Medical Dermatology Highlights 2017

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Associate, Dermatopathology
Geisinger Medical Center
I have no relevant financial relationships with commercial interest(s).
How do we come up with this talk?

What is most helpful in day to day practice?
What basic knowledge we should all be aware of?
What do I find interesting?
Worth more than their weight in gold?

D. Warren,¹ A. Buteau² and D. Diven¹

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²School of Medicine, University of Texas Medical Branch at Galveston, 301 University Boulevard, Galveston, TX 77555, U.S.A.

Summary

The cost of many topical prescription medications has increased in recent years. We have calculated that the cost per unit now exceeds that of many ‘valuable’ consumer items.
The cost of a cream

• Medication prices are skyrocketing
• Physicians are often unaware of medication pricing
• Study compared some common topicals with “goods that people can relate to”
  • Value per weight
  • Red Book wholesale prices
  • 2007 vs 2015 prices when available

Gold: $35/g

- Which is more expensive?
  - Vanos
  - Carac
  - Jublia
  - Zovirax
  - Penlac

Adele: $326/g

• Still not as much as:

Then and now

- Inflation in US from 2007-2015: 14.3%
- Average price increase: 350%

- “tongue in cheek project” → “realization of unsustainable pattern”
- Where do we go from here?

Efficacy and safety of ustekinumab treatment in adults with moderate-to-severe atopic dermatitis

Saakshi Khattri\textsuperscript{1,2,*} | Patrick M. Brunner\textsuperscript{1,*} | Sandra Garce\textsuperscript{1} | Robert Finney\textsuperscript{3} | Steven R. Cohen\textsuperscript{4} | Margeaux Oliva\textsuperscript{1,2} | Riana Dutt\textsuperscript{1,2} | Judilyn Fuentes-Duculan\textsuperscript{1} | Xiuzhong Zheng\textsuperscript{1} | Xuan Li\textsuperscript{1} | Kathleen M. Bonifacio\textsuperscript{1} | Norma Kunjravia\textsuperscript{1} | Israel Coats\textsuperscript{1} | Inna Cueto\textsuperscript{1} | Patricia Gilleaudeau\textsuperscript{1} | Mary Sullivan-Whalen\textsuperscript{1} | Mayte Suárez-Fariñas\textsuperscript{1,2,5,6} | James G. Krueger\textsuperscript{1} | Emma Guttman-Yassky\textsuperscript{1,2}
Rationale

• AD is strongly Th2/Th22 skewed with some Th1 and Th17 contributions
• AD is associated with IL-12 and IL-23 cytokines (even higher than psoriasis lesions!)
• Some case reports of ustekinumab (IL-12/23 inhibitor) showing efficacy in AD
The trial

• 33 adult patients with moderate to severe AD (SCORAD>15)
• Double blind, placebo controlled, crossover, 40 weeks
• Ustekinumab 0, 4, 16 weeks with crossover at 16, 20, and 32.
  • 45 or 90mg injections (depending on weight < or >100kg)
• Endpoint SCORAD 50% or greater improvement and biopsy characteristics
• Triamcinolone 0.025% cr BID in both groups
Significant decreases in inflammatory markers including Th1, Th2 and Th17 markers (more profound differences in Ustekinumab group)

Conclusions

• Addition of ustekinumab did not significantly change SCORAD50 response rate to triamcinolone
• Both groups showed marked improvement clinically, histologically, molecularly
• Ustekinumab does not adequately treat atopic dermatitis

Topical tofacitinib for atopic dermatitis: a phase IIa randomized trial


1Innovaderm Research, Montreal, QC, Canada
2K Papp Clinical Research and Probit Medical Research Inc., Waterloo, ON, Canada
3Centre de Recherche Dermatologique du Quebec Metropolitain, Quebec, QC, Canada
4Skin Centre for Dermatology and Probit Medical Research Inc., Peterborough, ON, Canada
5The Centre for Dermatology and Probit Medical Research Inc., Richmond Hill, ON, Canada
6Pfizer Inc., Collegeville, PA, U.S.A.
7Pfizer Inc., Groton, CT, U.S.A.


