Dupilumab and Live-Attenuated Vaccines: Experience With Prior Dupilumab Use and Yellow Fever Vaccine in Patients With Severe Asthma From Brazil

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LIBERTY ASTHMA TRAVERSE OLE STUDY (NCT02134028)

- Dupilumab, a fully human monoclonal antibody, blocks the shared receptor component for interleukin (IL)-4/IL-13, key and central drivers of type 2 inflammation in multiple diseases[1–4]
- The single-arm, open-label extension (OLE) LIBERTY ASTHMA TRAVERSE study (NCT02134028) evaluated long-term safety, tolerability, and efficacy of dupilumab in adult and adolescent patients with moderate-to-severe asthma who had previously completed a dupilumab asthma study (phase 2a EXPEDITION [NCT02573233], phase 2b DRI [NCT01854047], phase 3 QUEST [NCT02414854], or phase 3 VENTURE [NCT02528214])
- Patients who were enrolled in TRAVERSE received add-on subcutaneous dupilumab 300 mg every 2 weeks (q2w) for up to 96 weeks

BACKGROUND

- Dupilumab did not affect responses to certain studied inactivated vaccines in patients participating in clinical studies[5]
- The safety and tolerability of administration of live-attenuated vaccines such as yellow fever vaccine (YFV) with concomitant dupilumab treatment has not been previously evaluated
- The current practice is to avoid use of live-attenuated vaccines with dupilumab
- During the conduct of TRAVERSE, there was a yellow fever outbreak in Brazil, and patients in the affected area discontinued dupilumab to receive YFV
  - Patients were eligible to re-start dupilumab at investigator discretion following demonstration of adequate yellow fever neutralization titers
- Safety and efficacy endpoints of dupilumab continued to be monitored

STUDY OBJECTIVE

- **This post hoc analysis provides a descriptive summary of the experience of patients previously treated with dupilumab who received YFV while participating in the TRAVERSE study**
- **The analysis included evaluation of plaque reduction neutralization titers (PRNT), the established correlate of protection of YFV, as well as safety profile and tolerability of YFV**

METHODS

- Patients discontinued dupilumab treatment for at least 7 days prior to a single dose of YFV (YF-17D, Stamaril™)
- Study assessments
  - The following endpoints were evaluated:
    - Dupilumab serum concentrations on or before vaccination, and 28–54 days after vaccination
    - PRNT
    - Safety profile and tolerability of YFV
  - Due to the emergent and responsive nature of this event, endpoints were not captured at specific timepoints, and all endpoints were not captured for all patients

Table 1. Patient demographics and disease characteristics.

	Patients from QUEST		Patients from VENTURE		Combined
	Placebo/ dupilumab (n = 11)	Dupilumab/ dupilumab (n = 22)	Placebo/ dupilumab (n = 3)	Dupilumab/ dupilumab (n = 1)	All (N = 37)
Age, mean (SD), years	48.1 (11.3)	44.9 (11.8)	47.0 (17.1)	63.0 (NC)	46.5 (12.0)
Male, n (%)	5 (45.5)	5 (22.7)	1 (33.3)	1 (100)	12 (32.4)
BMI, mean (SD)	31.52 (5.27)	29.52 (6.21)	28.65 (5.64)	30.23 (NC)	30.06 (5.74)
Dupilumab serum concentration,[a] mg/L	56.5 (41.0)	58.0 (35.8)	85.6 (33.2)	45.2 (NC)	59.5 (36.7)
Race, n (%)					
Caucasian/White	5 (45.5)	14 (63.6)	2 (66.7)	0	21 (56.8)
Black/of African descent	3 (27.3)	5 (22.7)	1 (33.3)	1 (100)	10 (27.0)
Other	3 (27.3)	3 (13.6)	0	0	6 (16.2)
Ethnicity, n (%)					
Hispanic	7 (63.6)	17 (77.3)	0	0	24 (64.9)
Not hispanic	4 (36.4)	5 (22.7)	3 (100)	1 (100)	13 (35.1)
Ongoing atopic medical condition,[b] n (%)	9 (81.8)	21 (95.5)	3 (100)	1 (100)	34 (91.9)
Atopic dermatitis	1 (9.1)	2 (9.1)	0	0	3 (8.1)
Allergic rhinitis	7 (63.6)	21 (95.5)	3 (100)	1 (100)	32 (86.5)
Chronic rhinosinusitis	2 (18.2)	1 (4.5)	0	0	3 (8.1)
Hives, n (%)	1 (9.1)	1 (4.5)	1 (33.3)	0	3 (8.1)
BL IgE ≥100 IU/mL AND ≥1 BL aeroallergen specific-IgE ≥0.35 IU/mL, n (%)	6 (54.5)	14 (63.6)	2 (66.7)	0	22 (59.5)

Dupilumab/dupilumab patients received dupilumab in the parent study and placebo/dupilumab patients received placebo in the parent study.
[a]Obtained at last visit prior to vaccination.
[b]Ongoing atopic medical conditions included atopic dermatitis, allergic conjunctivitis, allergic rhinitis, chronic rhinosinusitis, nasal polyposis, food allergy, and hives history.
BL, baseline; BMI, body mass index; NC, not calculated; SD, standard deviation.

