Updates in Dermatology

Karthik Krishnamurthy, DO, FAOCD
Associate Professor
Residency Program Director
Conflicts of Interest

None
Overview

Navigating the old biologics, new biologics, and biosimilars

Other new drugs on the market

Outpatient propranolol usage

Interesting reports
ORBIT (Outcome and Retention Rate of Biologic Treatments for Psoriasis): A retrospective observational study on biologic drug survival in daily practice

Eva Vilarrasa, MD,a Jaume Notario, MD,a Xavier Bordas, PhD,c Anna López-Ferré, PhD,a Ignasi J. Gich, PhD,b and Luís Puig, PhDd

Barcelona, Spain

Background: Biologic drug survival in psoriasis reflects long-term performance in real-life settings. Previous studies have yielded inconsistent results.

Objectives: We sought to analyze long-term biologic survival and its associated variables in a large, real-life cohort of patients with moderate to severe chronic plaque psoriasis.

Methods: This was an observational retrospective study. Data were extracted from clinical records of 427 patients treated with biologic agents over a 4-year period. Drug survival was analyzed using the Kaplan-Meier method and the influence of several covariates was assessed using Cox regression.

Results: We analyzed 703 treatment courses. Overall median drug survival was 31.0 months. Cumulative probability of drug survival was lower in obese patients (23.0 months, 95% confidence interval 17.4-28.6) than in patients with body mass index less than 30 (37.3 months, 95% confidence interval 29.4-45.1, \( P = .001 \)), and it was significantly higher for ustekinumab than for any other biologic agent (log rank test \( P < .001 \)). Multivariate analysis showed that obesity, etanercept treatment, and strict adherence to approved doses were associated with an increased probability of drug withdrawal, whereas ustekinumab treatment, and PASI75 and PASI90 responses at week 16 prolonged drug survival.
Longevity of Biologics

Table II. Cumulative probability of drug survival according to biologic at different time intervals

<table>
<thead>
<tr>
<th>Percentage (95% CI)</th>
<th>1 y</th>
<th>2 y</th>
<th>3 y</th>
<th>4 y</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>69.0 (63.0-75.1)</td>
<td>53.2 (46.5-59.8)</td>
<td>41.9 (35.2-48.7)</td>
<td>34.9 (27.9-41.8)</td>
</tr>
<tr>
<td>Etanercept</td>
<td>70.9 (65.2-76.6)</td>
<td>52.6 (46.2-58.9)</td>
<td>39.1 (32.8-45.5)</td>
<td>30.5 (24.4-36.6)</td>
</tr>
<tr>
<td>Infliximab</td>
<td>68.8 (58.9-76.8)</td>
<td>54.2 (43.3-65.2)</td>
<td>45.5 (34.3-56.7)</td>
<td>42.4 (31.2-53.6)</td>
</tr>
<tr>
<td>Ustekinumab</td>
<td>77.2 (70.1-84.2)</td>
<td>68.5 (60.4-76.6)</td>
<td>61.8 (52.9-70.8)</td>
<td>57.8 (47.8-67.8)</td>
</tr>
</tbody>
</table>
Longevity of Biologics
Longevity of Biologics

CAPSULE SUMMARY

- Biological drug survival reflects long-term performance in real life.
- Ustekinumab treatment, and PASI75 and PASI90 responses at week 16, are independently associated with increased drug survival.
- These findings can promote adherence to biologic treatment.

Obesity (BMI > 30)

- 23 months vs 37.3 months drug survival
Biosimilars

What is a biosimilar?

• Concept sanctioned by the PPA/ACA of 2010
• An almost-identical copy of an existing biologic product
  • May need to be reverse-engineered
Biosimilars

How are they approved?

- Alternate FDA approval pathway to show similar efficacy
  - Cannot show increased efficacy
  - Extrapolation: Can be approved for all “reference product” indications but not required to be studied in each condition
  - Can gain “interchangeable” status by FDA
    - Must meet 3 demonstrative criteria
Biosimilars in the derm world

- Infliximab vs Infliximab-dyyb (Inflectra®) [NI]
- Etanercept vs Etanercept-szzs (Erelzi®) [NI]

- In the pipelines
  - Adalimumab vs ABP 501 (Amgen) vs GP2017 (Sandoz) vs CHS-1420 (Coherus) vs xxx (Abbvie??)
### Some Popular Targeted Reference Products

<table>
<thead>
<tr>
<th>Product</th>
<th>No. of biosimilars by reference product</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humira</td>
<td>30</td>
</tr>
<tr>
<td>Remicade</td>
<td>17</td>
</tr>
<tr>
<td>Epoetin alfa</td>
<td>85</td>
</tr>
<tr>
<td>Neupogen</td>
<td>59</td>
</tr>
<tr>
<td>Neulasta</td>
<td>24</td>
</tr>
<tr>
<td>Enbrel</td>
<td>31</td>
</tr>
<tr>
<td>Rituxan</td>
<td>50</td>
</tr>
<tr>
<td>Herceptin</td>
<td>38</td>
</tr>
<tr>
<td>Lantus</td>
<td>10</td>
</tr>
<tr>
<td>Avastin</td>
<td>25</td>
</tr>
<tr>
<td>Insulin and analogs</td>
<td>51</td>
</tr>
<tr>
<td>Interferons (alfa)</td>
<td>60</td>
</tr>
<tr>
<td>Interferons (beta)</td>
<td>27</td>
</tr>
<tr>
<td>Somatropins</td>
<td>34</td>
</tr>
<tr>
<td>Cancer indications</td>
<td>418</td>
</tr>
<tr>
<td>mAbs, mAb fragments</td>
<td>261</td>
</tr>
</tbody>
</table>