Rationale

• Tofacitinib - JAK1/3 inhibitor
  • Inhibits IL-4, IL-13, and other cytokines in Th2 pathway
• Oral (Xeljanz) approved for RA
  • Shows efficacy for Ps, IBD, AA
• Randomized, double blind, placebo controlled
• 69 adults mild-moderate AD (PGA 2 or 3)
• 2% tofacitinib ointment or vehicle twice daily

• EASI improvement 82%
• 68% clear or almost clear
• 76% improvement in BSA

• EASI50: 90%
• EASI75: 60%
• EASI90: 40%
Tofacitinib for atopic dermatitis

• Well tolerated
  • 1 case furuncle, 1 application site pain, 1 application site pruritus
  • More events in vehicle grp than with tofacitinib

• Low systemic absorption
  • Maximum: 2.72 ng/ml (compared to 17.3ng/ml with 5mg PO BID)
Conclusion

• Appears to be effective for atopic dermatitis
  • Crisaborole: 48-52% clear/almost clear (68% tofacitinib)
• Limitations: Small trial, short duration, mild-moderate disease
• Unknowns: moderate or severe disease, children, comparison to active treatment arm
• Worth further study

Pharmacology and therapeutics

**Hidradenitis suppurativa treated with tetracycline in combination with colchicine: a prospective series of 20 patients**

Kalliopi Armyra, MD, MSc, Anargyros Kouris, MD, MSc, PhD, Vasiliki Markantoni, MD, Andreas Katsambas, MD, PhD, and George Kontochristopoulos, MD, PhD

Hidradenitis

- Common, chronic, debilitating
- Poorly studied therapeutic options
- FDA approval: adalimumab
- Off label: topical and oral antibiotics, systemics

- Open, prospective study of 20 adults with HS
  - Minocycline 100mg/d and colchicine 0.5mg BID x 6 months
    - Then colchicine alone for 3 months
  - Measured PGA and DLQI

<table>
<thead>
<tr>
<th>Patient</th>
<th>Gender</th>
<th>Age, years</th>
<th>Disease duration, years</th>
<th>BMI, kg/m²</th>
<th>Diabetes mellitus</th>
<th>Smoking history, packs/month</th>
<th>Hurley stage Baseline/EoT</th>
<th>DLQI stage Baseline/EoT</th>
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<td>III/I</td>
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<td>12/6</td>
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<td>17</td>
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<td>15/8</td>
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<tr>
<td>18</td>
<td>M</td>
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<td>II/I</td>
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<td>II/I</td>
<td>10/6</td>
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<tr>
<td>20</td>
<td>F</td>
<td>36</td>
<td>6</td>
<td>21.5</td>
<td>No</td>
<td>No</td>
<td>II/I</td>
<td>12/5</td>
</tr>
</tbody>
</table>

BMI, body mass index; EoT, end of treatment; F, female; M, male.

Avg DLQI reduction of 8.7
Table 2 A physician’s global assessment (PGA) scale was used to evaluate the efficacy of treatment with minocycline and colchicine at 3, 6, and 9 months of therapy.

<table>
<thead>
<tr>
<th>PGA score</th>
<th>Patients, n (%)</th>
<th>At 3 months</th>
<th>At 6 months</th>
<th>At 9 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poor (0–25%)</td>
<td>1 (5%)</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Fair (25–50%)</td>
<td>6 (30%)</td>
<td>3 (15%)</td>
<td>1 (5%)</td>
<td></td>
</tr>
<tr>
<td>Good (50–75%)</td>
<td>10 (50%)</td>
<td>9 (45%)</td>
<td>11 (55%)</td>
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</tr>
<tr>
<td>Excellent (75–100%)</td>
<td>3 (15%)</td>
<td>8 (40%)</td>
<td>8 (40%)</td>
<td></td>
</tr>
</tbody>
</table>

Minocin stopped
Conclusions

- Small but compelling study
- Combination well tolerated (nausea, diarrhea but no one d/c therapy) and effective
- Colchicine maintained clearance

