The vaccine was not concurrently administered with dupilumab but was administered to patients on established dosing who temporarily paused dosing to receive the vaccine and then re-established dosing.

Siegfried et al[13] have reported on a cohort of 9 preschool-aged patients who were part of the LIBERTY atopic dermatitis preschool trial or the LIBERTY PRESCHOOL AD PED-OLE (Pediatric Open Label Extension) trial for moderate-to-severe atopic dermatitis. All patients had at least 85 days duration of dupilumab dosing before vaccination (weight-based dosing used), and 7 of 9 patients had more than 400 days of dosing. During the respective trials, these 9 patients received a live vaccine (n = 9 MMR, n = 5 VZV, n = 5 both), stratified by time between the last dupilumab dose and the vaccination of either <12 weeks (n = 5) or >12 weeks (n = 4). Although postvaccination titers were not determined, there was no occurrence of disseminated varicella, measles, mumps, or rubella in any recipient. There were variable gaps between vaccination and the last dupilumab dose (range, 7-192 days) and between vaccination and the next dupilumab dose (2-43 days).

The vaccine adverse event reporting system data up March 5, 2024, showed reports of immunization while concurrently using dupilumab for yellow fever (YF-VAX; 2 reports), MMR (MMR II; 3 reports), MMRV (Measles, Mumps, Rubella, and Varicella) (1 report),