### Companies With the Largest Biosimilars Pipelines

<table>
<thead>
<tr>
<th>Biosimilars (10 or more)</th>
<th>No. of biosimilars</th>
</tr>
</thead>
<tbody>
<tr>
<td>Harvest Moon Pharmaceuticals USA, Inc.</td>
<td>28</td>
</tr>
<tr>
<td>BioXpress Therapeutics S.A.</td>
<td>19</td>
</tr>
<tr>
<td>Zydus Cadilla Healthcare Ltd.</td>
<td>17</td>
</tr>
<tr>
<td>Biocon Ltd.</td>
<td>17</td>
</tr>
<tr>
<td>Mylan Labs.</td>
<td>14</td>
</tr>
<tr>
<td>Inbiopro Solutions Pvt Ltd.</td>
<td>14</td>
</tr>
<tr>
<td>Creative Biomart Inc.</td>
<td>13</td>
</tr>
<tr>
<td>Green Cross Corp.</td>
<td>12</td>
</tr>
<tr>
<td>Bio Sidus S.A.</td>
<td>12</td>
</tr>
<tr>
<td>AXXO GmbH</td>
<td>12</td>
</tr>
<tr>
<td>Dong-A Pharmaceutical.</td>
<td>12</td>
</tr>
<tr>
<td>Bionton S.A.</td>
<td>11</td>
</tr>
<tr>
<td>Chemo Group (Grupo Insud)</td>
<td>11</td>
</tr>
<tr>
<td>Novartis AG</td>
<td>10</td>
</tr>
<tr>
<td>LG Life Sciences Ltd.</td>
<td>10</td>
</tr>
<tr>
<td>Amega Biotech</td>
<td>10</td>
</tr>
<tr>
<td>Cassara Biotech</td>
<td>10</td>
</tr>
</tbody>
</table>
Brodalumab

An IgG2 mAb against IL-17A RECEPTOR (C,F) and IL-25

Brodalumab

Development history

• 3700 pts........6 suicides during clinical trials

• Those with psychiatric history were not excluded
  • 17% psychiatric disorders, 23% mod-severe depression/anxiety
  • 18X risk of suicide in this group

• 4/6 had a hx, however 2/6 had no history and passed the Columbia Suicide Severity Rating scale

• Amgen dumps drug: Astra-Zeneca + Valeant
A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis

Brodalumab

**AMAGINE-1 Trial**

**Study Schema**

- **Screening**: ≥ 7 days, ≤ 30 days
- **Induction**: Week 12
- **Withdrawal and retreatment with return of disease**: Week 52

**Groups**

- **R 1:1**:
  - 210 mg Q2W brodalumab: N = 222
  - Placebo: N = 220
- **R 1:1:1**:
  - 210 mg Q2W brodalumab: N = 83
  - If sPGA >2, 210 mg Q2W brodalumab: N = 45
  - 140 mg Q2W brodalumab: N = 57
  - If sPGA >2, 210 mg Q2W brodalumab: N = 92
  - Placebo: N = 59

**Placebo**: N = 219
Brodalumab

At Week 12

AMAGINE-1 Trial
Brodalumab

PASI 100 at Week 52

AMAGINE-1 Trial

British Journal of Dermatology (2016) 175, pp273–286
Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis


AMAGINE-2 & AMAGINE-3 Trials
Brodalumab

Study Schema

AMAGINE-2 & AMAGINE 3 Trials
Brodalumab

210 mg dose for the whole 52 weeks
Secukinumab is superior to ustekinumab in clearing skin of subjects with moderate to severe plaque psoriasis: CLEAR, a randomized controlled trial

Diamant Thaçi, MD, Andrew Blauvelt, MD, MBA, Kristian Reich, MD, Tsen-Fang Tsai, MD, Francisco Vanaclocha, MD, Külli Kingo, MD, PhD, Michael Ziv, MD, BSc, Andreas Pinter, MD, Sophie Hugot, MSc, Ruquan You, MSc, and Marina Milutinovic, MD

Lübeck, Göttingen, and Frankfurt, Germany; Portland, Oregon; Taipei, Taiwan; Madrid, Spain; Tartu, Estonia; Afula, Israel; Basel, Switzerland; and Shanghai, China
CLEAR Trial

Primary endpoint

Week 0 1 2 3 4 8 12 16 20 24 28 32 36 40 44 48 52
↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓ ↓↓

Secukinumab 300 mg

Week 0 4 16 28 40 52
↑ ↑ ↑ ↑ ↑

Ustekinumab^a 45 mg or 90 mg (according to body weight at baseline)
CLEAR Trial

**PASI 90 response**

**PASI 100 response**

**PASI 75 response**

**IGA mod 2011 0/1 response**

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*Secukinumab 300 mg (n = 331)*

*Ustekinumab (n = 333)*

*P ≤ .0001, †P < .001*
PHOENIX 1 & 2 Trial

Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomised, double-blind, placebo-controlled trial (PHOENIX 2)

Kim A Papp, Richard G Langley, Mark Lebwohl, Gerald G Krueger, Philippe Szapary, Newman Yeilding, Cynthia Guzzo, Ming-Chun Hsu, Yuhua Wang, Shu Li, Lisa T Dooley, Kristian Reich, for the PHOENIX 2 study investigators*

Lancet 2008; 371: 1675-84
PHOENIX 1 & 2 Trial

A. PASI 75

B. PGA 0/1

C. PASI 90

D. PASI 50

Placebo — Placebo — Ustekinumab 45 mg — Ustekinumab 45 mg
— Placebo — Ustekinumab 90 mg — Ustekinumab 90 mg

Lancet 2008; 371: 1675-84
Phase 3 Trials of Ixekizumab in Moderate-to-Severe Plaque Psoriasis

K.B. Gordon, A. Blauvelt, K.A. Papp, R.G. Langley, T. Luger, M. Ohtsuki, K. Reich, D. Amato, S.G. Ball, D.K. Braun, G.S. Cameron, J. Erickson, R.J. Konrad, T.M. Muram, B.J. Nickoloff, O.O. Osuntokun, R.J. Secrest, F. Zhao, L. Mallbris, and C.L. Leonardi, for the UNCOVER-1, UNCOVER-2, and UNCOVER-3 Study Groups*
UNCOVER-1 (vs placebo)

Figure 1. Response to Ixekizumab During the Induction Period in the UNCOVER-1 Trial.

