Update on Vitiligo, Acne, HS, Pyoderma gangrenosum

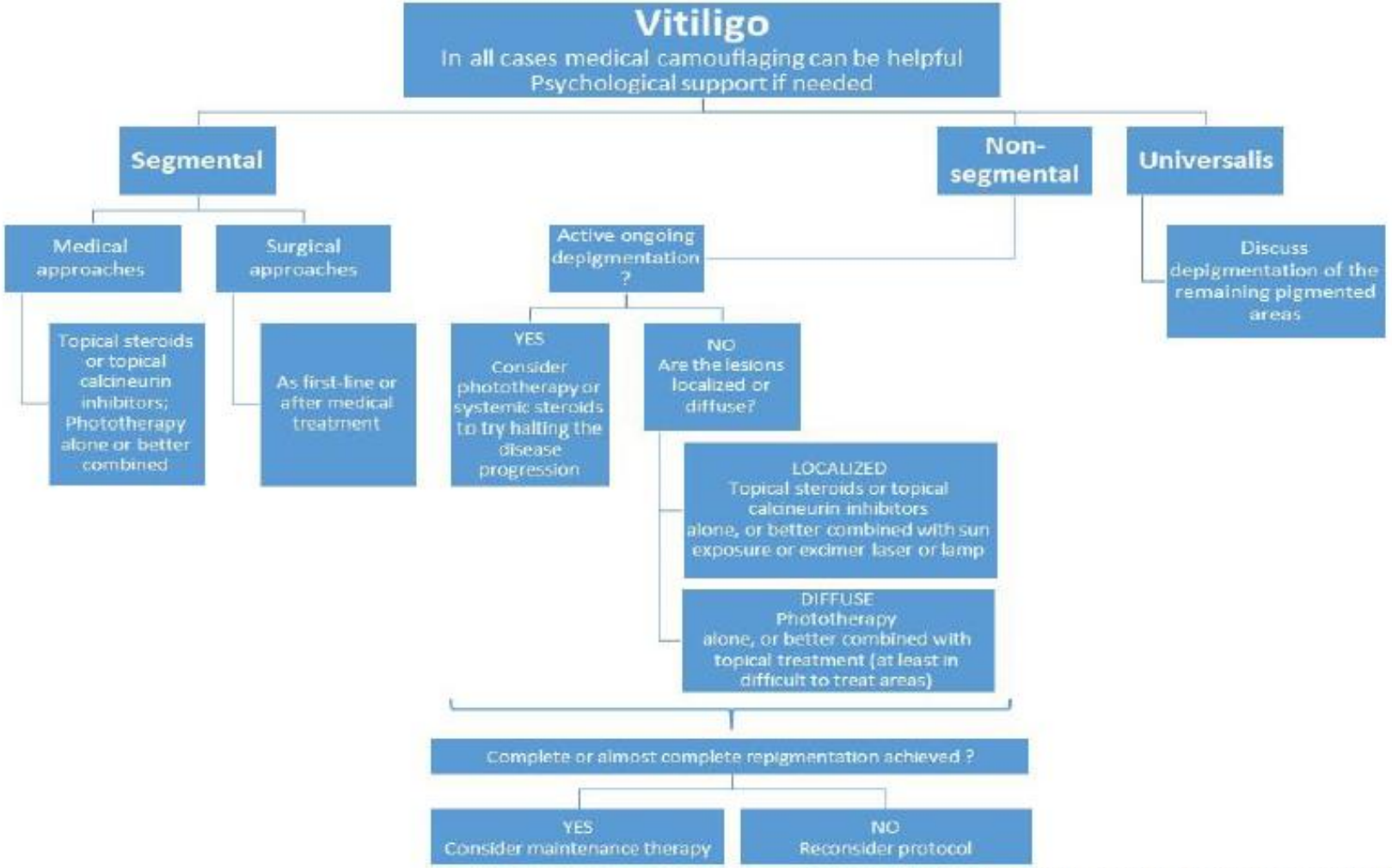
AAD San Diego 2018

Eilis Nic Dhonncha
Dermatology SpR
UCHG

Vitiligo

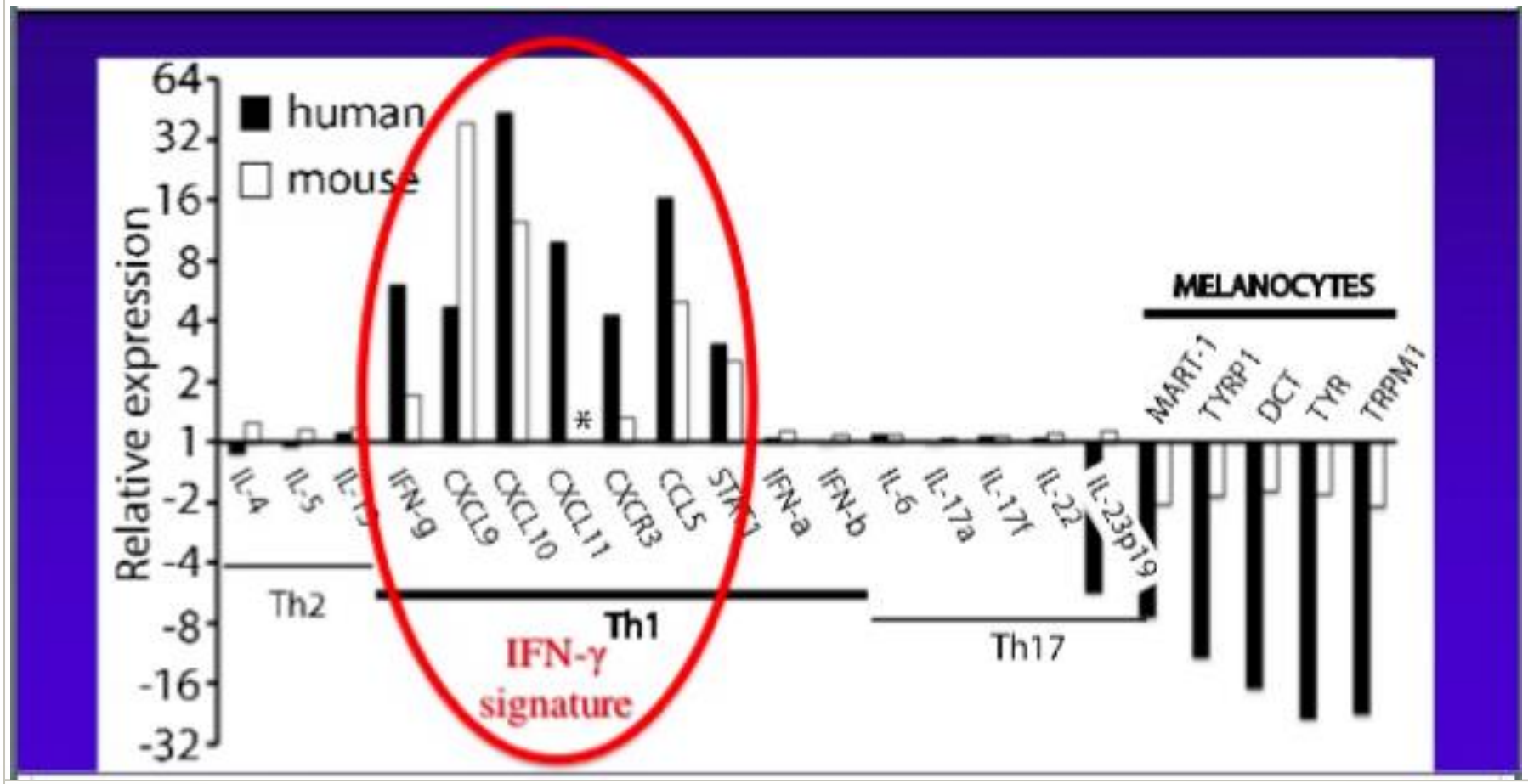
1. Advances in understanding of pathogenesis
2. New emerging therapies

Vitiligo treatment algorithm



