Psoriasis: Update on Modern Therapies

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DISCLOSURE OF RELEVANT RELATIONSHIPS WITH INDUSTRY

Psoriasis Cardiovascular Comorbidities
F10
Bruce Strober, MD, PhD

Baseline
Week 12

PASI Score = 43.9
PASI Score = 0.4
Phase 1 study: Safety and efficacy of BI 655130, an anti-IL-36 receptor antibody, in patients with acute generalized pustular psoriasis

**Patient eligibility**

- Age 18–75 years
- Known and documented history of GPP regardless of IL36RN mutation status
- Moderate to severe flare of GPP with ≥10% BSA involvement
- GPPGA score ≥3

**Exclusions**

- Immediate life-threatening flare of GPP or requiring intensive care
- Acute general pustulosis, TEN or Stevens-Johnson syndrome

**Summary of AEs through Week 20**

<table>
<thead>
<tr>
<th>AE</th>
<th>BI 655130 10 mg/kg (n=7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>7 (100)</td>
</tr>
<tr>
<td>Severe AE</td>
<td>0</td>
</tr>
<tr>
<td>Drug-related AE</td>
<td></td>
</tr>
<tr>
<td>Eosinophilia</td>
<td>4 (57.1)</td>
</tr>
<tr>
<td>Vomiting</td>
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</tr>
<tr>
<td>Chills</td>
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</tr>
<tr>
<td>Pain</td>
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<td>UTI</td>
<td>1 (14.3)</td>
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<tr>
<td>Infusion-related reaction</td>
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</tr>
<tr>
<td>Arthralgia</td>
<td>1 (14.3)</td>
</tr>
</tbody>
</table>

**AEs leading to discontinuation**

0

**Serious drug-related AEs**

0

**Preliminary evidence in support of safety and efficacy of IL-36R inhibition to treat GPP flares**

Patients with GPPGA 0/1 (%) achieved in 5 patients (71.4%) by Week 1, and in all patients by Week 4.

**Phase 1 study: Safety and efficacy of BI 655130 for acute generalized pustular psoriasis**

**Summary of AEs through Week 28**

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**Preliminary evidence in support of safety and efficacy of IL-36R inhibition to treat GPP flares**

GPPGA score 0/1 achieved in 5 patients (71.4%) by Week 1, and in all patients by Week 4.

**Psoriasis pathophysiology**

Small molecule: BMS-986165, a selective oral TYK2 inhibitor

**Inclusion criteria**
- BMI ≥ 18 kg/m²
- sPGA ≥ 3
- BSA ≥ 10%
- PASI ≥ 12

**Exclusion criteria**
- Use of UST, IL, or TNFi within 2 months
- Prior lack of response to IL, TNFi, or UST
- Use of UST, IL, or TNfi within 6 months or
- Prior biologic use
- 20 (44)
- 19 (43)
- 18 (41)
- 17 (42)
- 16 (40)
- 15 (39)
- 14 (38)
- 13 (37)
- 12 (36)
- 11 (35)
- 10 (34)
- 9 (33)
- 8 (32)
- 7 (31)
- 6 (30)
- 5 (29)
- 4 (28)
- 3 (27)
- 2 (26)
- 1 (25)

**Screening**
- 986165 12 mg (n=45)
- 986165 6 mg bid (n=45)
- 986165 3 mg bid (n=45)
- Placebo (n=45)

**Baseline characteristics**
- Male 46 (41%)
- Ethnicity:
  - Asian 6 (14%)
  - White 35 (80%)

**Primary endpoint**
- BMS-986165 does not affect biomarkers of JAK inhibition

**TYK2 mediates signaling of fewer cytokines compared with JAKs 1–3**
- BMS-986165 is a molecule that binds selectively to a regulatory domain of TYK2 and changes its conformation such that the kinase activity is inactivated
- This approach has more selectivity than any previous attempt to target the kinase domain of JAKs

**Safety**
- No serious adverse events were observed in the placebo group.
- The most common adverse events in the 986165 group were diarrhea, nausea, and headache.

**Key references**
- BMS-986165 is a selective oral TYK2 inhibitor
- This approach has more selectivity than any previous attempt to target the kinase domain of JAKs
- This trial demonstrates the efficacy and safety of BMS-986165 in patients with moderate to severe psoriasis.
Phase 2 trial: PASI responses over 12 weeks following treatment with BMS-986165

Phase 2 trial: Safety outcomes following 12 weeks’ treatment with BMS-986165

IL-17A and IL-17F inhibitor: Bimekizumab
Data suggest IL-17FF homodimer is an active signaling component in psoriasis. PASI 100 responses at Week 12 are robust and exceed those of IL-23 inhibitors, but caution is needed in interpretation as there are no head-to-head studies.