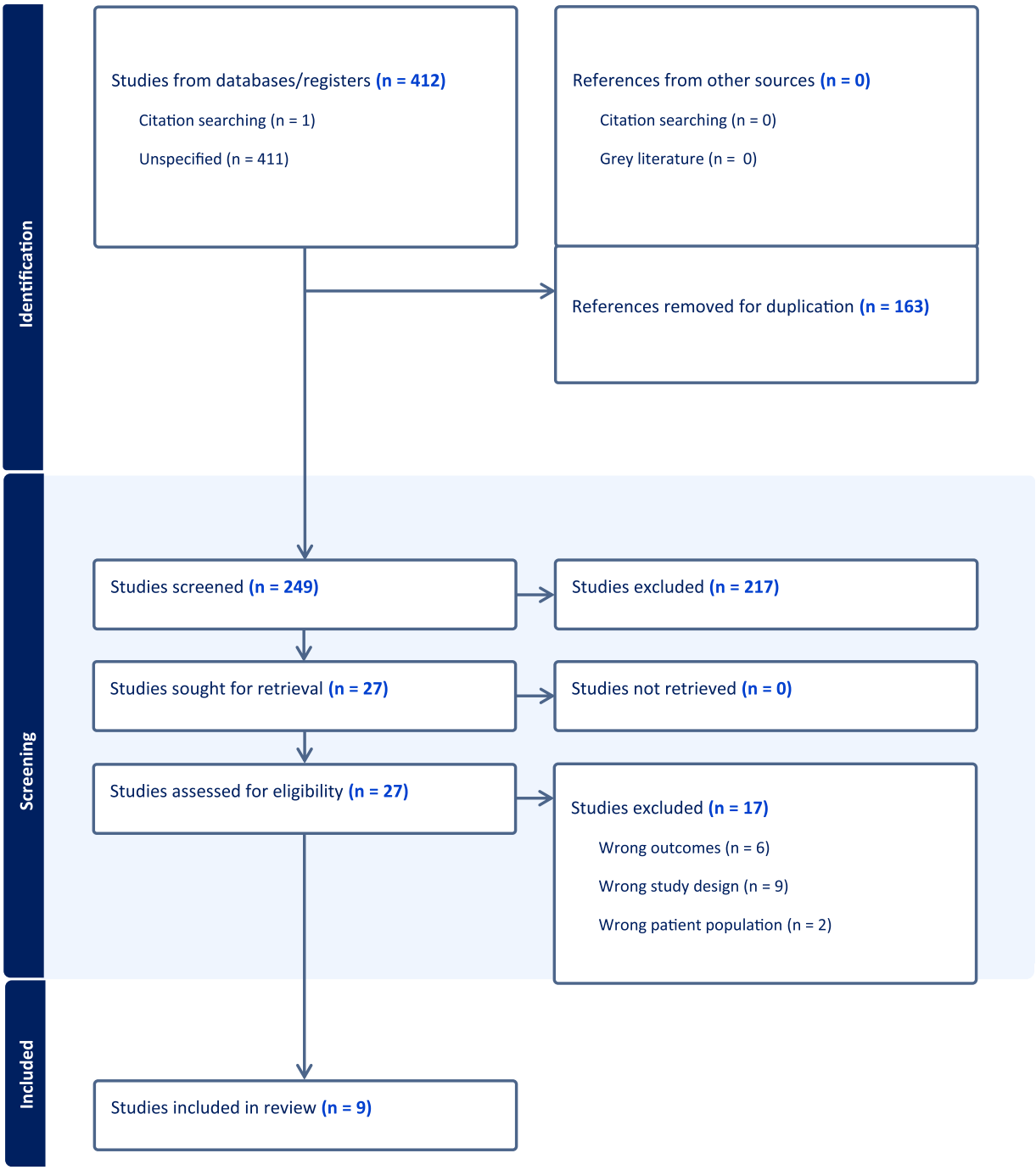

Figure 1. PRISMA flow diagram of the screening process. PRISMA, *Preferred Reporting Items for Systematic reviews* and Meta-Analyses.

varicella (varivax, 2 reports), rabies (IMOVAX [Sanofi Pasteur]; 1 report), smallpox or monkeypox (JYNNEOS [Bavarian Nordic], 2 reports), typhoid (VIVOTIF [Crucell Switzerland], 1 report), and zoster (Shingrix; 22 reports). All events reported only the concurrent immunization while on dupilumab with no adverse outcome and no nonserious expected immunization-related events (eg, nonserious headache, arthralgias, or fever not requiring intervention).

Although the data are limited, these 2 studies showed no evidence of disseminated infection or diminished humoral antibody response for established dupilumab patients who temporarily interrupted their course of care to receive a live, attenuated YF-17D vaccine and no occurrence of disseminated infection after MMR or VZV vaccine. The certainty of evidence is very low, and the risk of bias is high.

Does Dupilumab Inhibit the Development of Humoral Antibody Response to Nonlive Vaccine Agents?

The literature search identified 8 studies on patients who used dupilumab (4 studies) and other biologics, including dupilumab (4 studies) with an mRNA COVID-19 vaccine (6 studies), with YFV (1 study), or a toxoid or polysaccharide vaccine (1 study), and who had

