

Tralokinumab prevents flares in moderate-to-severe atopic dermatitis: post hoc analyses of a randomized phase 3 clinical trial (ECZTRA 3)

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Background

Atopic dermatitis (AD) is a chronic, inflammatory skin disease characterized by periods of acute symptomatic worsening (flares). Tralokinumab is a fully human, high-affinity, monoclonal antibody that specifically neutralizes interleukin (IL)-13 cytokine, a key driver of cutaneous barrier dysfunction, inflammation and dysbiosis in AD. Severe AD flares prompt rescue therapy with high-potency topical corticosteroids (TCS), systemic steroids, and antibiotics, and can lead to both emergency room visits and hospitalizations. Flare-prevention is one of the primary goals for long-term control of AD. Flares are commonly defined as a worsening of AD requiring treatment intensification or escalation (i.e. addition of high-potency TCS, oral corticosteroids, or immunosuppressants) that may impact the flare frequency measured, particularly in moderate-to-severe AD. Here we assessed the impact of tralokinumab treatment on flare prevention in adults with moderate to-severe AD.

Methods

ECZTRA 3 was a randomized, double-blind, placebo-controlled phase 3 clinical trial in adults with moderate-to-severe AD (NCT03363854)^a. Patients were treated with either 300 mg tralokinumab (n=252) or placebo (n=126) every 2 weeks (Q2W) in combination with TCS (mometasone furoate 0.1% cream applied on lesional skin as needed) for an initial 16 weeks. Thereafter, tralokinumab-treated patients continued on either Q2W or Q4W+TCS for an additional 16 weeks. AD flares, defined as worsening of the disease that required escalation/intensification of AD treatment including initiation or intensification of the supplied TCS ('per protocol flare'), were measured throughout the trial (32 weeks). We present post hoc analyses of flare occurrence, as defined by treatment intensification to either high-potency TCS, oral corticosteroids, and other systemic treatments ('rescue flare'). Adverse event (AE) reporting of 'dermatitis atopic' or 'dermatitis infected' were analyzed to reflect AD worsening to a degree beyond normal fluctuation ('AE flare'). Time to first flare was analyzed using a Cox proportional hazard model stratified by region and baseline IGA with planned treatment as covariate.

Results

Treatment groups were well-balanced with respect to AD severity at baseline (Week 0). Overall, 7 (2.8%) patients reported a 'rescue flare' in the tralokinumab+TCS group compared to 13 (10%) in the placebo+TCS group during the first 16 weeks, corresponding to a 74% risk reduction with tralokinumab (hazard ratio, HR= 0.26; CI_{95%}: 0.10-0.65; *P*=0.004). Similarly, 6 (2.4%) patients reported an 'AE flare' in the tralokinumab+TCS group versus 14 (11%) with placebo+TCS during the first 16 weeks, corresponding to an 80% risk reduction with tralokinumab (HR= 0.20; CI_{95%}: 0.08-0.53; *P*=0.001). The risk of a 'rescue flare' or 'AE flare' (which ever occurred first) was 77% lower with tralokinumab (HR=0.23; CI_{95%}: 0.11-0.50; *P*<0.001). The proportion of patients with a 'per protocol flare' during the initial 16-week treatment period was numerically lower in the tralokinumab+TCS group (28%, 70/252) compared to the placebo+TCS group (34%, 43/126, HR=0.79, 95% CI_{95%}: 0.54-1.16).

Among patients who received tralokinumab+TCS during the entire 32-week treatment period, the majority, i.e. 65% (163/252) did not report a 'per protocol flare', and nearly all did not report a 'rescue flare' (96%, 241/252) or an 'AE flare' (94%, 236/252) during the 32 weeks. The cumulative amount of TCS used was approximately 30% lower in tralokinumab+TCS group compared to the placebo+TCS group, both in the overall population and among patients who reported a 'per protocol flare' between Week 0 and 16.

Conclusions

Tralokinumab treatment reduced the risk of ‘rescue flares’ by 74% relative to placebo when used in combination with TCS in adults with moderate-to-severe AD. Nearly all patients (96%) remained free of ‘rescue flares’ with tralokinumab + TCS during the entire 32-week treatment period. We propose ‘rescue flares’ as a clinically relevant flares outcome measure in moderate-to-severe AD that highlights flares where moderate potency TCS treatment intensification is insufficient.

^aSilverberg JI, Toth D, Bieber T, et al, Tralokinumab plus topical corticosteroids for the treatment of moderate-to-severe atopic dermatitis: results from the double-blind, randomized, multicentre, placebo-controlled phase III ECZTRA 3 trial. *Br J Dermatol*. 2020 Sep 30. DOI: 10.1111/bjd.19573. Online ahead of print.