RESULTS

- Dupilumab concentrations were assessed in most patients 1–25 days before (n = 16) or on the same day of (n = 19) vaccination, with 2 patients missing a pre-vaccination pharmacokinetics (PK) sample
- Pre- and post-YFV PRNT were obtained in 23 of 37 patients; dupilumab serum concentrations were assessed on the day of vaccination in 15 of these patients

Table 2. Patients with pre- and post-vaccination pharmacokinetics and neutralizing antibody titer samples.

	Patients with PK pre-YFV sample on the same day of vaccination (n)	Patients with PK pre-YFV sample 1–25 days before vaccination (n)	Patients without PK pre-YFV sample (n)
PK population (N = 37)	19	16	2
Pre-/post-YFV PRNT titers obtained (n = 23)	15	8	0
Post-YFV PRNT titers only (n = 14)	4	8	2

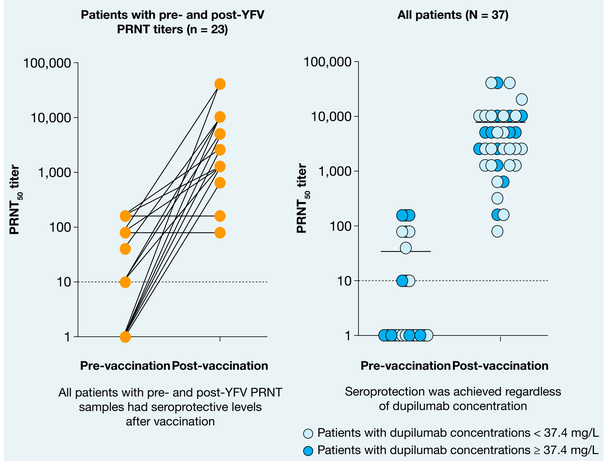
Table 3. Dupilumab pharmacokinetics in patients with pre- and post-vaccination serum samples and neutralizing antibody titers.

	Patients from QUEST		Patients from VENTURE		Combined
	Placebo/ dupilumab (n = 7)	Dupilumab/ dupilumab (n = 12)	Placebo/ dupilumab (n = 3)	Dupilumab/ dupilumab (n = 1)	All (N = 23)
Last visit before yellow fever vaccination					
Dupilumab serum concentration (mg/L), mean (SD)	56.0 (44.0)	59.2 (36.2)	85.6 (33.2)	45.2 (NC)	61.0 (37.2)
First visit after yellow fever vaccination					
Dupilumab serum concentration (mg/L), mean (SD)	14.4 (14.6)	8.3 (9.7)	26.9 (29.7)	6.8 (NC)	12.5 (15.0)

Safety profile

- Only 1 out of 37 patients reported a vaccine-related adverse events (AE)
  - Non-serious body ache, malaise, dizziness
  - Resolved within 2 weeks
  - Consistent with known vaccine safety profile
- The remaining 36 patients had no vaccine-related AE
- No vaccine hypersensitivity was reported

Figure. Plaque reduction neutralizing antibody titers pre- and post-vaccination.



Concentrations in serum above 37.4 mg/L were assumed to be therapeutic and consistent with saturating levels of IL-4Rα blockade, since 37.4 mg/L was the steady state mean trough concentration observed for asthma patients at 200 mg q2w in the parent phase 3 study.
A titer < 1:10 is defined as seronegative, and those values were designated "1."
$PRNT_{50}$, the reciprocal dilution in which 50% of the virus was neutralized.

Limitations

- Samples were collected as available due to the emergent and responsive nature of this substudy
- This is a post hoc analysis that provides a description of the experience for patients previously taking dupilumab who were provided YFV and was conducted in a small number of patients
- This analysis provides data to support further investigation into the safety and tolerability of live-attenuated vaccines during dupilumab administration

CONCLUSIONS

- **These data suggest that dupilumab had no apparent impact on the neutralizing titers to the live-attenuated YFV**
- **Further studies are warranted to investigate the effect of dupilumab on live-vaccine–induced immune responses**

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