Rifampicin + Clindamycin for HS

- Prospective, open label study
  - 26 patients

- Rifampicin 600mg daily and clindamycin 300mg BID
  - Clindamycin: IV 300mg q8hr x 5 d, then oral
  - Rationale: faster onset of action

- 12 week therapy with 1 yr follow up

- **Probiotics**: *Saccharomyces boulardii* 500mg/d

- Outcome: physician global assessment

- Response (>50% improvement) in 73%
- Adverse events (mild) in 31%, 3 discontinued tx
- At 1 year: 59% recur at mean of 4 mos
Conclusion

• Effective but risk of GI toxicity
• Some long term responses off therapy
• IV versus oral clindamycin?
• Both known to be anti-inflammatory as well as antimicrobial
  • Mechanism unclear

FEBRUARY 16, 2017

Top News in Dermatology

FDA approves new psoriasis drug

FDA Press Announcements

The U.S. Food and Drug Administration approved Siliq (brodalumab) to treat adults with moderate-to-severe plaque psoriasis. Siliq is administered as an injection. Siliq is intended for patients who are candidates for systemic therapy (treatment using substances that travel through the bloodstream, after being taken by mouth or injected) or phototherapy (ultraviolet light treatment) and have failed to respond, or have stopped responding to other systemic therapies.

Siliq’s active ingredient (brodalumab) binds to a protein that causes inflammation, inhibiting the inflammatory response that plays a role in the development of plaque psoriasis.

Siliq’s safety and efficacy were established in three randomized, placebo-controlled clinical trials with a total of 4,373 adult participants with moderate-to-severe plaque psoriasis who were candidates for systemic therapy or phototherapy. More patients treated with Siliq compared to placebo had skin that was clear or almost clear, as assessed by scoring of the extent, nature and severity of psoriatic changes of the skin.
Suicide Risk

• Drug is only available through Risk Evaluation and Mitigation Strategy (REMS)
  • Mycophenolate and Thalidomide

• “Prescribers must be certified with the program and counsel patients about this risk. Patients with new or worsening symptoms of depression or suicidality should be referred to a mental health professional, as appropriate.

• Patients must sign a Patient–Prescriber Agreement Form and be made aware of the need to seek medical attention should they experience new or worsening suicidal thoughts or behavior, feelings of depression, anxiety or other mood changes.

• Pharmacies must be certified with the program and must only dispense to patients who are authorized to receive Siliq.”
<table>
<thead>
<tr>
<th>Dataset, indication</th>
<th>N</th>
<th>Exposure Patient-years</th>
<th>Completed suicides, N</th>
<th>Suicide Behaviors/Attempts N</th>
<th>Suicides/100,000 PY</th>
<th>Attempts/100,000 PY</th>
<th>Suicides+Attempts/100,000 PY</th>
<th>Suicidal Ideation, N</th>
<th>Ideation/100,000 PY</th>
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</thead>
<tbody>
<tr>
<td>Brodalumab, all (updated from 120d SU)</td>
<td>6,243</td>
<td>10,438</td>
<td>6**</td>
<td>18</td>
<td>57.5</td>
<td>172.5</td>
<td>229.9</td>
<td>24</td>
<td>229.9</td>
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<tr>
<td>Brodalumab, Ps trials (from 120d SU)</td>
<td>4,464</td>
<td>9162</td>
<td>4**</td>
<td>15</td>
<td>43.7</td>
<td>163.7</td>
<td>207.4</td>
<td>22</td>
<td>240.1</td>
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<td>Adalimumab, Ps</td>
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<td>4,069</td>
<td>1**</td>
<td>0</td>
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<td>3</td>
<td>73.7</td>
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<td>Apremilast, Ps, PSA, RA‡</td>
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<td>1,483</td>
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<td>2</td>
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<td>134.9</td>
<td>202.3</td>
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<td>134.9</td>
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<td>Etanercept, Ps</td>
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<td>36.1</td>
<td>36.1</td>
<td>2</td>
<td>72.1</td>
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<td>Infliximab, Ps</td>
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<td>1,263</td>
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<td>237.5</td>
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<td>Ixekizumab, Ps‡</td>
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<td>0</td>
<td>9†</td>
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<td>140</td>
<td>140</td>
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<tr>
<td>Secukinumab Ps, PSA‡</td>
<td>3,928</td>
<td>3,225</td>
<td>0*</td>
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<td>1</td>
<td>31</td>
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<td>Unapproved biologic, Ps</td>
<td>2,520</td>
<td>3,011</td>
<td>2**</td>
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<td>66.4</td>
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<td>Ustekinumab, Ps Pooled w/o brodalumab, apremilast</td>
<td>3,117</td>
<td>6,791</td>
<td>1</td>
<td>0</td>
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<td>18,613</td>
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<td>14.5</td>
<td>50.7</td>
<td>65.2</td>
<td>7</td>
<td>25.4</td>
</tr>
</tbody>
</table>