Passeron T. Medical and maintenance treatments for vitiligo. *Dermatol Clin*. 2017;35:163-170

Gene expression similar in mouse and human vitiligo

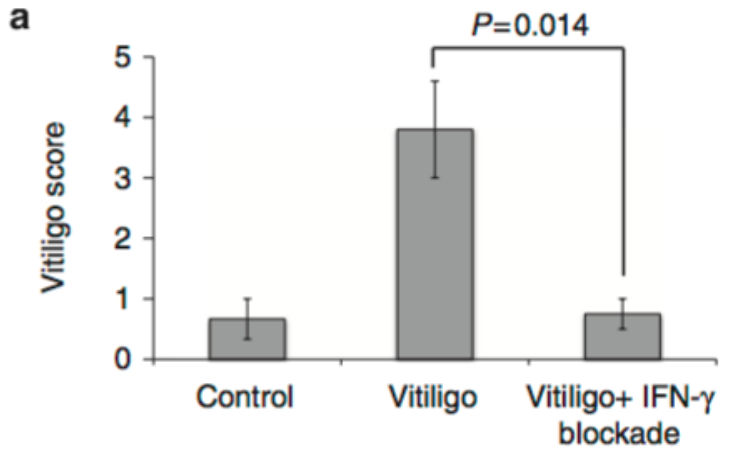


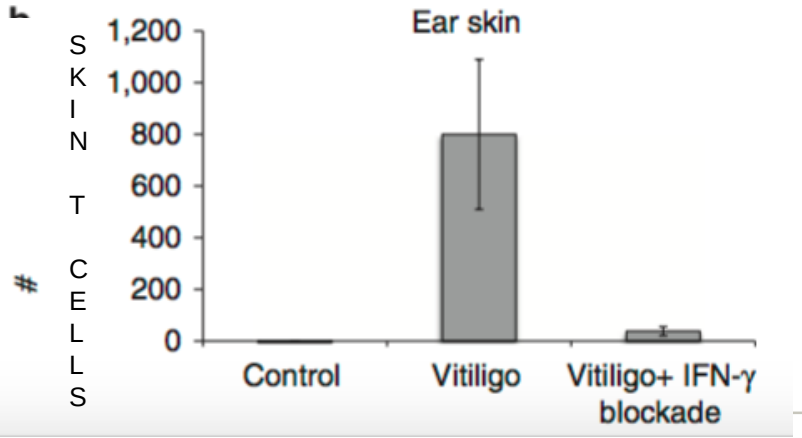
ORIGINAL ARTICLE

A Mouse Model of Vitiligo with Focused Epidermal Depigmentation Requires IFN-γ for Autoreactive CD8+ T-Cell Accumulation in the Skin