Table 1
Summary of the Articles Included in the Systematic Review

Author y, Study type	Country	Study population age (mean ± SD), sex, other exposures	Disease state	Type of vaccines administered	Outcomes	Results
Wechsler et al,[12] 2022 Case series	Brazil	Adults, n = 37 46.5 ± 12 y 67.6% Female	Patients with moderate-to-severe asthma enrolled in QUEST or VENTURE studies	Live attenuated vaccine (Yellow fever vaccine -YF-17D)	Plaque reduction neutralization titers, rate of disseminated infection	No instances of disseminated infection. All 37 patients achieved seroprotection.
Siegfried et al,[13] 2024 Case series	Multiple	Preschool age, n = 9 8-56 mo 11% Female	Moderate-to-severe AD, part of LIBERTY AD Preschool part A or LIBERTY AD PED-OLE studies	Live: MMR (n = 9), VZV (n = 5), both MMR/VZV (n = 5) Non-live: diphtheria/pertussis (n = 8), inactivated polio (n = 4), hepatitis A or Prevnar (n = 1 each)	Disseminated infection at 4 wk post-vaccination	No disseminated infection observed within 4 wk or after 4 wk post-vaccination. Vaccine titers not reported.
Blauvelt et al,[14] 2019 Randomized controlled trial	USA	Adults, n = 178 39.5 ± 14 y 51% Female	Moderate-to-severe AD patients for ≥3 y treated with 300 mg dupilumab vs placebo	Non-live: 1. Tdap, 2. MPSV4	≥4-fold or ≥2-fold increase from baseline anti-tetanus IgG, or ≥8 meningococcal serogroup C serum bactericidal assay titer, at wk 16	No difference in vaccine efficacy between groups. Tetanus: 83.3% dupilumab vs 83.7% placebo; meningococcal: 86.7% dupilumab vs 87.0% placebo.
Runnstrom et al,[15] 2022 Cohort study	USA	Adults, n = 30 44.5 y, 65% Female Benralizumab (n = 12), mepolizumab (n = 6), dupilumab (n = 30), or non-exposed (n = 36)	Adults with severe asthma or AD treated with benralizumab (n = 12) or mepolizumab (n = 6), or dupilumab (n = 30) and n = 36 healthy controls	BNT162b2 or mRNA-1273 COVID-19 vaccines	IgG titer in average MFI to wild-type SARS-CoV-2 RBD at d 25-49 post-second mRNA vaccine dose	Exposure to any monoclonal antibody vs controls (non-exposed and milder disease) MFI 105,950 vs 160,584. Did not separate dupilumab from other biologics.
Liao et al,[16] 2022 Cohort	USA	Adults, n = 21 64 ± 14 y, 68% Female Anti−IL-5 or dupilumab	Patients with asthma who were treated with biologics in the National Jewish Health electronic medical records research database who received the second or third dose of COVID-19 vaccine	BNT162b2 or mRNA-1273 COVID-19 vaccine	IgG BAU/mL to spike protein recombinant S1 domain	No significant difference in BAU/mL between groups. Mean BAU in patients receiving anti IL4/13 or anti IL-5 = 439 vs mean BUA in patients with asthma not receiving biologics = 330.
Pakhchanian et al,[17] 2022 Cohort study	USA	Adults, n = 3360 44.9 ± 24 y % Sex not reported Immunomodulatory or immunosuppressive; n dupilumab not reported	COVID-19 vaccinated patients with AD being treated with an immunomodulatory or immunosuppressant agent, including dupilumab	BNT162b2, mRNA-1273 and Ad26.COV2.S COVID-19 vaccines	Adverse events to 90 d measured at 1, 30, 60 and 90 d, and any hospitalization	Patients with a 1-y history of immunosuppressant or immunomodulatory therapy were at greater risk of all-cause hospitalization vs controls at the 30-d (RR 2.14, 95% CI 1.27-3.59), 60-d (RR 1.77, 95% CI 1.22-2.56), and 90-d (RR 1.68, 95% CI 1.25-2.27) follow-ups after vaccination. Stratification revealed that 1−y steroid use showed the greatest risk for hospitalization compared with controls. 1-y Dupilumab or immunosuppressant use showed no risk differences.
Ungar et al[19] 2023 Cohort	USA	Age ≥ 12 y, n = 64 38.53 ± 15.87 y 61% Female Dupilumab, systemic or topical treatments	Patients with moderate-to-severe AD, currently or previously on systemic therapy (including dupilumab, phototherapy, or oral immunomodulatory medications)	BNT162b2 or mRNA-1273	T cell IFN-γ/IL-2 to SARS-CoV-2 spike protein	More IFNγ+ producing cells among dupilumab treated compared to other 2 groups.

(*continued*)

Table 1 (*Continued*)

Author y, Study type	Country	Study population age (mean ± SD), sex, other exposures	Disease state	Type of vaccines administered	Outcomes	Results
Ungar et al[18] 2022 Cohort	USA	Age ≥ 12 y, n = 101 Dupilumab, systemic or topical treatments	Patients with moderate-to-severe AD, currently or previously on systemic therapy (including dupilumab, phototherapy, or oral immunomodulatory medications)	BNT162b2 or mRNA-1273	ELISA-based SARS-CoV-2 IgG antibody levels measured by 4 predefined levels: negative (<5 arbitrary unit [AU]/mL), weak (5-15 AU/mL), moderate (16-39 AU/mL), and strong (≥40 AU/mL)	No differences in antibody levels among groups.
Wieske et al[20] 2022 Cohort	Netherlands	Adults, n = 84 49.9 ± 13.7 62.8% Female Dupilumab	Multiple immune-mediated inflammatory disorders (including atopic dermatitis), which included a small proportion of subjects on dupilumab	mRNA (Pfizer-BioNTech, Moderna), or adenoviral (Oxford–AstraZeneca, or Janssen/Johnson & Johnson) COVID-19 vaccines	Anti–receptor-binding domain IgG antibody up to d 28 after third vaccination	Seroconversion rate in dupilumab vs controls RR 1.00 (95% CI 0.66-1.44), with 98% achieving seroconversion. Fold change in anti-RBD titers for dupilumab vs controls 0.64 (95% CI 0.49-083).