Suicide Risk

• Six clinical trials, about 6,200 participants: 6 completed suicides reported in patients receiving drug
  • 4 psoriasis, 1 RA, 1 PsA
  • 4 with NO history of psychiatric d/o
  • 40 events of suicidal ideation and behavior
  • 12-18 fold increased risk with history of suicidality
  • 1 excess suicide per 2600 person years of use

• No causal association has been established

• Psoriasis patients have 30-45% prevalence of psychiatric d/o including Major depression (15%) and suicidal ideation or behavior (7 to 21%)

Brodalumab and depression/anxiety

- Significant improvements in HADS scores for depression and anxiety (p<0.001)

Table 3: Hospital Anxiety and Depression Scale (HADS) scores at week 12: summary of HADS scores

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 220)</th>
<th>Brodalumab 140 mg Q2W (n = 219)</th>
<th>Brodalumab 210 mg Q2W (n = 222)</th>
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</thead>
<tbody>
<tr>
<td><strong>HADS depression score</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>216</td>
<td>216</td>
<td>221</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>5.3 ± 3.9</td>
<td>5.2 ± 4.1</td>
<td>5.5 ± 4.2</td>
</tr>
<tr>
<td>Median (IQR)</td>
<td>5.0 (2.0-8.0)</td>
<td>4.0 (2.0-8.0)</td>
<td>5.0 (2.0-9.0)</td>
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<tr>
<td>Week 12</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SE</td>
<td>5.5 ± 0.3</td>
<td>3.6 ± 0.3</td>
<td>3.5 ± 0.2</td>
</tr>
<tr>
<td>95% CI</td>
<td>4.4-6.6</td>
<td>3.1-4.1</td>
<td>3.0-3.9</td>
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<tr>
<td>** Treatment difference, LS mean ± SE**</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>P-value vs. placebo</td>
<td></td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
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</table>

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<tr>
<td><strong>HADS anxiety score</strong></td>
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<td>Week 12</td>
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<td>5.2 ± 0.3</td>
<td>4.9 ± 0.3</td>
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<tr>
<td>95% CI</td>
<td>4.7-6.9</td>
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<td>** Treatment difference, LS mean ± SE**</td>
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<tr>
<td>P-value vs. placebo</td>
<td></td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
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</table>

n, number of patients randomized; n1, number of patients who were randomized and had a valid measurement value at the specified week; n2, number of patients who were randomized and had a valid measurement value at the specified week, after imputation. P-values are based on an ANOVA model adjusted for baseline bodyweight (≤ 100 kg, > 100 kg), prior biological use (yes, no), geographical region (U.S.A., Canada, outside North America) and baseline HADS subscale score, and are nominal without multiplicity adjustment. Multiple imputation was used to impute missing data with three imputed datasets. Q2W, every 2 weeks; IQR, interquartile range; CI, confidence interval; LS, least squares.

Most improved. Far more worsened on placebo than on drug.