John E. Harris[1], Tajie H. Harris[2], Wolfgang Weninger[3,4], E. John Wherry[5], Christopher A. Hunter[2] and Laurence A. Turka[6]

- Mouse model of vitiligo with focused epidermal depigmentation
- Interferon-γ(IFN-γ) is required for autoreactive CD8+ T cell accumulation in the skin
- Neutralization of IFN-γ with antibody prevents CD8+ T cell accumulation and depigmentation, suggesting therapeutic potential



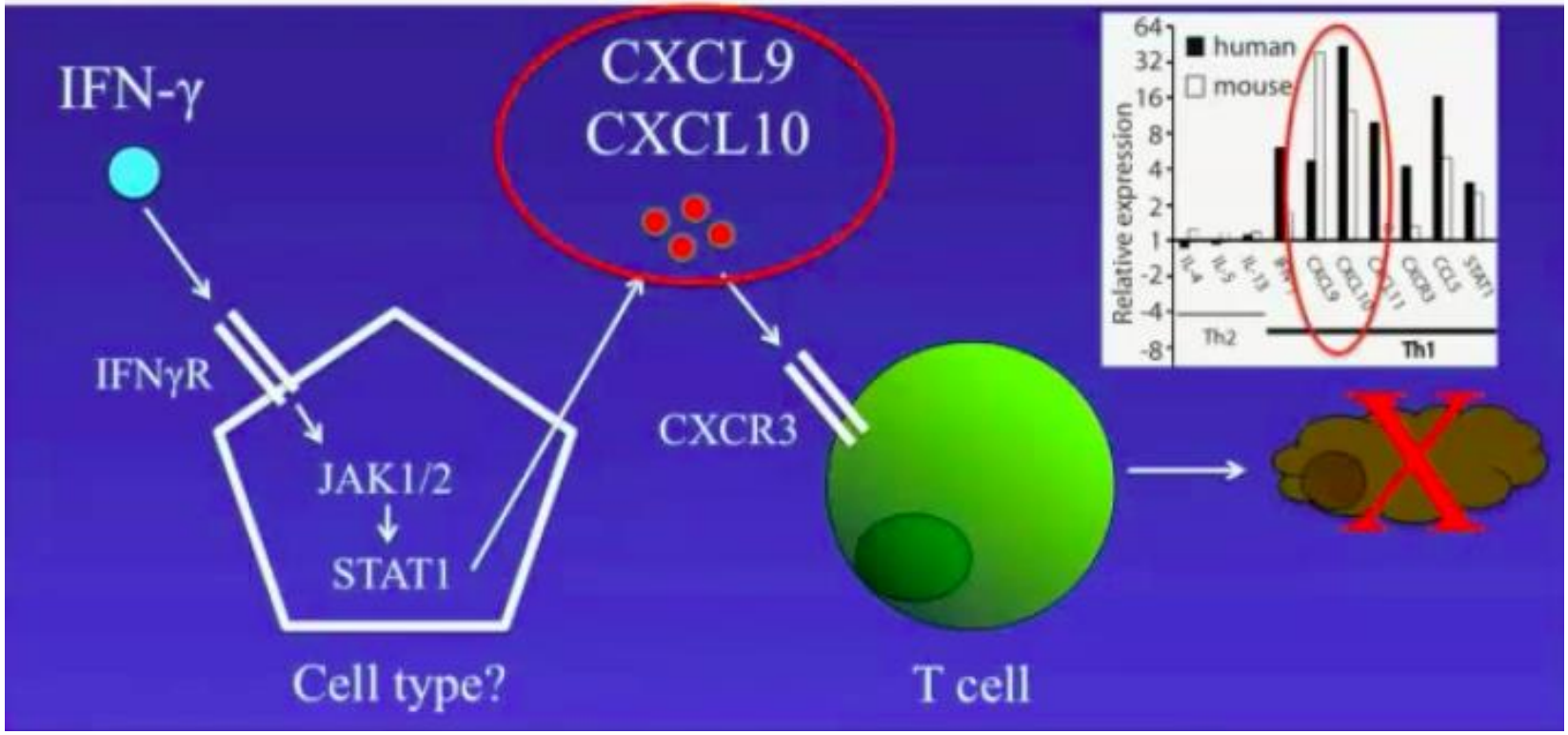


ORIGINAL ARTICLE

A Mouse Model of Vitiligo with Focused Epidermal Depigmentation Requires IFN-γ for Autoreactive CD8$^+$ T-Cell Accumulation in the Skin

John E. Harris[1], Tajie H. Harris[2], Wolfgang Weninger[3,4], E. John Wherry[5], Christopher A. Hunter[2] and Laurence A. Turka[6]