12 week data
UNCOVER-1 (vs placebo)

60 week data
Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials

Christopher E M Griffiths, Kristian Reich, Mark Lebwohl, Peter van de Kerkhof, Carle Paul, Alan Menter, Gregory S Cameron, Janelle Erickson, Lu Zhang, Roberta J Secrest, Susan Ball, Daniel K Braun, Olawale O Osuntokun, Michael P Heffernan, Brian J Nickoloff, Kim Papp, for the UNCOVER-2 and UNCOVER-3 investigators

Lancet 2015; 386: 541-51
UNCOVER-2 & 3 (vs placebo/etanercept)

Figure 2: Proportion of patients achieving PASI 75 from baseline through to week 12 in UNCOVER-2 (A) and UNCOVER-3 (B)

Lancet 2015; 386: 541-51
UNCOVER-2 & 3 (vs placebo/etanercept)

Figure 3: Proportion of patients achieving PASI 90 (A, B) and PASI 100 (C, D) from baseline through to week 12 in UNCOVER-2 and UNCOVER-3

Lancet 2015; 386: 541-51
UNCOVER Trials

11 Cases of Inflammatory Bowel Disease onset or exacerbation in the treated group in addition to 3 more in the placebo withdrawal arm (who received drug weeks 0-12).

2 suicide attempts in treated group (one did not disclose truthful history), none completed
Recap?

• Neutralizing Ab’s found in <5% of these new drugs, but did not have clinical relevance

• Secukinumab demonstrated superiority to Ustekinumab

• Brodalumab demonstrated superiority to Ustekinumab
  • Suicide risk is concerning

• Ixekizumab & Secukinumab also IL-17A inhibitors
  • Target the molecule, not the receptor (Brodalumab)
  • Clinical significance?
  • Inflammatory bowel disease is a concern for all IL-17 drugs
Tofacitinib

JAK1/JAK3 Inhibitor

Myeloid DC

p40 antibodies

IL-12

IL-23

TNFα

Th1

Th17

Th22

IL-17

IL-22

TNFα inhibitors

TNFα inhibitors

IL-22 antibodies

IL-17 or IL-17R antibodies

IL-19, IL-20, IL-24

Keratinocyte

Production of AMPs and chemokines; epidermal hyperplasia

Tofacitinib

JAK1/JAK3 Inhibitor

Tofacitinib versus etanercept or placebo in moderate-to-severe chronic plaque psoriasis: a phase 3 randomised non-inferiority trial

Hervé Bachelez, Peter C M van de Kerkhof, Robert Strohal, Alexey Kubanov, Fernando Valenzuela, Joo-Heung Lee, Vladimir Yakusevich, Sergio Chimenti, Jocelyne Papacharalambous, James Proulx, Pankaj Gupta, Huaming Tan, Margaret Tawadrous, Hernan Valdez, Robert Wolk, for the OPT Compare Investigators*
Tofacitinib

Figure 3: Patient outcomes

Lancet 2015; 386: 552-61
## Tofacitinib

<table>
<thead>
<tr>
<th></th>
<th>Tofacitinib 5 mg BID (N=329)</th>
<th>Tofacitinib 10 mg BID (N=330)</th>
<th>Etanercept 50 mg BIW (N=335)</th>
<th>Placebo (N=107)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oedema peripheral</strong></td>
<td>0</td>
<td>3 (0.9)</td>
<td>1 (0.3)</td>
<td>3 (2.8)</td>
</tr>
<tr>
<td><strong>Metabolism and nutrition disorders, n (%)</strong></td>
<td>31 (9.4)</td>
<td>38 (11.5)</td>
<td>17 (5.1)</td>
<td>5 (4.7)</td>
</tr>
<tr>
<td><strong>Hypercholesterolemia</strong></td>
<td>11 (3.3)</td>
<td>14 (4.2)</td>
<td>5 (1.5)</td>
<td>2 (1.9)</td>
</tr>
<tr>
<td><strong>Dyslipidemia</strong></td>
<td>10 (3.0)</td>
<td>15 (4.5)</td>
<td>3 (0.9)</td>
<td>1 (0.9)</td>
</tr>
<tr>
<td><strong>Change from baseline to Week 12 in CPK (IU/L), median (range)</strong></td>
<td>44 0 (-1247 0, 941 0)</td>
<td>61 0 (-1382 0, 558 0)</td>
<td>5 0 (-2965 0, 1335 0)</td>
<td>-5 0 (-411 0, 99 0)</td>
</tr>
</tbody>
</table>

**Other AE’s:**
- Neutropenia
- URI’s / nasopharyngitis

*Lancet 2015; 386: 552-61*
FDA declines to expand approval of Pfizer arthritis drug

Oct 14 U.S. health regulators declined to approve Pfizer Inc's oral rheumatoid arthritis drug Xeljanz to treat moderate to severe cases of the scaly skin condition plaque psoriasis, the drugmaker said on Wednesday.

Pfizer said it received a so-called complete response letter from the Food and Drug Administration. Such letters typically outline concerns and conditions that must be addressed in order to gain U.S. approval.

The FDA does not disclose the contents of the letters. Pfizer said it has been asked to provide additional safety analyses of Xeljanz for psoriasis, and that it will work closely with the agency to gain the additional approval.

"Pfizer remains committed to Xeljanz based on the strength of the clinical data for the treatment of psoriasis," Kenneth Verburg, Pfizer's head of global medicines development, said in a statement.