Abbreviations: AD, atopic dermatitis; AU, antibody unit; BUA, binding antibody unit; ELISA, enzyme-linked immunosorbent assay; IFN, interferon; IL, interleukin; MFI, median fluorescence intensity; MMR, measles/mumps/rubella vaccine; MPSV4, Quadrivalent meningococcal polysaccharide vaccine; mRNA, messenger RNA; RBD, receptor-binding domain; RR, risk ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; Tdap, Tetanus toxoid with reduced diphtheria toxoid and acellular pertussis vaccine; USA, United States of America; VZV, varicella zoster vaccine.

their humoral immune response assessed. Moreover, 6 studies were conducted in patients with atopic dermatitis, 1 study in patients with only asthma, and 1 study in patients with immune-mediated inflammatory disorders. Furthermore, 1 study included preschool-aged children, 2 studies included children aged 12 years and older, and the rest were studies of adults. Most studies assessed response concurrently with mRNA COVID-19 vaccination. Only 1 study was an RCT.

Non–COVID-19 Vaccine Response

In addition to the yellow fever study described above, we identified 1 study in which non-mRNA vaccines were studied. Blauvelt et al[14] performed an RCT among a total of 178 patients with moderate to severe eczema randomized to dupilumab treatment vs placebo and who were vaccinated against both tetanus toxoid and meningococcal polysaccharide. They noted similar immune responses in terms of antibody titer increases or overall titers between the dupilumab and placebo groups to the tetanus vaccine (83.3% vs 83.7%) and to meningococcal polysaccharide (86.7% vs 87.0%) at 16 weeks after vaccination. Dupilumab-treated patients were less likely to develop tetanus toxoid with reduced diphtheria toxoid and acellular pertussis vaccine-IgE by week 32 than placebo-treated participants (62.2% placebo vs 34.8% dupilumab; this was assayed to test dupilumab's ability to lower total IgE production).

COVID-19 Vaccine Response

Multiple observational studies addressed COVID-19 vaccinations in patients who concurrently received dupilumab.[15-20] Among mRNA –COVID-19 vaccine recipients, 1 study reported reduced postvaccination titers, and the remainder reported no difference in the postvaccination titers between persons on anti–IL-4 or -13 therapy and those not on anti–IL-4 o r-13 therapy.

Runnstrom et al[15] performed a prospective observational study after mRNA COVID-19 vaccination (with either brand) and assessed the IgG titer median fluorescence intensity in comparison with wild-type severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) receptor-binding domain in patients with asthma or eczema on anti –IL-5 (n = 18) or anti–IL-4 or -13 (n = 30) therapy and compared it with equivalent responses in healthy adults. They noted that on day 25 to 49 after vaccination, the antibody levels for patients who used biologic therapies were significantly lower than those in healthy adults (average median fluorescence intensity of 67,535 and 100,519, respectively; P = .012), and were approximately 67% of the level of the controls. Similar results were seen for other SARS-CoV-2 antigens, including the Delta variant receptor-binding domain and spike protein S1. However, this data set included patients with atopic dermatitis with hyper-IgE syndrome (n = 1) and patients with asthma who used high doses of inhaled steroids (number not specified), which may have been a confounder in their results.[21-23] In addition, dupilumab-specific differences were not reported, and the clinical relevance of this statistically significant decrease is not known.

All other studies reported no difference in the antibody response between patients who received dupilumab and the controls. In a retrospective cohort analysis of persons with asthma who received either 2 or 3 doses of an mRNA COVID-19 vaccine (with a 3:1 propensity score matching to controls, vaccinated with either brand), Liao et al[16] noted no significant reduction in the spike protein IgG binding recombinant domain S1 antibody binding antibody unit (a surrogate for COVID-19 neutralizing antibody), as measured using the Quanti-Vac enzyme-linked immunosorbent assay (EUROIMMUN), among persons treated with biologics (anti–IL-5 and anti–IL-4/13) and among those who did not receive biologics when measured at a mean of 58 days after their second mRNA vaccination; however, there were only 21 patients among the cases who received biologics,

and the number of patients who received anti–IL-4 or -13 was not specified.