Journal of Investigative Dermatology advance online publication, 2 February 2012; doi:10.1038/jid.2011.463



www.ScienceTranslationalMedicine.org 12 February 2014 Vol 6 Issue 223 223ra23

Science Translational Medicine

AAAS

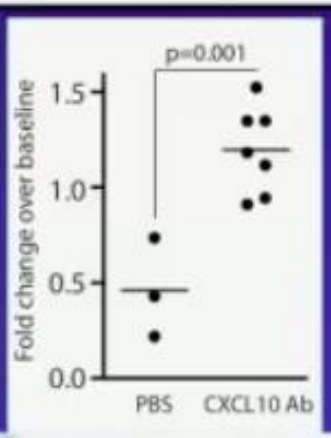
RESEARCH ARTICLE

VITILIGO

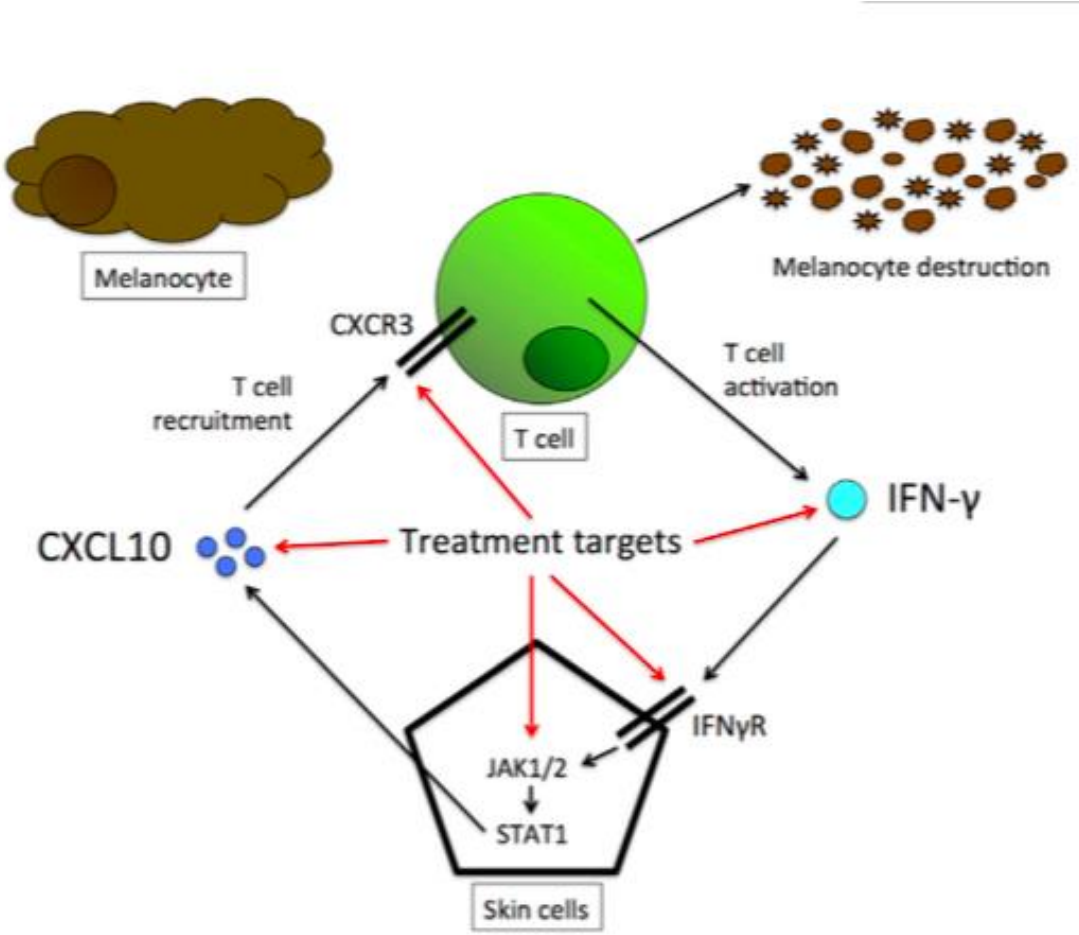
CXCL10 Is Critical for the Progression and Maintenance of Depigmentation in a Mouse Model of Vitiligo

Mehdi Rashighi,[1] Priti Agarwal,[1] Jillian M. Richmond,[1] Tajie H. Harris,[2]* Karen Dresser,[3] Ming-Wan Su,[4] Youwen Zhou,[4] April Deng,[3] Christopher A. Hunter,[2] Andrew D. Luster,[5] John E. Harris[1]†