Xeljanz, which was approved in 2012 to treat rheumatoid arthritis as an oral alternative to injected biotech medicines, has annual sales of about $500 million. (Reporting by Bill Berkrot; Editing by Matthew Lewis)
WARNING: SERIOUS INFECTIONS AND MALIGNANCY

See full prescribing information for complete Boxed Warning.

- Serious infections leading to hospitalization or death, including tuberculosis and bacterial, invasive fungal, viral, and other opportunistic infections, have occurred in patients receiving XELJANZ. (5.1)
- If a serious infection develops, interrupt XELJANZ until the infection is controlled. (5.1)
- Prior to starting XELJANZ, perform a test for latent tuberculosis; if it is positive, start treatment for tuberculosis prior to starting XELJANZ. (5.1)
- Monitor all patients for active tuberculosis during treatment, even if the initial latent tuberculosis test is negative. (5.1)
- Lymphoma and other malignancies have been observed in patients treated with XELJANZ. Epstein Barr Virus- associated post-transplant lymphoproliferative disorder has been observed at an increased rate in renal transplant patients treated with XELJANZ and concomitant immunosuppressive medications. (5.2)
Tofacitinib

Case Report/Case Series

Tofacitinib Citrate for the Treatment of Vitiligo
A Pathogenesis-Directed Therapy

Brittany G. Craiglow, MD; Brett A. King, MD, PhD

**IMPORTANCE** Vitiligo is a common condition that is often emotionally devastating for patients. At present, no reliably effective treatments are available.

**OBSERVATIONS** Recent advances in the understanding of the pathogenesis of vitiligo suggest that Janus kinase inhibitors may be a therapeutic option. We report a case of generalized vitiligo for which treatment with tofacitinib citrate, an oral Janus kinase 1/3 inhibitor, resulted in significant repigmentation.

**CONCLUSIONS AND RELEVANCE** The results suggest that tofacitinib and other Janus kinase inhibitors may be effective in the treatment of vitiligo. Additional studies will be needed to confirm their efficacy and to explore their safety.


Published online June 24, 2015.
Tofacitinib

A Before treatment

B After treatment

JAMA Dermatology  October 2015  Volume 151, Number 10
Tofacitinib

Treatment of recalcitrant atopic dermatitis with the oral Janus kinase inhibitor tofacitinib citrate

Lauren L. Levy, MD, Jennifer Urban, MD, and Brett A. King, MD, PhD
New Haven, Connecticut

Background: Treatment of moderate to severe atopic dermatitis (AD) is often inadequate.

Objective: We sought to evaluate the efficacy of the oral Janus kinase inhibitor tofacitinib citrate in the treatment of moderate to severe AD.

Methods: Six consecutive patients with moderate to severe AD who had failed standard treatment were treated with tofacitinib citrate. Response to treatment was assessed using the Scoring of AD index.

Results: Decreased body surface area involvement of dermatitis and decreased erythema, edema/papulation, lichenification, and excoriation were observed in all patients. The Scoring of AD index decreased by 66.6% from 36.5 to 12.2 (P < .05) during 8 to 29 weeks of treatment. There were no adverse events.

Limitations: Small sample size, lack of placebo control group, and the possibility of bias are limitations.

Conclusion: The oral Janus kinase inhibitor tofacitinib citrate may be beneficial in the treatment of moderate to severe AD. (J Am Acad Dermatol 2015;73:395-9.)
Topical tofacitinib for atopic dermatitis: A Phase 2a randomised trial
R. Bissonnette\textsuperscript{1}, K.A. Papp\textsuperscript{2}, Y. Poulin\textsuperscript{3}, M. Gooderham\textsuperscript{4}, M. Raman\textsuperscript{5}, L. Mallbris\textsuperscript{6}, C. Wang\textsuperscript{7}, V. Purohit\textsuperscript{7}, C. Mamolo\textsuperscript{7}, J. Papacharalambous\textsuperscript{7}, W.C. Ports\textsuperscript{7}
Topical tofacitinib for atopic dermatitis: A Phase 2a randomised trial
Topical tofacitinib for atopic dermatitis: A Phase 2a randomised trial
R. Bissonnette¹, K.A. Papp², Y. Poulin³, M. Gooderham⁴, M. Raman⁵, L. Mallbris⁶⁎, C. Wang⁷, V. Purohit⁷, C. Mamolo⁷, J. Papacharalambous⁷, W.C. Ports⁷

(c)

Proportion (SE) of patients achieving EASI90 response

Baseline | Week 1 | Week 2 | Week 4
---|---|---|---
0 | 0 | 0 | 0

Time point
Guselkumab (CNTO 1959 – Phase II)

An IgG1 mAb against IL-23 only

Guselkumab (CNTO 1959 – Phase II)

200 mg interval doses like Ustekinumab
Guselkumab (CNTO 1959 – Phase II)
Two Phase 3 Trials of Adalimumab for Hidradenitis Suppurativa

Alexa B. Kimball, M.D., M.P.H., Martin M. Okun, M.D., Ph.D.,
David A. Williams, M.D, M.P.H., Alice B. Gottlieb, M.D., Ph.D.,
Kim A. Papp, M.D., Ph.D., Christos C. Zouboulis, M.D., Ph.D.,
April W. Armstrong, M.D., Francisco Kerdel, M.D., Michael H. Gold, M.D.,
Seth B. Forman, M.D., Neil J. Korman, M.D., Ph.D.,
Evangelos J. Giamarellos-Bourboulis, M.D., Ph.D., Jeffrey J. Crowley, M.D.,
Charles Lynde, M.D., Ziad Reguiai, M.D., Errol-Propero Prens, M.D., Ph.D.,
Eihab Alwawi, B.S., Nael M. Mostafa, Ph.D., Brett Pinsky, Ph.D.,
Murali Sundaram, Ph.D., Yihua Gu, M.S., Dawn M. Carlson, M.D., M.P.H.,
and Gregor B.E. Jemec, M.D., D.M.Sc.
PIONEER-1 & 2

