WHAT'S NEW IN THE MEDICINE CHEST? PART 2

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ATOPIC DERMATITIS
SYSTEMIC BIOLOGIC THERAPY

Dupilumab
Fully Human Monoclonal Antibody - Targeted Biologic Therapy
Under Evaluation for Treatment of Atopic Dermatitis

Disclosures

Allergan**
Anacor*
Aqua/Almirall**
Bayer Dermatology**
BioPharmX*
Celgene**
Cutanea*
Dermira*
Ferndale*
Gaiderma**
Genentech*
LeoPharma**
Novartis*
Novan#
Pharmaderm**
Promius**
Sebacia*
SunPharma**
Unilever**
Viamet*
Consultant*, Speaker*, Researcher*
(Updated as of 9-29-16)

Systemic Biologic Therapies for Atopic Dermatitis

Dupilumab
Inhibition of IL-4 and IL-13 Signaling

Molecular Suppression of Atopic Disease (Dermatitis [AD] / Asthma)
Dose-dependent Modulation of Molecular Signature of Atopic Dermatitis

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**Dupilumab**
Clinical Studies in Atopic Dermatitis
Dose-Dependent Suppression of Clinical Disease

- Randomized, Double-Blind, Placebo-controlled Studies (N=207)
  - Two 4-week monotherapy studies (M4A, M4B + other)
  - One 12-week monotherapy study (M12, Europe)
  - One 4-week combination study (C4) with topical corticosteroids (TCs)
  - Once-weekly regimen – dose ranging evaluations
- Moderate-to-Severe Atopic Dermatitis
  - Not adequately controlled with topical therapy
- Endpoint assessments included Eczema Area and Severity Index (EASI) scores, IGA scores, Pruritus, Safety, Serum biomarkers, Disease transcriptome
- Quality of Life (QoL) analysis from clinical trials

1 Beck LA, et al. NEJM. 2014; JULY 10, 2014; 130-139.

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**Dupilumab**
Dose-Dependent Suppression of Clinical Disease
Monotherapy Trials (M4A, M4B, M12)

- M4A, M4B
  - Dupilumab n=51
  - Placebo=16
- M12
  - Dupilumab + TCs n=21
  - Placebo + TCs N=10

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**Pathophysiology & Cascades of Inflammation**
Atopic Dermatitis vs Psoriasis

**Oral Apremilast for Chronic Plaque Psoriasis**
PASI-75, PASI-50, and sPGA Response at Week 16

- PASI-75
- PASI-50
- sPGA

**Mean change from baseline**
Week 16 vs placebo

- PASI-75: 7.5 vs 0.7
- PASI-50: 7.5 vs 0.7
- sPGA: 40 vs 40

**Data at 16 weeks**

- Week 16: 75% of patients achieved PASI-75
- Week 52: 30% of patients achieved PASI-75
Mean Change in Pruritus Visual Analog Score (mm) Over 32 Weeks

**Oral Apremilast 30 mg Twice Daily for Plaque Psoriasis**

**Summary of Pooled Analysis at Week 16 (ESTEEM 1 & ESTEEM 2 Trials)**

- Efficacy noted in all subgroups regardless of baseline characteristics or prior therapies for psoriasis
- Pooled study groups: apremilast 30 mg BID, n=486; placebo BID, n=419
- Efficacy similar regardless of baseline Body Mass Index (BMI)
- PASI-75, PASI-50 and iPGA outcomes demonstrated superiority of oral apremilast as compared to oral placebo at Week 16 across all analyzed subgroups
- Higher overall PASI-75 response rate observed in subjects with PASI score ≥20 at baseline
- Higher overall PASI-75 response in subjects not previously treated with systemic therapy for psoriasis
- Favorable safety profile
  - No major systemic safety signals
  - Most common AEs involve gastrointestinal system (ie nausea, increased bowel movements)
  - Routine laboratory monitoring (CBC, serum chemistries, TB) not suggested in product monograph based on data review

