Biologics in Dermatology

David E. Cohen, M.D., M.P.H.
Charles and Dorothea Harris Professor and Vice Chairman for Clinical Affairs
Director of Allergic, Occupational and Environmental Dermatology
New York University Grossman School of Medicine Department of Dermatology
The emerging immunopathology of atopic dermatitis: Therapeutic targets

AP, antimicrobial peptide; DC, dendritic cell; KC, keratinocytes; IL-4Rα, IL-4 receptor alpha subunit

- Barrier disruption
- Decreased KC differentiation
- Decreased AP expression

- KC differentiation
- Hyperplasia
- Barrier inhibition
- S100 proinflammatory proteins

- T cell chemotaxis
- Th2 inhibition

**Antigen/microbiome changes**

- Disrupted barrier (↓filaggrin)

**Disrupted barrier**

- Itch/scratch cycle
- Pruritus

**Barrier disruption**
- Decreased KC differentiation
- Decreased AP expression

**Barrier inhibition**
- KC differentiation
- S100 proinflammatory proteins

**Itch/scratch cycle**
- Pruritus

**JAK/STAT signaling**
- Keratinocyte differentiation and barrier integrity
- Th2 differentiation
- Pruritus

**Therapeutic targets**

1. Anti–IL-4Rα: Dupilumab, CBP-201
2. Anti–IL-13: Tralokinumab, lebrikizumab
3. Anti–IL-33: MSTT1041A
4. Anti–IL-31: Nemolizumab
5. Anti–IL-1α: Bermekimab
6. Anti–OX40: GBR 830, KHK4083, KY1005 (anti–OX40L)
7. Oral JAK inhibitors: Abrocitinib, baricitinib, gusacitinib (ASN002), jaktinib, PF-06700841, SHR0302, upadacitinib

**Topical JAK inhibitors:** ARQ-252, ATI-502, delgocitinib, ruxolitinib
SOLO-1 and SOLO-2: Efficacy of **dupilumab** in moderate to severe AD at Week 16

For binary outcomes, patients were categorized as nonresponders from the time rescue medication was used; NRI

*P<0.0001 vs placebo

For binary outcomes, patients were categorized as nonresponders from the time rescue medication was used; NRI

Coprimary endpoint in EU and Japan; key secondary endpoint in other regions.

Simpson EL, et al. EADV 2016, D3T01.1C Sponsored by Sanofi and Regeneron Pharmaceuticals, Inc.

http://investor.regeneron.com/releasedetail.cfm?releaseid=974316

IL-4/13 inhibition
SOLO-1 and SOLO-2: Effect of dupilumab on EASI % change and itch from baseline

Censored analysis categorized patients who received rescue treatment as missing data from the time of rescue, missing data were imputed by multiple imputation. Results appear similar in the uncensored population; thus, no change due to rescue medication

*P<0.0001 vs placebo

Simpson EL, et al. EADV 2016, D3T01.1C Sponsored by Sanofi and Regeneron Pharmaceuticals, Inc.
SOLO-1 and SOLO-2: Safety profile of dupilumab through Week 28

| Event                                      | Placebo qw (n=222) | Dupilumab 300 mg q2w (n=229) | Dupilumab 300 mg qw (n=218) | Placebo qw (n=234) | Dupilumab 300 mg q2w (n=236) | Dupilumab 300 mg qw (n=237) |
|--------------------------------------------|--------------------|-------------------------------|-----------------------------|--------------------|-------------------------------|-------------------------------|
| ≥1 AE                                      | 145 (65)           | 167 (73)                      | 150 (69)                    | 168 (72)           | 154 (65)                      | 157 (66)                      |
| ≥1 SAE                                     | 11 (5)             | 7 (3)                         | 2 (1)                       | 13 (6)             | 4 (2)                         | 8 (3)                         |
| Death<sup>a</sup>                          | 0                  | 0                             | 0                           | 0                  | 1 (<1)                        | 1 (<1)                        |
| AEs leading to treatment discontinuation   | 2 (1)              | 4 (2)                         | 4 (2)                       | 5 (2)              | 2 (1)                         | 3 (1)                         |
| Infections and infestations<sup>b</sup>    | 63 (28)            | 80 (35)                       | 74 (34)                     | 76 (33)            | 65 (28)                       | 68 (29)                       |
| Skin infections (adjudicated)              | 18 (8)             | 13 (6)                        | 14 (6)                      | 26 (11)            | 14 (6)                        | 15 (6)                        |
| Non-skin infections                        | 49 (22)            | 69 (30)                       | 67 (31)                     | 57 (24)            | 58 (25)                       | 61 (26)                       |
| Herpes viral infections<sup>c</sup>        | 9 (4)              | 15 (7)                        | 9 (4)                       | 8 (3)              | 10 (4)                        | 12 (5)                        |

- Phase 3 study of dupilumab repeated the impressive efficacy seen in earlier phase trials
- Herpes infections and conjunctivitis are the 2 AEs of interest, but do not appear serious; etiology of conjunctivitis unknown

**Conjunctivitis 7-12% dupilumab; 2% placebo**

26% of patients in both studies reported a history of allergic conjunctivitis at study entry. Injection site reactions: 10-20% dupilumab; 7-8% placebo.