Table 4 Hospital Anxiety and Depression Scale scores at week 12: shifts in anxiety severity groups in patients who scored ‘moderate’ or ‘severe’ at baseline

<table>
<thead>
<tr>
<th>Week 12 shift, n (%)</th>
<th>Placebo (n = 27)</th>
<th>140 mg Q2W (n = 37)</th>
<th>210 mg Q2W (n = 42)</th>
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<td>Improved</td>
<td>8 (30)</td>
<td>25 (68)</td>
<td>28 (67)</td>
</tr>
<tr>
<td>To normal</td>
<td>2 (7)</td>
<td>12 (32)</td>
<td>18 (43)</td>
</tr>
<tr>
<td>Stayed the same</td>
<td>11 (41)</td>
<td>5 (14)</td>
<td>10 (24)</td>
</tr>
<tr>
<td>Worsened</td>
<td>6 (22)</td>
<td>3 (8)</td>
<td>2 (5)</td>
</tr>
</tbody>
</table>

Table 5 Hospital Anxiety and Depression Scale scores at week 12: shifts in depression severity groups in patients who scored ‘moderate’ or ‘severe’ at baseline

<table>
<thead>
<tr>
<th>Week 12 shift, n (%)</th>
<th>Placebo (n = 22)</th>
<th>140 mg Q2W (n = 30)</th>
<th>210 mg Q2W (n = 30)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Improved</td>
<td>10 (45)</td>
<td>23 (77)</td>
<td>22 (73)</td>
</tr>
<tr>
<td>To normal</td>
<td>2 (9)</td>
<td>14 (47)</td>
<td>13 (43)</td>
</tr>
<tr>
<td>Stayed the same</td>
<td>8 (36)</td>
<td>2 (7)</td>
<td>4 (13)</td>
</tr>
<tr>
<td>Worsened</td>
<td>3 (14)</td>
<td>1 (3)</td>
<td>1 (3)</td>
</tr>
</tbody>
</table>

Placebo: 24 moderate and three severe; 140 mg: 23 moderate and 14 severe; 210 mg: 31 moderate and 11 severe. Q2W, every 2 weeks. *Data are as observed, therefore percentages do not add up to 100%.

Conclusion

• High prevalence of psychiatric d/o in our patients
• Be especially careful with Brodalumab
  • Use the registry
• Counsel but reassure patients that most people feel better!

NEJM 2012; 366:1181.
An intensified dosing schedule of subcutaneous methotrexate in patients with moderate to severe plaque-type psoriasis (METOP): a 52 week, multicentre, randomised, double-blind, placebo-controlled, phase 3 trial

Richard B Warren, Ulrich Mrowietz, Ralph von Kiedrowski, Johannes Niesmann, Dagmar Wilsmann-Theis, Kamran Ghoreschi, Ina Zschocke, Thomas M Falk, Norbert Blödorn-Schlicht, Kristian Reich

Methotrexate

• How best to dose and titrate methotrexate?
• Previous studies 5 to 15mg/wk starting dose, varying escalation
• PASI75: 36-42% at 16-24 weeks
• Would SQ be more efficacious? (it is for RA)

Methotrexate

- Randomized, double blind trial of SQ Methotrexate 17.5mg/wk vs Placebo
- 120 adults
- Phase 1: 0-16 weeks: MTX or placebo
- Phase 2: 16-52 weeks: MTX (open label)
- If PASI50 not reached by 8 weeks, dose increased to 22.5mg/wk
- If PASI75 not reached by 24 weeks, increase to 22.5mg/wk
- Folic acid 5mg 24hr after each dose

• PASI75: 41% at 16wk, 51% at 24wk
• PASI90: 27-28% at 52wk
• 78% of responders maintained clearance at 52wks
SQ Methotrexate

- 31% needed dose escalation by 8 wk
- 8 dropped out due to lack of efficacy
- 23 dropped out due to side effects (20%)
  - 23% elevated LFTs – half (12%) stopped MTX
  - 3% discontinued due to nausea/vomiting
  - 2% discontinued due to lymphopenia grd 3

Conclusion

• Intensified dosing can be effective, safe in majority of patients
• PASI75 at 16 weeks (40%) similar to previous studies
• Not as effective as (most) biologics
• Few dropouts due to lack of efficacy
• Remains viable option for many patients

ORIGINAL ARTICLE

Efficacy and safety of permethrin 5% topical gel vs. placebo for rosacea: a double-blind randomized controlled clinical trial