CXCL10 antibody reverses vitiligo



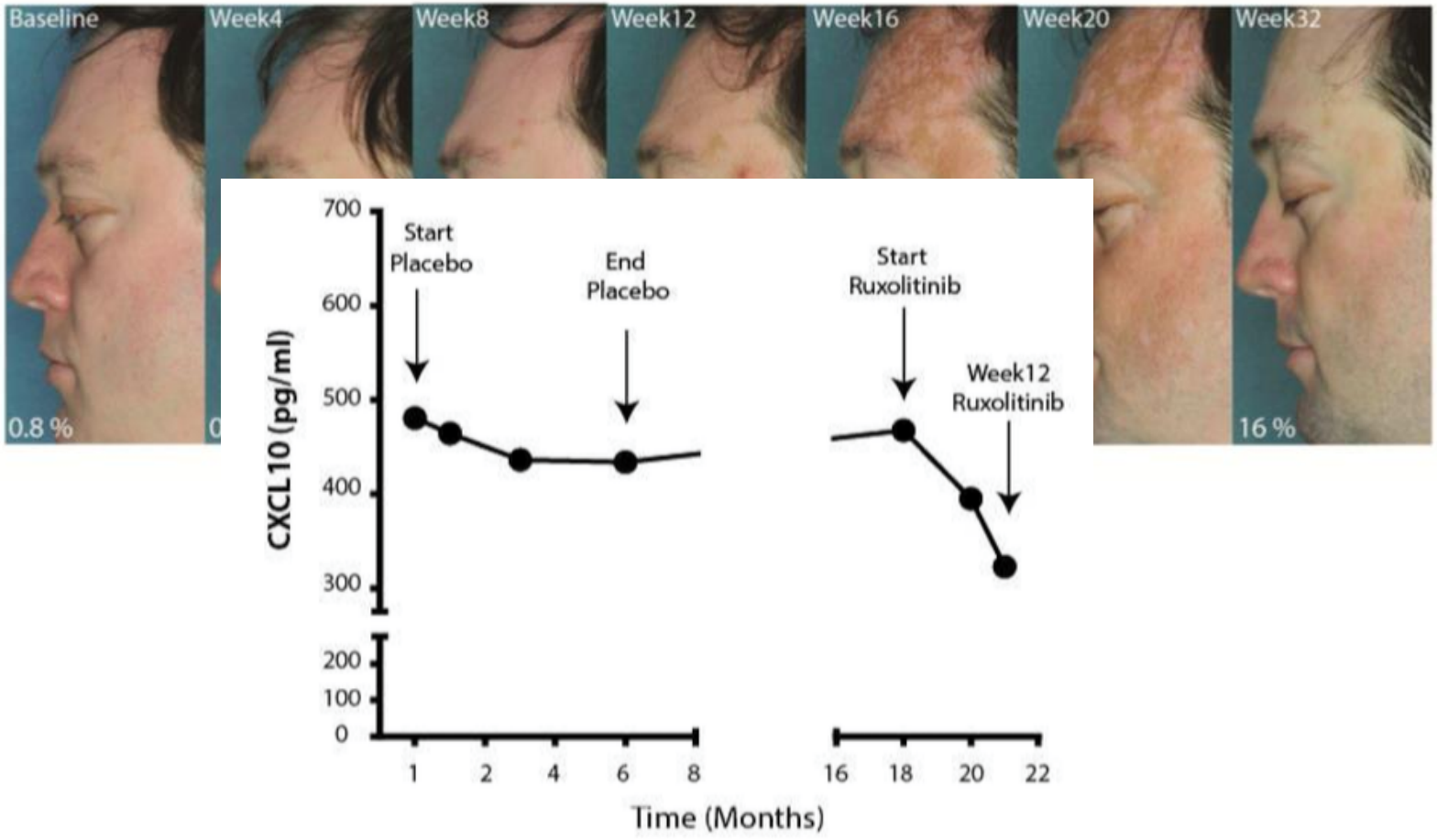
Potential therapeutic targets



J Am Acad Dermatol. 2016 Feb;74(2):370-1. doi: 10.1016/j.jaad.2015.09.073. Epub 2015 Dec 11.

Rapid skin repigmentation on oral ruxolitinib in a patient with coexistent vitiligo and alopecia areata (AA).

Harris JE[1], Rashighi M[2], Nguyen N[3], Jabbari A[3], Ulerio G[3], Clynes R[3], Christiano AM[4], Mackay-Wiggan J[5].



ORIGINAL ARTICLE

Treatment of vitiligo with the topical Janus kinase inhibitor ruxolitinib

Brooke Rothstein, BA,[a] Deep Joshipura, MBBS, MD,[a] Ami Saraiya, MD,[a] Rana Abdat, MD,[a] Huda Ashkar, MD,[a] Yana Turkowski, MD,[a] Vaneeta Sheth, MD,[b] Victor Huang, MD,[c] Shiu Chung Au, MD,[a] Courtney Kachuk, RN,[a] Nicole Dumont,[a] Alice B. Gottlieb, MD, PhD,[a,d] and David Rosmarin, MD[a]

Boston and Newton, Massachusetts; and Valhalla, New York

- 20 week, open-label, proof-of-concept study
- 11 patients, minimum 1% BSA
  - 54.5% men
  - Mean age, 52 years
- The primary outcome was percent improvement in Vitiligo Area Scoring Index (VASI) from baseline to week 20
- A mean improvement of 23% in overall VASI scores was observed in all enrolled patients at week 20 (P = .02)
- Four patients with significant facial involvement at baseline had a mean improvement of 76% in facial VASI scores at week 20 (P = .001)
- Adverse events were minor

ORIGINAL ARTICLE

Repigmentation in vitiligo using the Janus kinase inhibitor tofacitinib may require concomitant light exposure

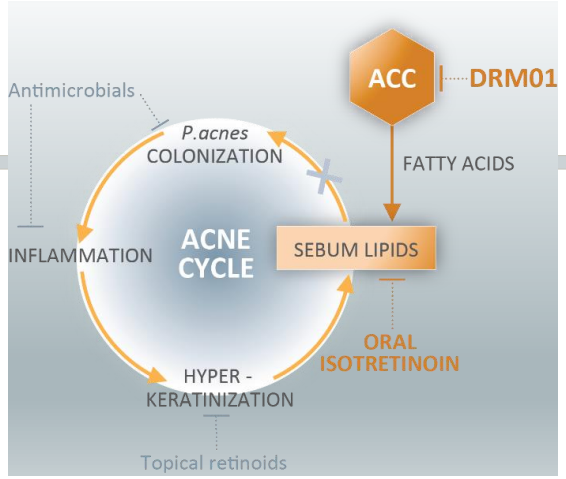
Lucy Y. Liu, BA,[a] James P. Strassner, BS,[b] Maggi A. Refat, MD,[b] John E. Harris, MD, PhD,[b] and Brett A. King, MD, PhD[c]
New Haven, Connecticut, and Worcester, Massachusetts