---

<sup>a</sup>Deaths were judged not to be treatment-related; 1 severe asthma attack (patient had a history of asthma since 1990), 1 suicide (patient had a history of depression and suicidal ideation, and family history of suicide); <sup>b</sup>MedDRA System Organ Class; <sup>c</sup>MedDRA High Level Term Simpson EL, et al. EADV 2016, D3T01.1C Sponsored by Sanofi and Regeneron Pharmaceuticals, Inc.
LIBERTY AD SOLO CONTINUE: Randomized double-blind trial of altered dosing frequencies with dupilumab monotherapy among adult patients with AD

Key inclusion criteria:
• Patients who achieved IGA 0/1 or EASI 75 from baseline to Week 16 in SOLO 1 and 2

Endpoints include:
• % change in EASI from SOLO CONTINUE baseline to Week 36
• % of patients maintaining EASI 75 from SOLO CONTINUE baseline to Week 36
• Mean change in NRS itch from SOLO CONTINUE baseline to Week 35
• Mean change in DLQI from SOLO CONTINUE to Week 36

Serra-Baldrich E et al. EADV 2019, P0281 Sponsored by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.
LIBERTY AD SOLO CONTINUE: Mean changes from baseline in EASI score, peak pruritus and DLQI, and EASI 75 response

Efficacy outcomes at Week 36 of the SOLO CONTINUE trial

Change in EASI

Peak pruritus NRS score

Maintenance of EASI 75 response

Change in DLQI

Extension of dosing interval in responding patients not a valuable option for dupilumab in many patients

Missing data imputed using multiple imputation for continuous endpoints. Patients receiving rescue treatment (topical or systemic AD therapies) or discontinued considered non-responders

Serra-Baldrich E et al. EADV 2019, P0281 Sponsored by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.
Incidence of conjunctivitis was low and similar for DUP and placebo

| n (%) | Placebo (n=82) | DUP 300 mg q8w (n=84) | DUP 300 mg q4w (n=87) | DUP 300 mg qw/q2w (n=167) |
|-------|----------------|------------------------|------------------------|---------------------------|
| ≥ 1 TEAE | 67 (81.7) | 65 (77.4) | 64 (73.6) | 118 (70.7) |
| TEAE leading to permanent study treatment discontinuation | 3 (3.7) | 0 | 2 (2.3) | 0 |
| Death | 0 | 0 | 1a (1.1) | 0 |
| Treatment-emergent SAE | 1 (1.2) | 3 (3.6) | 4 (4.6) | 7 (4.2) |
| TEAEs occurring in ≥ 5% patients | | | | |
| AD | | | | |
| Nasopharyngitis | 40 (48.8) | 27 (32.1) | 30 (34.5) | 34 (20.4) |
| Upper respiratory tract infection | 11 (13.4) | 11 (13.1) | 11 (12.6) | 32 (19.2) |
| Headache | 6 (7.3) | 7 (8.3) | 5 (5.7) | 13 (7.8) |
| Oral herpes | 2 (2.4) | 3 (3.6) | 5 (5.7) | 8 (4.8) |
| Influenza | 3 (3.7) | 5 (6.0) | 2 (2.3) | 3 (1.8) |
| Bronchitis | 1 (1.2) | 0 | 5 (5.7) | 4 (2.4) |
| Conjunctivitisb | 1 (1.2) | 0 | 5 (5.7) | 3 (1.8) |
| Condictivitis | | | 4 (4.6) | 9 (5.4) |
| Non-herpetic skin infectionsc | 8 (9.8) | 5 (6.0) | 1 (1.1) | 4 (2.4) |
| Injection site reaction | 7 (8.5) | 7 (8.3) | 6 (6.9) | 18 (10.8) |

aHomicide; bIncluding the preferred terms: conjunctivitis (bacterial, viral, allergic), and atopic keratoconjunctivitis; cAdjudicated, including tinea versicolor, folliculitis, impetigo, bacterial skin infection, limb abscess, localized infection, staphylococcal skin infection, subcutaneous abscess, tinea cruris

Serra-Baldrich E et al. EADV 2019, P0281 Sponsored by Sanofi Genzyme and Regeneron Pharmaceuticals, Inc.
ECZTRA 1 and 2: Phase 3, randomized, double-blind, placebo-controlled trials of tralokinumab monotherapy for adults with moderate to severe AD

Inclusion criteria
- IGA score ≥3, ≥10% BSA involved, EASI score ≥16
- 2-week washout for TCS/TCI
- TCS permitted as rescue therapy

ECZTRA 1 and 2: Patients achieving coprimary endpoints at Week 16 (NRIb)