K. Raoufinejad,1,† P. Mansouri,2,† M. Rajabi,1,* Z. Naraghi,3 R. Jebraeli4

1Department of Clinical Pharmacy, Faculty of Pharmacy, Pharmaceutical Sciences Branch, Islamic Azad University, Tehran, Iran
2Skin and Stem Cell Research Center, Tehran University of Medical Sciences, Tehran, Iran
3Departments of Dermatology and Pathology, Tehran University of Medical Sciences, Tehran, Iran
4Department of Dermatology, Tehran Medical Branch, Islamic Azad University, Tehran, Iran

*Correspondence: M. Rajabi. E-mail: mehdijr@acl.co.uk
Permethrin for rosacea

- *Demodex folliculorum* increased density in skin of patients with rosacea
  - Ivermectin approved
  - Cochrane review: inconclusive evidence for permethrin
- Prospective, double-blind, split-face, placebo-controlled trial
- 5% permethrin gel vs placebo
  - Both twice daily
- 34 adults with papulopustular rosacea and ≥5 mites per cm2 (standard skin surface biopsy technique)

### Table 1 Comparison of *Demodex* density (medians) between the placebo and permethrin groups at the baseline, 2nd, 5th, 8th, and 12th weeks

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n = 20)</th>
<th>Permethrin (n = 20)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>217.5</td>
<td>274.1</td>
<td>0.304</td>
</tr>
<tr>
<td>Week 2</td>
<td>185.0</td>
<td>171.5</td>
<td>0.433</td>
</tr>
<tr>
<td>Week 5</td>
<td>135.1</td>
<td>64.4</td>
<td>0.091</td>
</tr>
<tr>
<td>Week 8</td>
<td>92.7</td>
<td>12.0</td>
<td>0.006</td>
</tr>
<tr>
<td>Week 12</td>
<td>98.4</td>
<td>8.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

*Mann–Whitney U-Test.*

- Reduced *Demodex* density between groups
Permethrin superior in reduction of papules and pustules (p=0.040) and improvement in PGA (p=0.022)
Permethrin also decreased telangiectasia compared to baseline (p=0.025)
Permethrin for rosacea

• Side effects common but mild (dryness or burning, itching, erythema)
  • 2 cases of numbness related to permethrin
  • (functions as sodium channel blocker = nerve blockade)

Conclusion

• Causes marked reduction in *Demodex* density
  • ?contamination of contralateral cheek
• Improves some clinical characteristics of rosacea
• Off-label option for recalcitrant papulopustular rosacea, esp if high numbers of *Demodex*

Phototherapy using narrowband ultraviolet B and psoralen plus ultraviolet A is beneficial in steroid-dependent antihistamine-refractory chronic urticaria: a randomized, prospective observer-blinded comparative study

A. Bishnoi, D. Parsad, K. Vinay and M.S. Kumaran

Department of Dermatology, Venereology and Leprology, Postgraduate Institute of Medical Education and Research, Chandigarh, India


Summary
Chronic Urticaria

• Daily hives for >6 weeks
• Therapies:
  • 2\textsuperscript{nd} generation antihistamines (up to 4fold)
    • Up to 50% inadequate response
  • Omalizumab, montelukast, ciclosporin, methotrexate
    • Expense, potential for toxicity
• Need for additional safe, affordable, effective therapies
UV for Chronic Urticaria

- Randomized, prospective, observer-blinded comparative trial
- 50 patients
  - Refractory urticaria (failed 4fold doses of AHs; repeated courses of oral corticosteroids)
  - PUVA (0.6mg/kg 8MOP) or nb-UVB at standard doses three times weekly for 90 days (Fitzpatrick III-V types)
  - Followed off UV for additional 90d
  - Levocetirizine 10mg/d allowed during trial, then down to 5mg/d
- Outcomes: outcome scoring scale (OSS) and urticarial activity score (UAS)