**Oral Apremilast 30 mg Twice Daily for Plaque Psoriasis Two Year (104 Weeks) Safety Data Summary (ESTEEM 1 Trial)**

- Apremilast demonstrated an acceptable safety profile and was generally well tolerated for up to 104 Weeks of exposure
- Most AEs were mild or moderate in severity and did not lead to discontinuation.
- Incidence rates of major cardiac events, solid tumors, hematological malignancies, and serious infections comparable between the apremilast and placebo arms
- No increase in incidence rates was noted with longer term exposure to apremilast between 52-104 weeks
- Majority of subjects receiving apremilast maintained body weight within 5% of baseline independent of duration of exposure.
- No increase in the number of subjects with significant weight loss with longer term apremilast exposure
- No new safety signals for apremilast were identified in the second year of exposure as compared with the first year

**Oral Apremilast 30 mg Twice Daily for Plaque Psoriasis Three Year (182 Weeks) Safety Data Summary (ESTEEM 1 & 2)**

- No increases in severity or frequency of adverse events (AEs) with long-term apremilast treatment up to Week 182; comparison among apremilast-treated subjects over time
- Rates of major cardiac events, malignancies, depression, and suicidality were comparable across the apremilast-exposure periods
- No serious opportunistic infections or reactivation of tuberculosis.
- No clinically relevant changes on laboratory measurements were reported
- Pooled safety analyses from two ESTEEM trials in subjects with ≥20% consistent with pooled safety analyses from three PALACE trials
- Evaluated over the same apremilast exposure periods
- Results consistent among the trials including patient population receiving concomitant DMARDs*, including methotrexate
- Apremilast demonstrated an favorable safety profile and was generally well tolerated
- No safety signals or significant AE incidence changes for up to 182 weeks of apremilast exposure; no significant changes as compared to previous two-year analysis

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**Clients**

Poster Presentation, EADV, Amsterdam, Netherlands, 2014.

**Poster Presentation, SAFE, Amsterdam, Netherlands, 2016.
**Betamethasone Dipropionate-Calcipotriene Aerosol Foam**

- Propellant aerosol foam, emollient, alcohol-free

**Calcipotriene-Betamethasone Dipropionate (CAL-BD) Aerosol Foam (AF) for Chronic Plaque Psoriasis (CPPso) in Adults**

- Efficacy with use of CAL-BD aerosol has been shown to be superior to CAL-BD ointment
  - Based on PGA and mPASI
- Efficacy and tolerability/safety of CAL-BD aerosol foam applied once daily is supported by multiple studies
  - Adults with up to 30% BSA involving the trunk and extremities
- Rapid reduction in pruritus has also been shown
- CAL-BD aerosol foam applied once daily for 4 weeks
  - More efficacious than CAL-BD topical suspension applied once daily for 8 weeks

**Treatment Success (by PGA)**

**Week 4:** Significantly more subjects in Cal/BD aerosol foam arm achieved PASI-75 (P<.001)

Similar trends were seen in PASI-50 improvement for Cal/BD aerosol foam. Week 4: 28.3% in Cal/BD aerosol foam arm achieved PASI-50 vs 28.0% in vehicle-treated arm (P<.001)

mPASI – Head Excluded

**Calcipotriene-Betamethasone Dipropionate (CAL-BD) Aerosol Foam (AF) for Chronic Plaque Psoriasis (CPPso) in Adults**

- CAL-BD aerosol foam demonstrated greater potency than CAL-BD ointment
  - Evaluated by vasoconstrictor assay
- Skin sensitization was not observed and irritation potential was low with CAL-BD aerosol foam and vehicle aerosol foam
  - Evaluated in a cumulative irritation study
- Skin penetration into and through skin of both CAL and BD at all time points
  - CAL-BD aerosol foam >> CAL-BD ointment (2 hrs, 6 hrs, 21 hrs)
- Maximum use-systemic exposure trial with CAL-BD aerosol foam
  - No evidence of Cryoglobulinemia, cutaneous patch test
  - No evidence of adrenal corticosteroid hormone (ACTH) testing at end of study
  - No abnormal values were noted in serum and urinary calcium parameters