ECZTRA 1: ≥4-point reduction in worst itchc NRS from baseline through Week 16 (NRIb)

ECZTRA 1 and 2: Tralokinumab respondersd maintaining EASI 75 response at Week 52 (NRIp)

*S≤0.01, †P<0.001 vs placebo; aAnd EASI ≥12 at screening; bPatients who used rescue TCS were considered nonresponders and missing data imputed with nonresponder imputation; cWorst itch assessed daily (weekly values average); dPatients achieving EASI 75 at Week 16

Simpson EL, et al. AAD 2020, Late-breaking research: Clinical trials
Pooled safety of tralokinumab from 5 Phase 2 and 3 placebo-controlled trials for adults with moderate to severe atopic dermatitis

- Pooled safety from three Phase 3 (ECZTRA 1–3) and two Phase 2 (ECZTRA 5, Phase 2b) trials
- Data from initial 16-week (ECZTRA trials) and 12-week (Phase 2b) periods

### Baseline demographics

| n (%) unless specified | Tralokinumab q2w (n=1605) | Placebo (n=680) |
|------------------------|----------------------------|-----------------|
| Age ≥65 years old      | 77 (5)                     | 32 (5)          |
| Mean BSA affected, % ±SD | 51 ±24                     | 50 ±25          |
| IGA 3                  | 840 (52)                   | 362 (53)        |
| >3                     | 765 (48)                   | 318 (47)        |

### Overall safety summary

| n (adjusted %) | Tralokinumab q2w (n=1605; pt-y=473) | Placebo (n=680; pt-y=193) |
|----------------|---------------------------------------|---------------------------|
| Any AE         | 1080 (66)                             | 449 (67)                  |
| Serious AE     | 37 (2)                                | 18 (3)                    |
| Severity of AE |                                       |                           |
| Mild           | 881 (53)                              | 326 (49)                  |
| Moderate       | 518 (32)                              | 258 (39)                  |
| Severe         | 77 (5)                                | 40 (6)                    |
| AE leading to drug withdrawal | 38 (2.3)                          | 20 (3)                    |

### Most frequent adverse events leading to discontinuation

| n (adjusted %) | Tralokinumab q2w (n=1605; pt-y=473) | Placebo (n=680; pt-y=193) |
|----------------|---------------------------------------|---------------------------|
| Atopic dermatitis | 7 (0.4)                              | 10 (1.5)                  |
| Injection site reaction | 5 (0.3)                       | 0                         |
| Eosinophilia     | 3 (0.2)                               | 0                         |
| Conjunctivitis   | 2 (0.1)                               | 0                         |

- Outcomes of adverse events were similar with tralokinumab and placebo-treated patients: 60% of events were recovered or resolved
- Safety profile of tralokinumab through 52 weeks was consistent with the initial 12/16-week treatment periods based on frequency of AEs, SAEs, severe Aes, and AEs leading to discontinuation

Cumulative safety record appears good, without remarkable adverse events and with low numbers of drug discontinuation

Study demonstrates specific IL-13 blockade shows similar safety as seen with dupilumab (although not possible to make a direct comparison between trials)

pt-y, patient-years of exposure; aCochran-Mantel-Haenszel weights applied to calculate adjusted AE rates; bBy MedDRA preferred term

Simpson E, et al. EADV 2020, P0218 Sponsored by LEO Pharma
Phase 2b randomized, double-blind, placebo-controlled trial: Efficacy and safety of lebrikizumab monotherapy for adults with moderate to severe AD

Inclusion criteria
- IGA score ≥3, ≥10% BSA involved, EASI score ≥16
- 1-week washout for TCS/TCI
- TCS rescue was permitted; patients using TCS rescue were included in the primary analysis

Sensitivity analysis: Patients achieving EASI 75 at Week 16 (NRI for TCS rescue, LOCF for missing data)

Primary analysis: Patients achieving ≥4-point reduction from baseline in pruritus NRS through Week 16 (AO, including TCS rescue)

Key safety event, n (%)

|                          | Placebo q2w | LBK 125 mg q4w | LBK 250 mg q4w | LBK 250 mg q2w |
|--------------------------|-------------|----------------|----------------|----------------|
| Herpes infections        |             |                |                |                |
| Oral herpes              | 2 (4)       | 2 (3)          | 4 (5)          | 2 (3)          |
| Herpes zoster            | 0           | 0              | 0              | 0              |
| Genital herpes           | 0           | 1 (1)          | 0              | 0              |
| Herpes simplex           | 1 (2)       | 1 (1)          | 0              | 0              |
| Eczema herpeticum        | 1 (2)       | 0              | 0              | 0              |
| Conjunctivitis           | 0           | 1 (1)          | 3 (4)          | 2 (3)          |

*P=0.004, †P<0.001 vs placebo

Guttman-Yassky E, et al. JAMA Dermatol 2020;156:411–20