<table>
<thead>
<tr>
<th></th>
<th>Group A (PUVA)</th>
<th>Group B (NB-UVB)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline mean aUAS7</td>
<td>4.9 ± 0.8</td>
<td>5.0 ± 0.7</td>
</tr>
<tr>
<td>Baseline mean OSS</td>
<td>1.6 ± 0.5</td>
<td>1.3 ± 0.5</td>
</tr>
<tr>
<td><strong>Primary end point</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean aUAS7 at end of treatment (day 90)</td>
<td>1.9 ± 0.7</td>
<td>1.4 ± 0.7, (P &lt; 0.05 intergroup)</td>
</tr>
<tr>
<td><strong>Secondary end points</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At end of treatment (day 90)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean OSS</td>
<td>3.9 ± 0.3</td>
<td>4.0 ± 0.3</td>
</tr>
<tr>
<td><strong>Clearance</strong></td>
<td>0</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Marked improvement</td>
<td>23 (92%)</td>
<td>23 (92%)</td>
</tr>
<tr>
<td>Moderate improvement</td>
<td>2 (8%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Minimal improvement</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Mean IgE levels (IU mL⁻¹)</td>
<td>441.7 ± 407.3</td>
<td>330.6 ± 251.1</td>
</tr>
<tr>
<td>Reduction in IgE levels</td>
<td>279.6 ± 395.7 (P = 0.002)</td>
<td>72.5 ± 211.7</td>
</tr>
<tr>
<td>Number of patients with raised IgE levels (&gt; 100 IU mL⁻¹)</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Number of patients with positive ASST</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Number of patients with positive APST</td>
<td>10</td>
<td>8</td>
</tr>
<tr>
<td>At completion of follow-up (day 180)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean aUAS7</td>
<td>1.5 ± 0.8</td>
<td>1.4 ± 1.0</td>
</tr>
<tr>
<td>Mean OSS</td>
<td>3.9 ± 0.5</td>
<td>4.0 ± 0.6</td>
</tr>
<tr>
<td><strong>Clearance</strong></td>
<td>1 (4%)</td>
<td>3 (12%)</td>
</tr>
<tr>
<td>Marked improvement</td>
<td>22 (88%)</td>
<td>20 (80%)</td>
</tr>
<tr>
<td>Moderate improvement</td>
<td>1 (4%)</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Minimal improvement</td>
<td>1 (4%)</td>
<td>0</td>
</tr>
<tr>
<td>Relapse</td>
<td>0</td>
<td>1 (4%)</td>
</tr>
<tr>
<td>Patient satisfaction score</td>
<td>7.6</td>
<td>7.9</td>
</tr>
</tbody>
</table>

APST, autologous plasma skin test; ASST, autologous serum skin test; aUAS7, average urticaria activity score summed up over a week and divided by 7 (range 0—6); IgE, immunoglobulin E; NB-UVB, narrowband ultraviolet B; OSS, outcome scoring scale; PUVA, psoralen and ultraviolet A
Fig 2. (a) Trend of urticaria activity score in PUVA and NB-UVB groups. ★ Statistically significant reduction in urticaria activity score was seen in the NB-UVB group at these time points (P < 0.05), including primary endpoint (day 90) (graphs plotted after repeated-measure ANOVA application with Bonferroni corrections). (b) Trend of outcome scoring scale in PUVA and NB-UVB groups. ★ The rise in outcome scoring scale was statistically significant in NB-UVB group at these time points (P < 0.05), graphs plotted after repeated-measure ANOVA application with Bonferroni corrections). NB-UVB, narrowband ultraviolet B; PUVA, psoralen plus ultraviolet A.
UV for Chronic Urticaria

• Significant reduction in UAS7 by day 15
• Durable responses
• Well tolerated: nausea in PUVA group (24%)
• No dropouts!
Conclusion

• Good therapeutic option

• Comparable response to omalizumab
  • Reduction in UAS7: 22 (omalizumab) vs 25 (nbUVB), similar baseline severity

• Sustained response on 5mg levocetirizine

• Well tolerated

• Should be considered prior to systemic/immunosuppressive therapy

Mutations in Three Genes Encoding Proteins Involved in Hair Shaft Formation Cause Uncombable Hair Syndrome