Conclusions: IL-17 inhibitors

- Robust and fast-acting efficacy
  - Dosing: more frequent
  - Consistent dosing required; treatment breaks and interval lengthening bad
- Efficacy for psoriatic arthritis → apparently equivalent to TNF-inhibitors for most aspects
  - Peripheral and axial disease
  - Inhibition of progression of joint destruction
- Efficacy in special areas: scalp, genital, palmoplantar, nails
- Reduction of systemic inflammation? Left to be seen.
- Avoid in patients with inflammatory bowel disease

**Guselkumab vs Secukinumab H2H**

![BE ABLE 1: PASI responses over 12 weeks with bimekizumab for moderate to severe psoriasis](image)

![ECLIPSE: Phase 3 trial comparing 1-year efficacy of guselkumab and secukinumab for patients with moderate to severe psoriasis](image)
IL-23 (p19) inhibitors: Tildrakizumab (approved for moderate to severe psoriasis)

- PASI 100: PGA score of clear or minimal with ≥2-grade reduction from baseline
  - *P<0.001 vs placebo; †P<0.05, ‡P<0.001 vs ETN; P-values unadjusted for multiplicity; calculated using the Cochran-Mantel-Haenszel test stratified by body weight (≤90 kg, >90 kg) and prior biologic exposure for psoriasis.

Data as observed; NRI at Week 12

Reich K, et al. EADV 2016, D3T01.1I

reSURFACE 2: PASI and PGA responses with tildrakizumab in chronic plaque psoriasis

<table>
<thead>
<tr>
<th>Study</th>
<th>PASI 75</th>
<th>PASI 90</th>
<th>PASI 100</th>
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<tr>
<td>TIL 100 mg</td>
<td>28</td>
<td>42</td>
<td>58</td>
</tr>
<tr>
<td>TIL 200 mg</td>
<td>39</td>
<td>48</td>
<td>59</td>
</tr>
<tr>
<td>Placebo</td>
<td>22</td>
<td>37</td>
<td>48</td>
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Responders (%)

- PASI 75: 40
- PASI 90: 20
- PASI 100: 20

Weeks

- Patients who took ≥1 dose of Part 1 study medication based on the treatment actually received
- reSURFACE 1: Study medication withdrawn;
- reSURFACE 2: Patient on TIL 100 mg died, had alcoholic cardiomyopathy and hepatic steatosis, although cause of death was undetermined

IL-23 (p19) inhibitors: Risankizumab (approved for moderate to severe psoriasis)

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Responders (%)

- PASI 75: 40
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Weeks

- Patients who took ≥1 dose of Part 1 study medication based on the treatment actually received
- reSURFACE 1 and 2: Safety summary for Weeks 12–28

<table>
<thead>
<tr>
<th>Study</th>
<th>Episodes</th>
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</tr>
</thead>
<tbody>
<tr>
<td>ReSURFACE 1</td>
<td>118</td>
<td>133</td>
<td>29</td>
</tr>
<tr>
<td>ReSURFACE 2</td>
<td>118</td>
<td>133</td>
<td>29</td>
</tr>
</tbody>
</table>

Serious AEs:

- 7 (2.3)
- 6 (2.0)
- 1 (1.4)
- 1 (1.4)
- 6 (2.0)
- 9 (3.1)
- 14 (4.8)
- 2 (2.8)
- 1 (1.4)

Deaths:

- 0
- 0
- 0
- 0
- 0
- 0
- 0
- 0
- 0

Discontinued due to AEs:

- 3 (1.0)
- 1 (0.3)
- 0
- 0
- 1 (0.3)
- 1 (0.3)
- 3 (1.0)
- 0
- 1 (1.4)

Most common AEs:

- Nasopharyngitis: 12 (4.0)
- URTI: 12 (4.0)
- Arthropathy: 12 (4.0)
- SP: 12 (4.0)
- Local reaction: 12 (4.0)

Data are no. patients (%)

*patients who took ≥1 dose of Part 1 study medication based on the treatment actually received

IL-23 (p19) inhibitors: Tildrakizumab (approved for moderate to severe psoriasis)

- IL-23 (p19) inhibitors: Risankizumab (approved for moderate to severe psoriasis)
ultIMMa-1 and ultIMMa-2: PASI 90 responses with risankizumab through Week 52

Gordon KB, et al. AAD 2018, Late-breaking Research: Clinical Trials; Sponsored by AbbVie and Boehringer Ingelheim

ultIMMa-1 and ultIMMa-2: Safety of risankizumab from Weeks 0–16

Conclusions: IL-23 inhibitors

- Robust and long-lasting efficacy
  - Dosing: infrequent and variable (e.g., every 2 or 3 months)
  - Likely an MoA more tolerant of dosing “laziness”
- Most IL-23 inhibitors provide better efficacy and apparently equivalent safety to ustekinumab
  - Over time, will replace ustekinumab and become first-line
- Efficacy for
  - psoriatic arthritis → phase 2 reveals TNF-i level efficacy for ACR 20/50/70, dactylitis and enthesitis; inhibition of radiographic progression?
  - In practice, efficacy is inconsistent and is reminiscent of ustekinumab
  - reduction of systemic inflammation?
- Appropriate for patients with IBD

Certolizumab pegol: TNF-inhibitor
(approved for moderate to severe psoriasis)
CIMPASI-1 and CIMPASI-2: Maintenance of response with certolizumab pegol during 32-week rerandomized maintenance period

<table>
<thead>
<tr>
<th>CRIB: Prospective, postmarketing, multicenter, PK study of placental transfer of certolizumab pegol</th>
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- 21 pregnant women (RA, Crohn’s disease, PsA, and AS patients) at ≥30 weeks gestation received CZP and doses within 35 days prior to delivery; 16 infants delivered, 2 infants were excluded;
- CZP levels were sampled from mothers, infants, and umbilical cord at delivery and infants at Weeks 4 and 8.