**Graphs**

**A PIONEER I, Period 1: All Patients**
- Adalimumab weekly, N=153
- Placebo, N=154

**B PIONEER II, Period 1: All Patients**
- Adalimumab weekly, N=163
- Placebo, N=163

**C PIONEER I, Period 2: Patients with Wk-12 Response**
- Placebo, N=22
- Adalimumab every other wk, N=20
- Adalimumab weekly, N=21

**D PIONEER II, Period 2: Patients with Wk-12 Response**
- Placebo, N=31
- Adalimumab every other wk, N=32
- Adalimumab weekly, N=31

**E PIONEER I, Period 2: Patients without Wk-12 Response**
- Placebo, N=37
- Adalimumab every other wk, N=28
- Adalimumab weekly, N=27

**F PIONEER II, Period 2: Patients without Wk-12 Response**
- Placebo, N=20
- Adalimumab every other wk, N=21
- Adalimumab weekly, N=20
PRIMARY ENDPOINT:

HiSCR (Hidradenitis Suppurativa Clinical Response Measure)
≥ 50% reduction in inflammatory lesion count
(abscesses + inflammatory nodules)

no increase in abscesses or draining fistulas
when compared with baseline.
Other tools

Sartorius Hidradenitis Suppurativa Score

• Anatomic region involved (axilla, groin, genital, gluteal, or other inflammatory region left and/or right): 3 points per region involved

• Number and scores of lesions (abscesses, nodules, fistulas, scars): 2 points for each nodule, 4 points for each fistula, 1 point for each scar, 1 point each for "other"

• Longest distance between 2 relevant lesions (i.e., nodules and fistulas, in each region, or size if only 1 lesion): Less than 5 cm, 2 points; less than 10 cm, 4 points; more than 10 cm, 8 points

• Lesions clearly separated by normal skin in each region: If yes, 0 points; if no, 6 points
Color Doppler ultrasound assessment of morphology and types of fistulous tracts in hidradenitis suppurativa (HS)

Ximena Wortsman, MD, Ariel Castro, MSc, and Andres Figueroa, MD

Santiago, Chile
Doppler Ultrasound

Fistulas > 0.1mm
Edema
Vascularity
Fibrosis

New “measure” for staging, tailoring treatment, and assessing response objectively
A Randomized, Double-blind, Vehicle-Controlled, Parallel Group Study of the Dose-Response Profile of A-101 ($H_2O_2$) Solution in Subjects with Seborrheic Keratosis of the Face
Hate treating SKs????

Pre-Treatment with A-101

Post-treatment with A-101
The 12-month analysis from Basal Cell Carcinoma Outcomes with LDE225 Treatment (BOLT): A phase II, randomized, double-blind study of sonidegib in patients with advanced basal cell carcinoma

Reinhard Dummer, MD,a Alexander Guminski, MD, PhD,b Ralf Gutzmer, MD,c Luc Dirix, MD,d Karl D. Lewis, MD,e Patrick Combemale, MD,f Robert M. Herd, MD,g Martin Kaatz, MD,h,i Carmen Loquai, MD,j Alexander J. Stratigos, MD,k Hans-Joachim Schulze, MD,l Ruth Plummer, MD,m Sven Gogov, MD,n Celine Pallaud, PhD,n Tingting Yi, PhD,o Manisha Monc, PhD,o Anne Lynn S. Chang, MD,p Frank Cornéllis, MD,q Ragini Kudchadkar, MD,q Uwe Trefzer, MD,q John T. Lear, MD,t Dalila Sellami, MD,o and Michael R. Migden, MDt

Zürich and Basel, Switzerland; Sydney, Australia; Hannover, Jena, Gera, Mainz, Münster, and Berlin, Germany; Antwerp and Brussels, Belgium; Aurora, Colorado; Lyon, France; Glasgow; Newcastle upon Tyne, and Manchester, United Kingdom; Athens, Greece; East Hanover, New Jersey; Redwood City, California; Atlanta, Georgia; and Houston, Texas
Results: Objective response rates in the 200- and 800-mg arms were 57.6% and 43.8% in locally advanced BCC and 7.7% and 17.4% in metastatic BCC, respectively. Among the 94 patients with locally advanced BCC who responded, only 18 progressed or died and more than 50% had responses lasting longer than 6 months. In addition, 4 of 5 responders with metastatic BCC maintained an objective response. Grade 3/4 adverse events and those leading to discontinuation were less frequent with sonidegib 200 versus 800 mg (38.0% vs 59.3%; 27.8% vs 37.3%, respectively).
New Drugs

**IaBCC, per Central Review**

<table>
<thead>
<tr>
<th>ORR (95% CI)</th>
<th>Primary Sonidegib 200 mg (n = 66)</th>
<th>12 Month Sonidegib 200 mg (n = 66)</th>
<th>Primary Sonidegib 800 mg (n = 128)</th>
<th>12 Month Sonidegib 800 mg (n = 128)</th>
</tr>
</thead>
<tbody>
<tr>
<td>47.0% (34.6-59.7)</td>
<td>7.6 1.5</td>
<td>7.6 1.5</td>
<td>21.9 1.5</td>
<td>18.0 0.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 43.9 3.0</td>
</tr>
<tr>
<td>20 3.0 4.5</td>
</tr>
<tr>
<td>40 3.0 4.5</td>
</tr>
<tr>
<td>60 3.0 4.5</td>
</tr>
<tr>
<td>80 3.0 4.5</td>
</tr>
<tr>
<td>100 3.0 4.5</td>
</tr>
</tbody>
</table>