**Halobetasol Lotion BID vs Halobetasol Cream BID x 14 Days**

Plaque Psoriasis / Age ≥18 years / Moderate-Severe (IGA ≥3) / BSA ≤20%

**Change from Baseline Severity**

Mean BSA = 17%

**Halobetasol Lotion (Branded)** N=21

**Halobetasol Cream (Branded)** N=22

**GLOBAL ASSESSMENT**

Compliance of drug treatment: Cal/BD aerosol foam vs. Cal/BD vehicle (%)

**TARGET LESION >5cm**

By: John JQ. Submitted for publication, 2016.

**Del Rosso JQ. Submitted for publication, 2016.**


Multiple imputation applied for missing data. Odds ratio calculated using the Cochran-Mantel-Haenszel method adjusted for pooled centers.

Mean BSA = 17%
Halobetasol Lotion BID vs Halobetasol Cream BID x 14 Days
Plaque Psoriasis / Age ≥18 years / Moderate-Severe (IGA >3) / BSA ≤20%

<table>
<thead>
<tr>
<th>% SUBJECTS CLEAR, ALMOST CLEAR, MILD END OF STUDY</th>
</tr>
</thead>
<tbody>
<tr>
<td>--</td>
</tr>
<tr>
<td>Halobetasol Lotion (BRANDED) N=21</td>
</tr>
<tr>
<td>Halobetasol Cream (BRANDED) N=22</td>
</tr>
</tbody>
</table>

BASELINE END OF TREATMENT
DATA ON FILE, SUN PHARMA 2016

Betamethasone Dipropionate Emollient Spray vs Vehicle BID
Moderate Plaque Psoriasis / Mean BSA 13% / Elbows (25%) Knees (12%)
Pooled Treatment Success Analysis (N=538; 2A:1V)

<table>
<thead>
<tr>
<th>% SUBJ Clear, Almost Clear, MILD</th>
<th>Day 8</th>
<th>Day 15*</th>
<th>Day 29**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Betamethasone Dipropionate</td>
<td>p=0.001</td>
<td>p=0.001</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>Dipropionate Emollient Spray</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vehicle</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Primary endpoint  **Secondary endpoint
Treatment success was defined as IGA = 0 or 1 and ≥2 grade reduction from baseline
ITT population. P-values calculated using Cochran-Mantel-Haenszel test

Physical Characteristics of a Lotion Converted to Spray Application

Betamethasone Dipropionate Emollient Spray Twice Daily
Chronic Plaque Psoriasis – Right Elbow

BASELINE  4 WEEKS

Courtesy of James Q. Del Rosso, DO

Betamethasone Dipropionate Emollient Spray Twice Daily
Chronic Plaque Psoriasis – Abdomen

BASELINE  2 WEEKS

Courtesy of James Q. Del Rosso, DO
**Augmented Betamethasone Dipropionate (AugBD) vs Vehicle Treatment**

**Seborrheic Keratosis (SK) Observational Study**

**Location and Number of Lesions by Gender (N=405)**

<table>
<thead>
<tr>
<th>Location</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Faces</td>
<td>4.1</td>
<td>3.4</td>
</tr>
<tr>
<td>Neck/Hairline</td>
<td>4.2</td>
<td>3.7</td>
</tr>
<tr>
<td>Trunk</td>
<td>15.5</td>
<td>15.9</td>
</tr>
<tr>
<td>Arms</td>
<td>7.1</td>
<td>4.4</td>
</tr>
<tr>
<td>Overall</td>
<td>30.9</td>
<td>23.3</td>
</tr>
</tbody>
</table>