Pakhchanian et al[17] performed a retrospective cohort study of the TriNetX database (75 million records) to identify COVID-19–vaccinated adults (either BNT162b2, mRNA-1273, or Ad26.COV2.S COVID-19 vaccine) with eczema to investigate if COVID-19 vaccination was associated with increased adverse effects or breakthrough COVID-19 infection among recipients concurrently treated with an immunomodulatory or immunosuppressant agent. Among a total of 3360 patients with a more than 1-year history of any immunosuppressant or immunomodulatory therapy, there was a greater risk for all-cause hospitalization at 30 days (risk ratio [RR] 2.14; 95% CI: 1.27-3.59), 60 days (RR 1.77; 95% CI: 1.22-2.56), and 90 days (RR 1.68; 95% CI: 1.25-2.27) after vaccination than among controls. The authors noted that the increase in risk seemed to be the consequence of systemic corticosteroid exposure. Furthermore, a subgroup analysis that focused specifically on patients exposed to dupilumab (number not specified) showed no increased risk for adverse outcomes, adverse events of special interest, or breakthrough COVID-19 infection when compared with controls.

Ungar et al[18] performed a retrospective study of SARS-CoV-2 IgG antibody levels in children and adults aged 12 years and older with moderate-to-severe eczema that were measured 14 days after receiving a second mRNA COVID-19 vaccine. A total of 180 samples (eczema treatments included dupilumab, n = 101; systemic agents, n = 15; topicals, n = 64) were collected from 180 individuals at least 14 days after their second mRNA COVID-19 vaccine (either brand), and the IgG antibody responses were compared among the 3 treatment groups. No differences in the SARS-CoV-2 IgG antibody levels among treatment groups were noted. The same research group also explored postvaccination T-cell responses in a similar population of dupilumab-treated patients (n = 64) and compared them with responses in topical treatment patients (n = 52) or systemic immunomodulator–treated patients (n = 9).[19] They noted a significantly higher percentage of interferon-gamma producing cells (suggesting antiviral immunity) among dupilumab-treated patients than among patients treated with systemic immunomodulators and a nonsignificant trend toward higher levels in the dupilumab-treated patients when compared with the topical treatments group.

Lastly, Wieske et al[20] studied Dutch patients with immune-mediated inflammatory disorders who were treated with potentially immunosuppressive systemic therapies, including 58 subjects who received dupilumab (not considered immunosuppressive). These patients were vaccinated with either the mRNA COVID-19 vaccine or the adenoviral vector COVID-19 vaccine, and the study compared the relative risk for SARS-CoV-2 IgG antibody seroconversion (anti–receptor-binding domain IgG titer) among persons on these therapies with those who did not receive therapy and with healthy controls. Patients who were treated with dupilumab had a 98% seroconversion rate (eg, titer > 4 Arbitrary Units [AU]) and a 1.0 RR of seroconversion when compared with controls, but when exploring the magnitude of the fold change in titer, they only had a predicted fold change of 0.64 RR for anti–receptor-binding domain titers between the second and third vaccine doses when compared with controls.

Overall, there seems to be a low risk that the administration of a nonlive vaccine to patients who are receiving uninterrupted dupilumab impairs humoral immune responses. However, this may be biased by the small number of patients studied and influenced by shorter study times with some concern for diminishing the response with longer study intervals.