**mBCC, per Central Review**

<table>
<thead>
<tr>
<th>ORR (95% CI)</th>
<th>Primary Sonidegib 200 mg (n = 13)</th>
<th>12 Month Sonidegib 200 mg (n = 13)</th>
<th>Primary Sonidegib 800 mg (n = 23)</th>
<th>12 Month Sonidegib 800 mg (n = 23)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15.4% (1.9-45.4)</td>
<td>7.7 4.3</td>
<td>7.7 4.3</td>
<td>13.0 4.3</td>
<td>13.0 4.3</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Patients, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 76.9 15.4</td>
</tr>
<tr>
<td>20 64.6 17.4</td>
</tr>
<tr>
<td>40 65.2 17.4</td>
</tr>
<tr>
<td>60 73.9 17.4</td>
</tr>
<tr>
<td>80 73.9 17.4</td>
</tr>
<tr>
<td>100 73.9 17.4</td>
</tr>
</tbody>
</table>
Hedgehog pathway inhibition in advanced basal cell carcinoma: latest evidence and clinical usefulness

Sirunya Silapunt, Leon Chen and Michael R. Migden
## New Drugs

**Table 1. Response rate comparison in sonidegib and vismodegib.**

<table>
<thead>
<tr>
<th></th>
<th>BOLT (200 mg sonidegib)</th>
<th>BOLT (800 mg sonidegib)</th>
<th>ERIVANCE (150 mg vismodegib)</th>
<th>12-month update</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Primary analysis</td>
<td>Primary analysis</td>
<td>Primary analysis</td>
<td></td>
</tr>
<tr>
<td></td>
<td>laBCC (n = 42)</td>
<td>mBCC (n = 13)</td>
<td>laBCC (n = 93)</td>
<td>mBCC (n = 23)</td>
</tr>
<tr>
<td>Proportion of patients with objective response</td>
<td>18 (43%)</td>
<td>2 (15%)</td>
<td>35 (38%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td>Central review (BOLT); Independent review (ERIVANCE)</td>
<td>27 (43%)</td>
<td>10 (30%)</td>
<td>30 (48%)</td>
<td>11 (33%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>2 (5%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>13 (21%)</td>
<td>0</td>
<td>14 (22%)</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>16 (38%)</td>
<td>2 (15%)</td>
<td>35 (38%)</td>
<td>4 (17%)</td>
</tr>
<tr>
<td></td>
<td>14 (22%)</td>
<td>10 (30%)</td>
<td>16 (25%)</td>
<td>11 (33%)</td>
</tr>
<tr>
<td>Disease control, %</td>
<td>93%</td>
<td>92%</td>
<td>80%</td>
<td>83%</td>
</tr>
<tr>
<td></td>
<td>81%</td>
<td>94%</td>
<td>83%</td>
<td>94%</td>
</tr>
</tbody>
</table>

laBCC, locally advanced basal cell carcinoma; mBCC, metastatic basal cell carcinoma.
Table 3. Summary Statistics of Pooled Analysis of Vismodegib Efficacy and Adverse Effects

<table>
<thead>
<tr>
<th></th>
<th>Range of Raw Proportions Between the Studies, %</th>
<th>Weighted Average (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Total</td>
<td>laBCC</td>
</tr>
<tr>
<td>Complete and partial response</td>
<td>43.2-100</td>
<td>28.0-100.0</td>
</tr>
<tr>
<td>Complete response</td>
<td>0.0-54.2</td>
<td>0.0-54.1</td>
</tr>
<tr>
<td>Partial response</td>
<td>29.3-66.7</td>
<td>25.5-66.7</td>
</tr>
<tr>
<td>Stable disease</td>
<td>0.0-53.4</td>
<td>0.0-48.2</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>0.0-50.0</td>
<td>0.0-28.6</td>
</tr>
<tr>
<td>Median duration of treatment</td>
<td>11-51.6 wk</td>
<td>11-64.8 wk</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>0.0-38.5 NR</td>
<td>NR</td>
</tr>
<tr>
<td>Discontinued due to adverse effects</td>
<td>0.0-53.8 NR</td>
<td>NR</td>
</tr>
<tr>
<td>Muscle spasms</td>
<td>20.0-100.0 NR</td>
<td>NR</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>20.0-75.0 NR</td>
<td>NR</td>
</tr>
<tr>
<td>Weight loss</td>
<td>16.0-83.3 NR</td>
<td>NR</td>
</tr>
<tr>
<td>Fatigue</td>
<td>7.7-40.4 NR</td>
<td>NR</td>
</tr>
<tr>
<td>Alopecia</td>
<td>20.0-75.0 NR</td>
<td>NR</td>
</tr>
<tr>
<td>New-onset SCC</td>
<td>0.8-20.0 NR</td>
<td>NR</td>
</tr>
<tr>
<td>Amenorrhea</td>
<td>27.6-100.0 NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

Tedizolid for 6 days versus linezolid for 10 days for acute bacterial skin and skin-structure infections (ESTABLISH-2): a randomised, double-blind, phase 3, non-inferiority trial

Gregory J Moran, Edward Fang, G Ralph Corey, Anita F Das, Carisa De Anda, Philippe Prokocimer
New Drugs

**Figure 2: Clinical response rates based on objective assessments**

- **Tedizolid 200 mg once daily (n=332)**
  - 48-72 h*: 85%
  - End of treatment+: 87%

- **Linezolid 600 mg twice daily (n=334)**
  - 48-72 h*: 83%
  - End of treatment+: 88%

*Lancet Infect Dis 2014; 14: 696-705*
### New Drugs

![Graph showing early clinical response at the 48-72 h visit by subgroup in the intention-to-treat population](image)

**Figure 3:** Early clinical response at the 48-72 h visit by subgroup in the intention-to-treat population

*Lancet Infect Dis 2014; 14: 696-705*
New Drugs

- Oritavancin non-inferior to Vancomycin in the treatment of ABSSSI
  - Trial 1: Orbactiv: 82.3% vs. Vancomycin: 78.9% responders
  - Trial 2: Orbactiv: 80.1% vs Vancomycin: 82.9% responders
  - Oritavanci is a Single Dose IV
  - Also showed a 19% decrease in AE’s compared to Vancomycin/Cephalexin