Certolizumab pegol: PEGylated anti-TNFα antibody fragment

Infections and infestations

- TEAEs of interest
- AE leading to discontinuation
- All TEAEs per 100 pt

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Antigen (TNFα) binding site

- Monoclonal
- Fc fragment
- Does not bind C1q or fix complement
- Does not bind Fc receptor

TNF monoclonal antibodies

- Adalimumab and infliximab

- EBV infection
- Herpes dermatitis
- Herpes zoster
- Oral fungal infection
- Latent TB

- Oral candidiasis; 0
- 0
- 0
- 0
- 0
- 0
- 0
- 0
- 0

- Nail Candida; 0
- 0
- 0
- 0
- 0
- 0
- 0
- 0
- 0

- Both basal cell carcinomas. Patients who switched doses could be counted in both CZP groups. Patients randomized to CZP 200 mg q2w who received 400 mg q2w in escape arm were counted in both CZP groups.
**CRIB: Maternal and infant plasma and umbilical cord levels of certolizumab pegol**

- **Plasma CZP levels (n=14 mother–infant pairs)**
  - Mothers: BLQ
  - Infants: 0.1–100 µg/mL
  - LLOQ = 0.032 µg/mL

- **Plasma CZP levels in umbilical cord (n=15)**
  - Mothers: BLQ
  - Infants: 0.1–100 µg/mL
  - LLOQ = 0.032 µg/mL

**Conclusions: certolizumab**

- TNF inhibitor
  - Efficacy comparable to adalimumab, maybe slightly better
  - Less immunogenicity?

- Efficacy for
  - psoriatic arthritis
  - reduction of systemic inflammation

- Appropriate for patients with IBD and other TNF-inhibitor responsive diseases

- No transplacental transfer, and also not delivered to breast milk

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**Apremilast**: PDE-4-inhibitor (approved for moderate to severe psoriasis)

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**Phase 2 open-label study: Change in PASI score with apremilast in pediatric patients with moderate to severe plaque psoriasis**

- **Adolescents (12–17 years), APR20 (n=13)**
  - Week 12: Change from baseline (%): -40.2 ± 9.9
  - Week 24: Change from baseline (%): -37.5 ± 10.2

- **Adolescents (12–17 years), APR30 (n=14)**
  - Week 12: Change from baseline (%): -38.9 ± 11.1
  - Week 24: Change from baseline (%): -36.5 ± 11.0

- **Children (6–11 years), APR20 (n=21)**
  - Week 12: Change from baseline (%): -32.6 ± 10.0
  - Week 24: Change from baseline (%): -30.4 ± 10.5

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**Analyses were performed on the safety population, which included patients who received at least 1 dose of APR.**

- **Adolescents (12–17 years), APR20 (n=13)**
  - Mean change in PASI score: -40.2 ± 9.9
- **Adolescents (12–17 years), APR30 (n=14)**
  - Mean change in PASI score: -38.9 ± 11.1
- **Children (6–11 years), APR20 (n=21)**
  - Mean change in PASI score: -32.6 ± 10.0

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**Apremilast: PDE-4-inhibitor (approved for moderate to severe psoriasis)**

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**Conclusions:**

- TNF inhibitor
  - Efficacy comparable to adalimumab, maybe slightly better
  - Less immunogenicity?

- Efficacy for
  - psoriatic arthritis
  - reduction of systemic inflammation

- Appropriate for patients with IBD and other TNF-inhibitor responsive diseases

- No transplacental transfer, and also not delivered to breast milk
ESTEEM and PALACE: Changes in weight and A1c after 16 weeks of apremilast in patients with psoriasis and PsA

- Reduction in A1c and weight with APR were greater for patients with higher baseline A1c
- Patients using insulin and APR experienced weight loss
- PDE4 inhibition may influence insulin resistance

Apremilast summary

- Oral twice-daily dosing
- Modest efficacy for psoriasis – lowest of all commonly prescribed medications
- No laboratory monitoring
- Safety and tolerability
  - Weight loss, nausea, diarrhea
  - Weight loss correlates with elevated HgB A1C and insulin use
  - Very rare association with depression and suicide
  - Psoriatic arthritis, lower efficacy than TNFa-inhibitors
  - Future labeled indications in pediatric and “moderate” severity populations

Current treatment paradigm

Key points for patients with moderate to severe psoriasis

- Choose therapy based on individual patient characteristics
- Psoriasis treatment is NOT stepwise (ie not required to fail on topicals)
- One drug or modality may succeed when others fail
- Combination therapy may be desirable in some patients
- Consider psoriatic arthritis

Thank you

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