- Retrospective case series
- 10 patients
- Oral Tofacitinib 5mg or 10mg OD/BD
- 5 patients achieved some re-pigmentation
  - Sunlight exposure
  - Low-dose NBUVB photherapy
- 5 patients who did not experience repigmentation
  - 1 reported significant sunlight exposure
  - 4 avoided sunlight or practiced photoprotection
- Treatment of vitiligo with JAK inhibitors appears to require light exposure

Acne

1. Emerging topical therapies
2. New systemic therapy – late breaking abstract

Olumacostat glasaretil - OG (DRM 01)



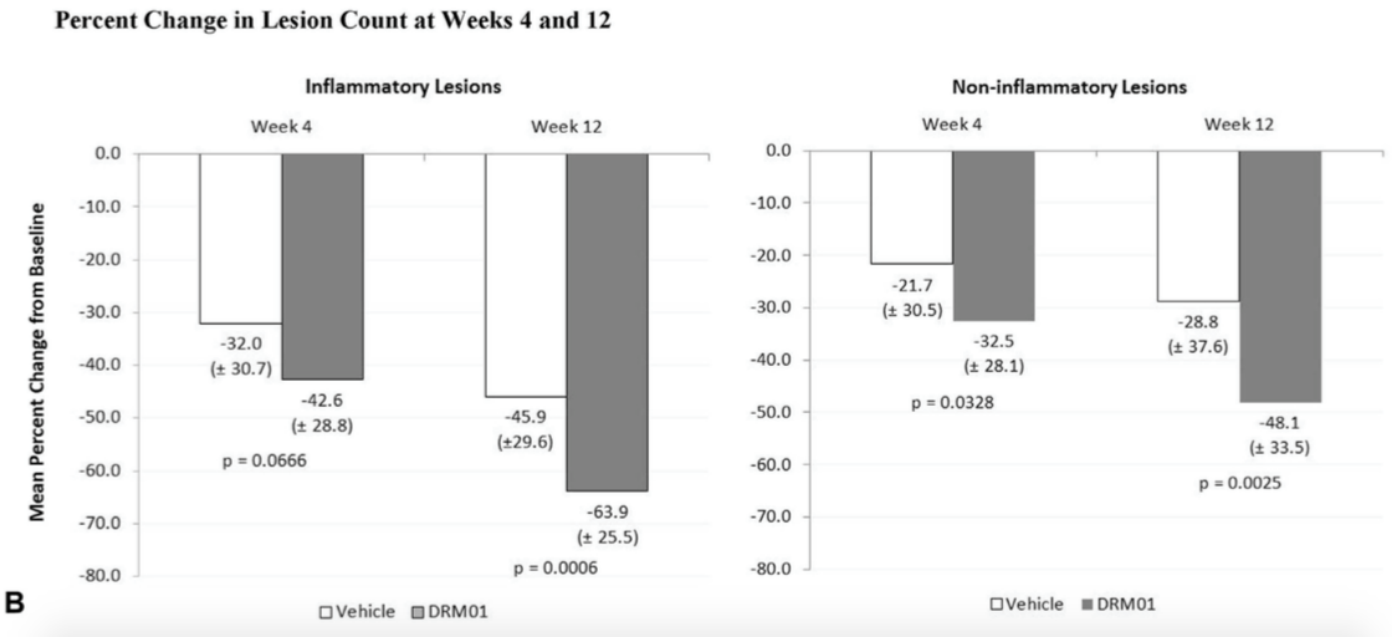
- Prodrug
- Novel topical sebum inhibitor
- Targets key regulator of sebum production, inhibits acetyl coenzyme – A carboxylase
  - Inhibits in vitro human sebocyte lipid production in cultures
  - Decreases in vivo sebaceous gland size (hamster ears)
- OG-mediated sebum suppression may reduce P. acnes growth and biofilm formation, comedogenesis, and inflammation
- 7.5% gel, twice daily application