- Dalbavancin non-inferior to Vancomycin in the treatment of ABSSSI
  - Trial 1: Dalvance: 83.3% vs Vancomycin/Linezolid: 81.8%
  - Trial 2: Dalvance: 76.8% vs Vancomycin/Linezolid: 78.3%
  - The vancomycin group allowed to switch over to linezolid day 3
  - Dalbavancin dosing: day 1 and day 8 (weekly) IV

- Both showed good MRSA activity
- Similar side effect profile (nephro- and ototoxicity not established)
Trimethoprim–Sulfamethoxazole versus Placebo for Uncomplicated Skin Abscess

# TMP/SMX and Abscesses

**Table 3. Cure Rates among Patients with a Drained Cutaneous Abscess in Three Trial Populations.**

<table>
<thead>
<tr>
<th>Trial Population</th>
<th>Cure of Abscess</th>
<th>Difference (95% CI)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Trimethoprim—Sulfamethoxazole</td>
<td>Placebo</td>
<td>percentage points</td>
</tr>
<tr>
<td></td>
<td>no./total no. (%)</td>
<td>percentage points</td>
<td></td>
</tr>
<tr>
<td>Modified intention-to-treat 1</td>
<td>507/630 (80.5)</td>
<td>454/617 (73.6)</td>
<td>6.9 (2.1 to 11.7)</td>
</tr>
<tr>
<td>Per-protocol:†</td>
<td>487/524 (92.9)</td>
<td>457/533 (85.7)</td>
<td>7.2 (3.2 to 11.2)</td>
</tr>
<tr>
<td>FDAGEEP</td>
<td>218/601 (36.3)</td>
<td>204/605 (33.7)</td>
<td>2.6 (−3.0 to 8.1)</td>
</tr>
</tbody>
</table>
Initiation and Use of Propranolol for Infantile Hemangioma: Report of a Consensus Conference

AUTHORS: Beth A. Drolet, MD,a Peter C. Frommeilt, MD,a Sarah L. Chamlin, MD,a Anita Haggstrom, MD,a Nancy M. Bauman, MD FACS FAAP,a Yvonne E. Chiu, MD,¹ Robert H. Chun, MD,a Maria C. Garzon, MD,h Kristen E. Holland, MD,f Leonardo Liberman, MD,f Susan MacLellan-Tobert, MD,j Anthony J. Mancini, MD,a Denise Metry, MD,a Katherine B. Puttgen, MD,i Marcia Seefeldt, RN,tm Robert Sidbury, MD,n Kendra M. Ward, MD MS,¹ Francine Blei, MD,p Eulalia Baselga, MD,¹ Laura Cassidy, PhD,¨ David H. Darrow, MD,ü Shawna Joachim,¹ Eun-Kyung M. Kwon, BA,f Kari Martin, MD,¹ Jonathan Perkins, DO,ñ Dawn H. Siegel, MD,a Robert J. Boucek, MD,a and Ilona J. Frieden, MD¹

PEDIATRICS Volume 131, Number 1, January 2013
Propranolol & IH

A

Inpatient Initiation of Propranolol: Suggested for infants < 8 weeks of gestationally corrected age or with co-morbid conditions

- Inpatient Initiation
  - See text for indications and contraindications

Check BP and HR at 1 and 2 hrs after first 1-3 doses

- Not Tolerated

Reduce starting dose and gradually increase to 0.33 mg/kg po

Escalate at slower rate of 0.5 mg/kg po q8 hrs
Gradually increase to target dose of 0.66 mg/kg

Plan to discharge on 1 mg/kg/day and assess dose efficacy

Increase dose to 0.66 mg/kg po q8 hrs
Check BP and HR at 1 and 2 hrs after first 1-3 doses

- Tolerated

Prepare for discharge, counsel parents to:
1. Ensure minimum of 6 hrs between doses
2. Recognize signs of hypotension, bradycardia and hypoglycemia
3. Feed regularly and hold medication if po intake compromised

Discharge to home

B

Outpatient Initiation of Propranolol: Suggested for infants > 8 weeks of gestationally corrected age and adequate social support.

- Tolerated

Initiate propranolol 0.33 mg/kg po q6 hrs
(1mg/kg/day)
Clinician to check BP and HR at 1 and 2 hours after first dose

Counsel parents to:
1. Ensure minimum of 6 hrs between doses
2. Recognize signs of hypotension, bradycardia and hypoglycemia
3. Feed regularly and hold medication if po intake compromised

Discharge to home

- Tolerated for 3-7 days

Increase dose to 0.5 mg/kg po q6 hrs
(1.5 mg/kg/day)
Clinician to check BP and HR at 1 and 2 hours after first dose

Not Tolerated

Increase dose to 0.66 mg/kg po q8 hrs

- Tolerated for 3-7 days

Consider keeping at 1mg/kg/day and assess dose efficacy

- Not Tolerated

Increase dose to 0.66 mg/kg po q6 hrs

PEDIATRICS Volume 131, Number 1, January 2013
Inpatient hospitalization for initiation is suggested for the following: Infants ≤8 weeks of gestationally corrected age, or any age infant with inadequate social support, or any age infant with comorbid conditions affecting the cardiovascular system, the respiratory system including symptomatic airway hemangiomas or blood glucose maintenance.
Propranolol & IH

Outpatient Use of Oral Propranolol and Topical Timolol for Infantile Hemangiomas: Survey Results and Comparison with Propranolol Consensus Statement Guidelines

Monique G. Kumar, M.D., Carrie Coughlin, M.D., and Susan J. Bayliss, M.D.