Modified Delphi Panel Results

In late October 2023, the 28 Delphi panelists were sent the narrative summary of the systematic review for evidence context, along with 3 statements regarding the administration of live vaccines to patients on dupilumab therapy to assess their level of agreement or disagreement with the following statements: (1) “It is safe to administer live vaccines to patients receiving dupilumab” (to assess the safety of this process); (2) “Patients mount appropriate antibody response to vaccines while on dupilumab” (to assess the robustness of a perceived immune response in such patients); and (3) “I would recommend giving live vaccines to patients on dupilumab after a shared decision-making discussion with the patient and/or their family” (to assess if the respondent would recommend that their patients receive live vaccines if they were also on dupilumab therapy). Table 2 details the voting responses and respondent comments. All 3 questions exceeded the prespecified threshold for agreement in a single round of voting with only 1 instance of disagreement (1 respondent for question 3). This represents a very high level of consensus agreement that the process is safe, that a robust immune response would be anticipated, and that the practice would be recommended to patients following a shared decision-making process.

Discussion

Although more robust data beyond these 9 studies are not available to provide a better assessment of the issue, there is no known human or animal model–based safety or efficacy concern as to why patients who receive treatment with dupilumab could not be given concomitant live vaccines if indicated. The issue was not studied as a subgroup analysis during dupilumab clinical trials, and the contraindication was listed in the package insert in section 5.6.[1] Of note, the company-specific language states that “It is unknown if administration of live vaccines during DUPIXENT treatment will impact the safety or effectiveness of these vaccines. Limited data are available regarding co-administration of DUPIXENT with non-live vaccines.”[1] Given this warning, there remains a dearth of experience and no data that suggest that it is dangerous or that there are specific concerns for disseminated infection or reduced protection.

This systematic review shows limited evidence in 46 subjects that live vaccination (to measles, mumps, rubella, varicella, or yellow fever) during interrupted dupilumab dosing is not associated with disseminated infection and does not seem to inhibit the formation of yellow fever IgG titers.[12,13] Furthermore, short-term data from 5 studies, including 414 patients, supported no concerns regarding impaired formation of IgG titers after nonlive vaccination (primarily mRNA COVID-19 vaccine), although 1 study suggested that antibody titers may not reach the level of those in healthy controls with respect to mRNA COVID-19 vaccination.[14-18] However, these studies are of low quality, the evidence is of very low certainty (meaning additional studies could shift the findings and recommendation), the overall numbers of patients studied and the diversity of vaccine types used in these studies are limited, the patients included those who used steroids, which may have complicated the analysis, and it is unclear if the reduced titer issue is a COVID-19 specific phenomenon or one that would be seen with other vaccines.

Further substantiating the evidence synthesis, the expert consensus from the modified Delphi panel strongly supports that when considering administering live vaccines while concurrently on dupilumab treatment, this practice is felt to be safe, is not expected to lead to a dampened immune response, and is a practice that the voting members would recommend for their patients in the context of a shared decision-making discussion. Consensus on this was reached after 1 round of voting with only a single dissenting vote across the 3 questions and was thus greater than 89% for each item. Respondent comments did highlight that there are very limited data that have explicitly studied the safety and efficacy of this practice but also acknowledged the absence of any data that suggest that this practice is unsafe or that there is any theoretical evidence as to why this practice would be unsafe or cause harm. Three experts commented on the small reduction in titers noted in 2 studies (only 1 of

Table 2
Delphi Results (N = 28, 1 round)