**Seborrheic Keratosis (SK) Observational Study**

**Methods of Compensation and Disguise (N=406)**

<table>
<thead>
<tr>
<th>Method of Compensation</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wore a bathing suit (turtlenecks, scarves, long sleeved shirts)</td>
<td>16%</td>
<td>17%</td>
</tr>
<tr>
<td>Avoided wearing make-up</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>Avoided wearing the SKs</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>Wore my hair in a certain style to cover the SKs</td>
<td>7%</td>
<td>8%</td>
</tr>
<tr>
<td>Used non-medicated treatment on the SKs</td>
<td>5%</td>
<td>5%</td>
</tr>
</tbody>
</table>

**Worries about the SKs (N=154)**

- 31% of patients worried about the SKs not looking normal
- 16% of patients worried that the SKs will be noticeable
- 12% of patients worried that the SKs would be a bother
- 7% of patients worried that the SKs would be a problem

**Methods of Compensation and Disguise**

- 39% of patients wore garments that would allow the SKs to show
- 31% of patients avoided wearing clothing that would allow the SKs to show
- 28% of patients avoided wearing clothing that would allow the SKs to show
- 24% of patients avoided wearing clothing that would allow the SKs to show
- 16% of patients avoided wearing clothing that would allow the SKs to show
- 13% of patients avoided wearing clothing that would allow the SKs to show

**Patient Concerns – Health vs Appearance (N=139)**

- 53% of patients worried about the SKs being something serious or something that seriously worried them
- 33% of patients worried about the SKs being something serious and/or something important
- 26% of patients worried about the SKs being something serious and/or something important to them
- 17% of patients worried about the SKs being something serious and/or something that might be serious
- 14% of patients worried about the SKs being something serious and/or something that might be serious

**Was Your Primary Concern in Asking About SKS?**

- Health 5%
- Appearance 17%
- Health vs Appearance 78%

**Mostly a concern about health 5%**

**Mostly a concern about appearance 17%**

**More about appearance than health 14%**

**More about health than appearance 45%**

**Health and Appearance**

- Women significantly more likely to have received prior treatment for their SKs because they did not like the look
- Men are significantly more likely to have received prior treatment for their SKs because their spouse or partner

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**Methods of Compensation and Disguise**

- 39% of patients avoided wearing clothing that would allow the SKs to show
- 31% of patients wore garments that would hide the SKs
- 28% of patients wore garments that would hide the SKs
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- 7% of patients wore garments that would hide the SKs
- 5% of patients wore garments that would hide the SKs
High Concentration $H_2O_2$ Topical Solution (A-101) for Seborrheic Keratoses

**Mechanism of Action**

**PRE-TREATMENT**
- Application of A-101
- Apoptotic and Necrotic SK Cell Death
- Antioxidant Defense System of Skin Neutralizes A-101 by Breaking $H_2O_2$ to $H_2O$ and $O_2$.

**POST-TREATMENT**
- Sloughing of SK Cells
- Lipid Membrane Peroxidation/Lysis
- Proteins Denaturation
- DNA & Mitochondrial Damage (Oxidation)

**Ingenol Mebutate Gel: Prediction of Efficacy for Actinic Keratoses Based on Composite Local Skin Reaction (LSR) Scores on Day 4**

<table>
<thead>
<tr>
<th>Composite LSR Score at Day 4</th>
<th>Expected Percentage Reduction in AKs</th>
<th>90% Prediction Limits</th>
</tr>
</thead>
<tbody>
<tr>
<td>5</td>
<td>68.6%</td>
<td>16.7% to 100.0%</td>
</tr>
<tr>
<td>10</td>
<td>80.7%</td>
<td>50.0% to 100.0%</td>
</tr>
<tr>
<td>15</td>
<td>88.1%</td>
<td>62.5% to 100.0%</td>
</tr>
</tbody>
</table>

- Higher LSR Scores Predicted Greater AK Reduction
- At Low Scores, the LSR had No Predictive Value
- Predicted neither treatment success nor treatment failure


NOT ALL PATIENTS READ THE TEXTBOOK...
...REPEAT THERAPIES...
...TREAT LONGER...

...THANK YOU...