F. Buket Ü. Basmanav,1,2,3 Laura Cau,4,23 Aylar Tafazzoli,1,23 Marie-Claire Méchin,4,23 Sabrina Wolf,1 Maria Teresa Romano,1 Frederic Valentin,5 Henning Wiegmann,5 Anne Hucheneq,4 Rima Kandil,1 Natalie Garcia Bartels,6 Arzu Kilic,7 Susannah George,8 Damian J. Ralser,1 Stefan Bergner,1 David J.P. Ferguson,9 Ana-Maria Oprisoreanu,10 Maria Wehner,1 Holger Thiele,11 Janine Altmüller,11,12 Peter Nürnberg,11,13,14 Daniel Swan,15 Darren Houniet,15 Aline Büchner,16 Lisa Weibel,16,17 Nicola Wagner,18 Ramon Grimalt,19 Anette Bygum,20 Guy Serre,4 Ulrike Blume-Peytavi,6 Eli Sprecher,21 Susanne Schoch,10 Vinzenz Oji,5 Henning Hamm,22 Paul Farrant,8 Michel Simon,4,23 and Regina C. Betz1,23,*
Uncombable hair syndrome

• Mostly sporadic but some AD or AR patterns
• Usually isolated finding
  • Rare: ectodermal dysplasia, retinopathy pigmentosa, juvenile cataracts, polydactyly
• Silvery, blond, or straw-colored hair that stands from the scalp, impossible to comb
• Affects children and improves with age
• SEM: hairs have triangular or heart-shaped cross section, longitudinal groove

Uncombable hair syndrome

- Exome sequencing of affected individuals
- Construction of protein-deficient mice

<table>
<thead>
<tr>
<th>Country</th>
<th>Gene</th>
<th>Mutation</th>
<th>Consequence</th>
<th>Clinical Description</th>
</tr>
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<tbody>
<tr>
<td>United Kingdom</td>
<td>PADI3</td>
<td>c.881C&gt;T, homozygous</td>
<td>p.Ala294Val</td>
<td>this study</td>
</tr>
<tr>
<td>Denmark</td>
<td>PADI3</td>
<td>c.881C&gt;T, homozygous</td>
<td>p.Ala294Val</td>
<td>Nissen and Svendsen²⁴</td>
</tr>
<tr>
<td>Germany</td>
<td>PADI3</td>
<td>c.335T&gt;A, homozygous</td>
<td>p.Leu112His</td>
<td>this study</td>
</tr>
<tr>
<td>Germany</td>
<td>PADI3</td>
<td>c.881C&gt;T, c.335T&gt;A</td>
<td>p.Ala294Val, p.Leu112His</td>
<td>this study</td>
</tr>
<tr>
<td>Germany</td>
<td>PADI3</td>
<td>c.881C&gt;T, c.335T&gt;A</td>
<td>p.Ala294Val, p.Leu112His</td>
<td>this study</td>
</tr>
<tr>
<td>Germany</td>
<td>PADI3</td>
<td>c.881C&gt;T, c.1813C&gt;A</td>
<td>p.Ala294Val, p.Pro605Thr</td>
<td>this study</td>
</tr>
<tr>
<td>Germany</td>
<td>PADI3</td>
<td>c.335T&gt;A, c.1813C&gt;A</td>
<td>p.Leu112His, p.Pro605Thr</td>
<td>this study</td>
</tr>
<tr>
<td>Switzerland</td>
<td>PADI3</td>
<td>c.881C&gt;T, c.1732A&gt;T</td>
<td>p.Ala294Val, p.Lys578*</td>
<td>this study</td>
</tr>
<tr>
<td>Turkey</td>
<td>TGM3</td>
<td>c.1351C&gt;T, homozygous</td>
<td>p.Gln451*</td>
<td>Kilic et al.²⁶</td>
</tr>
<tr>
<td>Germany</td>
<td>TCHH</td>
<td>c.991C&gt;T, homozygous</td>
<td>p.Gln331*</td>
<td>this study</td>
</tr>
</tbody>
</table>
Uncombable hair syndrome

• TCHH: gene for trichohyalin – inner root sheath structural protein
• PADI3 and TGM3 cause posttranslational modifications to trichohyalin

Conclusion

• PADI3 and also TCHH, TGM3 mutations seen in uncombable hair
• Good boards fodder

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