Statement	% Agree (n)	% Disagree (n)	Free-text comments
1. It is safe to administer live vaccines to patients receiving dupilumab.	89.3 (25)	0 (0)	• Very limit data • Not all live vaccines are equal. Not all patients with eczema treated with dupilumab have atopic dermatitis. • There is no immunologic basis to suggest this would be unsafe. • I think the issue is the concern for lack of response, not danger of receiving the vaccine • Small numbers of patients but data are reassuring in both children and adults • There are no convincing data of harm or decreased response to vaccination while on dupilumab • Literature on this subject is scant, as is reported clinical evidence and outcomes … hence the rationale for this Delphi study. However, the literature presently available is from 2020-2022, the 2 papers contradict each other, and the work preceded the age reduction in dupilumab down to 6 mo+ for AD. From a practical standpoint, as a practicing clinical immunologist who prescribes dupilumab, my anecdotal experience does not suggest any reason to withhold/alter vaccine schedules or provide ppx in any fashion for patients on dupilumab. Similarly, although I have not assessed vaccine recall in patients on drug, I have not observed adverse infectious events. Lastly, we do put patients with hyper-IgE syndrome (STAT3 LOF) with severe AD on dupilumab and do not note (small numbers obviously) adverse events to warrant avoiding this practice. • Very limited data, but no conceptual concern. • Although there does not appear to be evidence of harm, the data are insufficient to support a statement that live vaccines are safe in patients on dupilumab • Although there does not appear to be evidence of harm, the data are insufficient to support a statement that live vaccines are safe in patients on dupilumab • Case series are supportive but data is lacking
2. Patients mount appropriate antibody response to vaccines while on dupilumab.	92.9 (26)	0 (0)	• Very limit data • Based on limited data that I have seen. • There is no immunologic basis to suggest this would not be the case. • Small reduction in antibody titers in some studies but not clinically significant • I say moderate because I do not have data to support my assertion. No concerns clinically however. • Moderate evidence of low certainty supports this. • The decrease in fold change antibody titers to the COVID-19 vaccine is notable, but the COVID-19 vaccines studied are not the most robust vaccines nor a fully understood measure of immunity. The 2019 study on childhood vaccine titers is encouraging and reassuring. • Data are mixed - in some studies and for some vaccines, antibody responses are lower than in comparison group not on dupilumab; I would be cautious about using the word "appropriate" as we often do not know what level of antibody response is needed to confer immunity over a specified duration.
3. I would recommend giving live vaccines to patients on dupilumab after a shared decision-making discussion with the patient and/or their family.	89.3 (25)	3.6 (1)	• I have done this in the past • Based upon the current evidence, there have been no observations of increased harm. There are limited observations on efficacy of live vaccines in the presence of dupilumab, but this would not disfavor attempting a needed immunization. Immunizations are commonly given to patients without certainty of an immune response in the hopes of efficacy and protection. • SDM to consider possible interruption of therapy around live vaccination • The theoretical risks weighed against the basic research into IL-4′s and IL-13′s role in clearing viral infections as well as KO mice studies plus the clinical research data provided in the metanalysis plus the health benefit of vaccination against MMR&V tilts solidly to the side of benefit. Because of such, I would have no problem recommending live vaccination to patients receiving dupilumab in shared decision-making

Abbreviations: AD, atopic dermatitis; IL, interleukin; KO, knockout; LOF, loss of function; MMR&V, Measles, Mumps, Rubella, and Varicella; SDM, shared decision making; STAT3, signal transducer and activator of transcription 3.

which was an IgG titer) but felt that this was unlikely to be a clinically significant issue. In addition, many experts commented on the overall limitations of the data (Table 2).

Although the systematic review and expert consensus do not support any demonstrated or theoretical safety concern, no robust studies with large patient numbers exist that could support a narrow CI that indicates safety. Furthermore, such studies are unlikely to be conducted or funded, which complicates the ability to alter regulatory agencies' recommendations on administering live vaccines to patients on dupilumab. Although the conservative nature of a cautious approach is understandable to do no harm, this approach may obscure patient values and preferences in the context of shared decision-making; patients may wish to receive live vaccines while on dupilumab despite the limited safety evidence. This approach was nearly unanimously supported by the disease-state experts in the Delphi panel. Preventing access to otherwise recommended vaccines could cause potential inadvertent harm and increase the risk for natural contraction of the otherwise preventable disease. In addition, one must consider the possible harm of discontinuing dupilumab for periods of time to administer vaccines, especially for an indication such as poorly controlled asthma. Therefore, the risk for harm from action vs inaction should be carefully weighed in a shared decision-making capacity to allow a patient to make an informed decision consistent with their unique preferences.

In conclusion, this systematic review and Delphi panel provide evidence to support that there is no evidence that co-administration of live vaccines to patients who are receiving dupliumab is unsafe. Although the number of studies and patients studied are sparse, the risk for patient harm is based on an unsubstantiated theoretical concern that lacks scientific evidence that dupilumab may cause immune suppression that would either hinder titer response, decrease vaccine efficacy, or predispose the recipient to infection with a live vaccine component. However, there was very strong consensus among disease-state experts in supporting that this process would be safe, allow for durable immune response to be mounted, and that it would be appropriate to recommend live vaccination in such patients after the vaccinating clinician and patient engaged in a shared decision-making process.

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