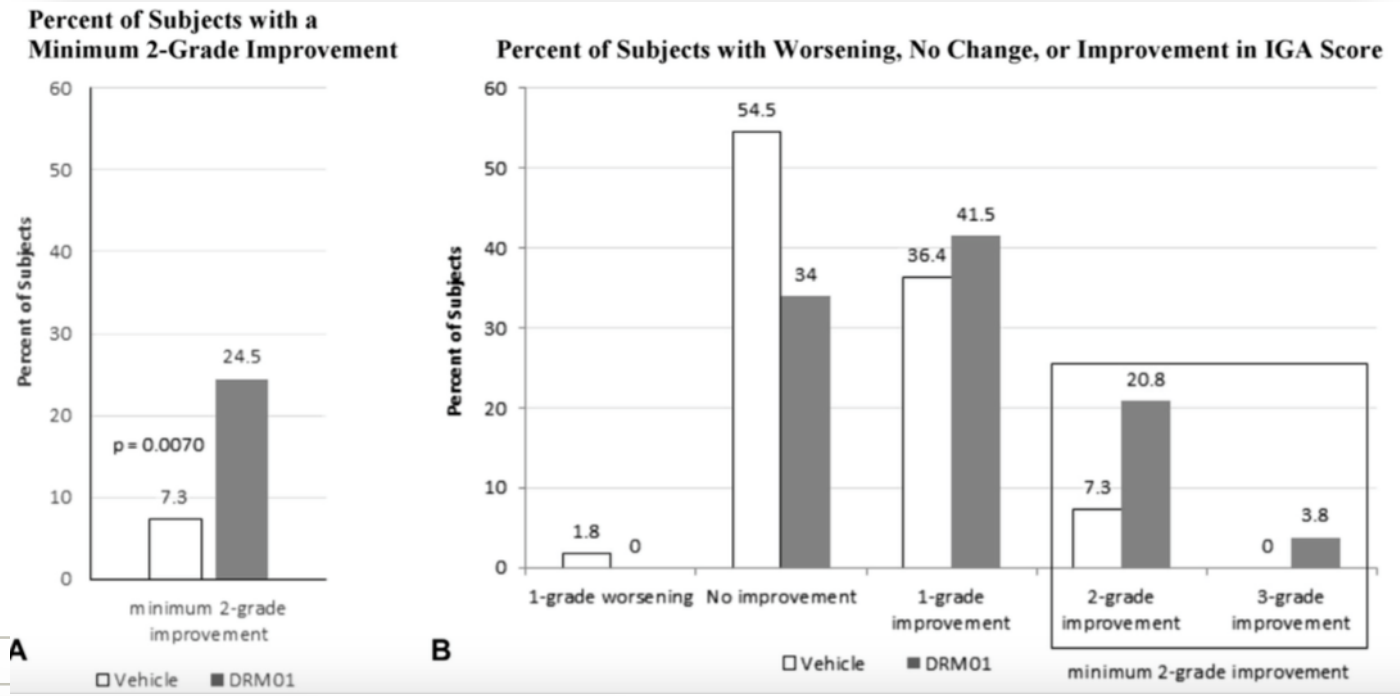
Bissonnette R, Poulin Y, Drew J, Hofland H, Tan J. Olumacostat glasaretil, a novel topical sebum inhibitor, in the treatment of acne vulgaris. A phase IIa, multicenter, randomized, vehicle-controlled study. *J Am Acad Dermatol* 2017;76(1):33-39

Olumacostat glasaretil - OG (DRM 01)

- Phase II multicenter, randomized, vehicle-controlled study; 12 weeks
- 108 patients, ≥18 years, moderate to severe acne
- Met primary endpoints
  - Change in inflammatory and non-inflammatory lesion count
  - Proportion of patients minimum ≥2 grade improvement IGA
- Well-tolerated
  - Erythema, dryness
- Phase III trial underway

Bissonnette R, Poulin Y, Drew J, Hofland H, Tan J. Olumacostat glasaretil, a novel topical sebum inhibitor, in the treatment of acne vulgaris. A phase IIa, multicenter, randomized, vehicle-controlled study. *J Am Acad Dermatol* 2017;76(1):33-39


Percent Change in Lesion Count at Weeks 4 and 12
Inflammatory Lesions
Week 4
Week 12
Mean Percent Change from Baseline
0.0
-10.0
-20.0
-30.0
-40.0
-50.0
-60.0
-70.0
-80.0
-32.0
(± 30.7)
-42.6
(± 28.8)
p = 0.0666
-45.9
(±29.6)
-63.9
(± 25.5)
p = 0.0006
Vehicle
DRM01
B
Non-inflammatory Lesions
Week 4
Week 12
-21.7
(± 30.5)
-32.5
(± 28.1)
p = 0.0328
-28.8
(± 37.6)
-48.1
(± 33.5)
p = 0.0025
Vehicle
DRM01


Percent of Subjects with a Minimum 2-Grade Improvement
Percent of Subjects
60
50
40
30
20
10
0
24.5
p = 0.0070
7.3
minimum 2-grade improvement
A
Vehicle
DRM01
Percent of Subjects with Worsening, No Change, or Improvement in IGA Score
Percent of Subjects
54.5
34
41.5
36.4
20.8
7.3
1.8
0
3.8
0
1-grade worsening
No improvement
1-grade improvement
2-grade improvement
3-grade improvement
minimum 2-grade improvement
B
Vehicle
DRM01

Late-breaking : Evaluation of the Efficacy, Safety, and Tolerability of SB204 4% Once Daily in Subjects with Moderate to Severe Acne Vulgaris Treated Topically for Up to 52 Weeks

- Two phase 3, randomised, vehicle-controlled studies
- ≥ 9 years of age with moderate to severe acne vulgaris
- Efficacy and safety compared to vehicle (1:1)
- 2637 subjects
  - 601 enrolled into a 40-week long term open label safety study
- At the 12-week endpoint, SB204 demonstrated statistically significant reductions compared to vehicle in:
  - Inflammatory lesion counts (-12.48 vs. -10.88; $p<0.001$)
  - Non-inflammatory lesion counts (-15.06 vs. -12.70; $p<0.001$)
  - Total lesion counts (-27.52 vs. -23.57; $p<0.001$)
- Improvement ≥2 in the IGA was 21% vs. 16% ($p=0.003$)
- Well-tolerated

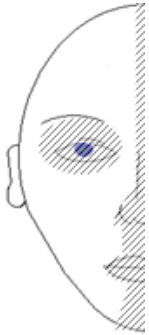
Late-breaking : Evaluation of the Efficacy, Safety, and Tolerability of SB204 4% Once Daily in Subjects with Moderate to Severe Acne Vulgaris Treated Topically for Up to 52 Weeks