Division of Dermatology, Departments of Internal Medicine and Pediatrics, School of Medicine, Washington University and St. Louis Children’s Hospital, St. Louis, Missouri
# Propranolol & IH

## TABLE 1. Summary of Consensus Guideline Recommendations for Outpatient Use of Propranolol for the Treatment of Infantile Hemangiomas

<table>
<thead>
<tr>
<th>Summary of consensus guidelines</th>
<th>Survey results, %</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Preassessment:</strong></td>
<td></td>
</tr>
<tr>
<td>Screen for possible risks that could be associated with propranolol</td>
<td></td>
</tr>
<tr>
<td>- Wheezing</td>
<td>86</td>
</tr>
<tr>
<td>- Heart murmur</td>
<td>79</td>
</tr>
<tr>
<td>- Poor feeding</td>
<td>74</td>
</tr>
<tr>
<td>- Dyspnea</td>
<td>67</td>
</tr>
<tr>
<td>- Family history of heart block or arrhythmia</td>
<td>59</td>
</tr>
<tr>
<td>- Tachypnea</td>
<td>52</td>
</tr>
<tr>
<td>- Diaphoresis</td>
<td>35</td>
</tr>
<tr>
<td>Contraindications to propranolol therapy: cardiogenic shock, sinus bradycardia, hypotension,</td>
<td></td>
</tr>
<tr>
<td>greater than first-degree heart block, heart failure, bronchial asthma, hypersensitivity to</td>
<td></td>
</tr>
<tr>
<td>propranolol</td>
<td></td>
</tr>
<tr>
<td>Perform or obtain documentation of recent normal cardiovascular and pulmonary history and</td>
<td></td>
</tr>
<tr>
<td>examination</td>
<td></td>
</tr>
<tr>
<td>Obtain baseline vital signs before starting therapy:</td>
<td></td>
</tr>
<tr>
<td>- Heart rate</td>
<td>96</td>
</tr>
<tr>
<td>- Blood pressure</td>
<td>93</td>
</tr>
<tr>
<td>Routine ECG not advocated unless:</td>
<td>65*</td>
</tr>
<tr>
<td>- Heart rate is below normal for age</td>
<td></td>
</tr>
<tr>
<td>- Family history of congenital heart conditions or arrhythmias or maternal history of</td>
<td></td>
</tr>
<tr>
<td>connective tissue disease</td>
<td></td>
</tr>
<tr>
<td>- History of arrhythmias or an arrhythmia is auscultated during examination</td>
<td></td>
</tr>
<tr>
<td>Echocardiography is not necessary in the absence of abnormal clinical findings.</td>
<td></td>
</tr>
<tr>
<td><strong>Initiation:</strong></td>
<td></td>
</tr>
<tr>
<td>Outpatient initiation is appropriate for infants of at least 8 weeks gestationally corrected</td>
<td></td>
</tr>
<tr>
<td>age with adequate social support and without significant comorbidities</td>
<td></td>
</tr>
<tr>
<td>Doses should be administered during daytime hours with a feeding shortly after administration</td>
<td></td>
</tr>
<tr>
<td>Use the 20 mg/5 mL formulation of propranolol for therapy</td>
<td></td>
</tr>
<tr>
<td>- Start dose at 1 mg/kg/day</td>
<td>33</td>
</tr>
<tr>
<td>- Recommend three times a day dosing frequency</td>
<td>55</td>
</tr>
<tr>
<td>- Titrate propranolol dose up to the target dose (usually 1–3 mg/kg/day)</td>
<td>89</td>
</tr>
<tr>
<td><strong>Monitoring:</strong></td>
<td></td>
</tr>
<tr>
<td>Monitor heart rate and blood pressure measurements:</td>
<td></td>
</tr>
<tr>
<td>- At baseline</td>
<td>96/93†</td>
</tr>
<tr>
<td>- 1–2 hours after receiving the initial dose</td>
<td></td>
</tr>
<tr>
<td>- After each significant dose increase (&gt;0.5 mg/kg/day)</td>
<td></td>
</tr>
<tr>
<td>- One set of measurements after achieving the target dose</td>
<td></td>
</tr>
<tr>
<td>Routine screening of serum glucose is not indicated</td>
<td></td>
</tr>
<tr>
<td>- Counsel families that propranolol should be held in any setting with restricted oral intake</td>
<td>29†</td>
</tr>
<tr>
<td>(illness, imaging)</td>
<td></td>
</tr>
</tbody>
</table>

*Pediatric Dermatology Vol. 32 No. 2 171–179, 2015*
The most often cited reasons for why practitioners did not follow these monitoring guidelines were that regular monitoring of vital signs was not necessary and that adequate staffing was not available to perform suggested monitoring.
FDA News Release

FDA approves Differin Gel 0.1% for over-the-counter use to treat acne

First retinoid approved for over-the-counter use

For Immediate Release  July 8, 2016

Release

The U.S. Food and Drug Administration today approved Differin Gel 0.1% (adapalene), a once-daily topical gel for the over-the-counter (OTC) treatment of acne. Differin Gel 0.1% is approved for use in people 12 years of age and older.
OTC Retinoid

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THANK YOU FOR SERVING YOUR COUNTRY

Julianne Hough
Singer/Academy Award Winner

Orange Park MEDICAL CENTER
Laser for Permanent Fillers

Management of Complications Caused by Permanent Fillers in the Face: A Treatment Algorithm

Daniel Cassuto, M.D.
Marco Pignatti, M.D.
Lucrezia Pacchioni, M.D.
Giulia Boscaini, M.D.
Antonio Spaggiari, M.D.
Giorgio De Santis, M.D.

Modena and Milan, Italy

Plastic and Reconstructive Surgery
Issue: Volume 138(2), August 2016, p 215e–227e
Laser for Permanent Fillers

- Dermalive/Dermadeep: 12%
- Silicone Oil: 11%
- Artecoll/Artefill: 14%
- Bio-Alcamid/Formacryl: 20%
- Aquamid: 30%
- Unidentified: 13%
Laser for Permanent Fillers
Laser for Permanent Fillers
Laser for Permanent Fillers
Laser for Permanent Fillers
References