- In the long-term safety study:
  - Additional reductions of >50% in inflammatory and non-inflammatory lesions
  - Indicated that treatment with SB204 for up to 52 weeks has sustained treatment benefit
  - Favourable AE profile

Overall, SB204 demonstrated statistically significant efficacy after 12 weeks compared to vehicle on multiple endpoints in the treatment of acne vulgaris with a favorable long-term safety profile

Effect of A/BPO 0.3%/2.5% vs Vehicle on the Risk of Formation of Atrophic Acne Scars Moderate to Severe Acne

- Split-face, Investigator-blinded, Vehicle Controlled
- 67 patients; IGA 3 or 4
- Once daily application
- Primary outcome:
  - Total atrophic scar count per half of face at week 24
- 24 weeks, 8 visits
  - Wk 1, 4, 8, 12, 16, 20, 24

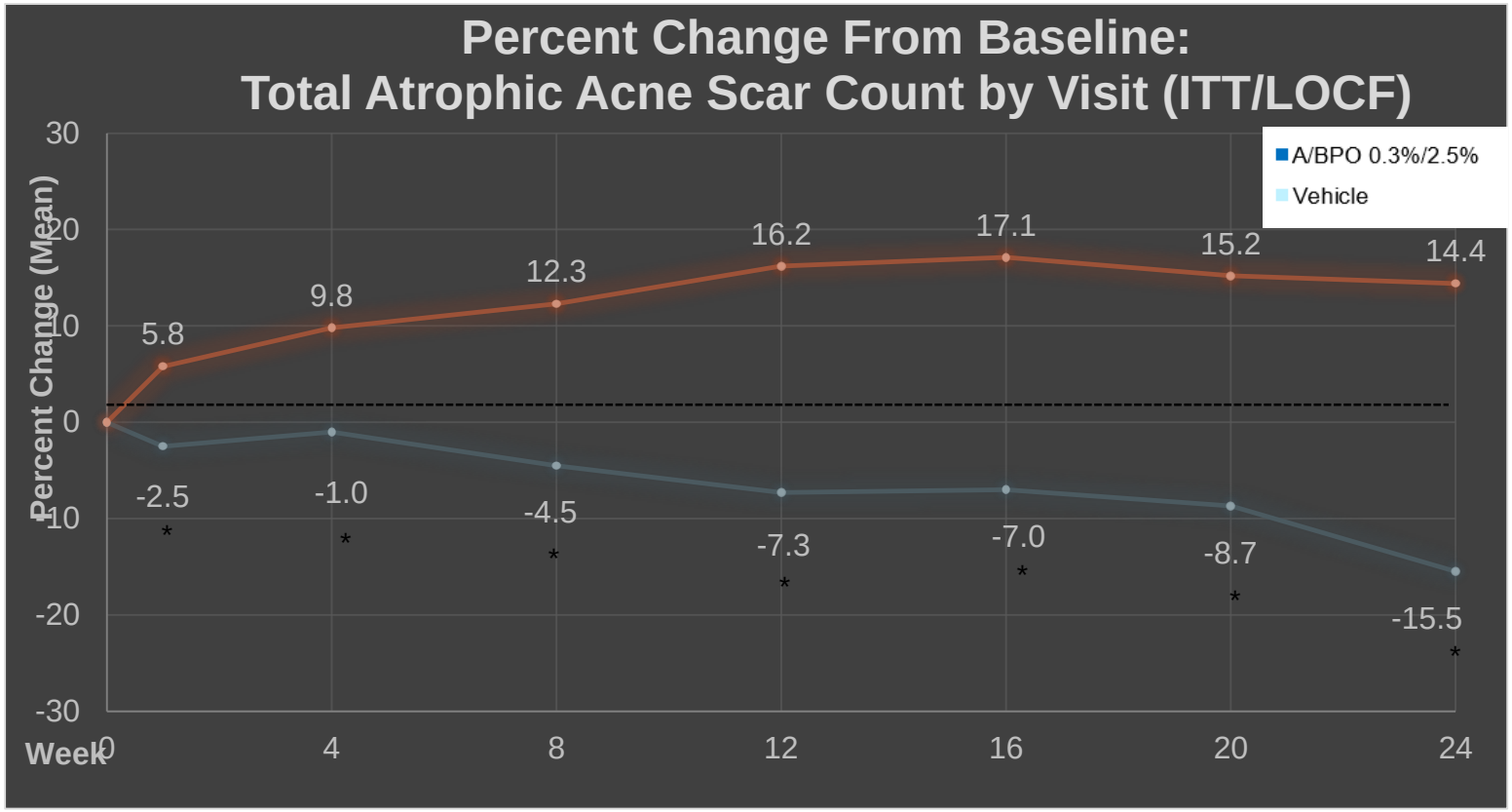


A/BPO
0.3%/2.5%

Vehicle

Dreno et al. Poster, Winter Clinical,Maui HI 2018

A/BPO 0.3%/2.5% vs Vehicle and Scar Formation Risk in Moderate to Severe Acne: Percent Change From Baseline - Total Atrophic Scar Count



Dreno et al. Poster, Winter Clinical, Maui HI, 2018

Topical therapies

- Topical minocycline foam 4% (FMX 101)
  - Phase III trials x 2 underway
  - 12 weeks; OD application FMX 101 vs. vehicle
  - Over 900 patients; moderate to severe acne
  - Primary endpoints:
    - Reduction in inflammatory lesion count
    - ↓IGA
- Cortexolone 17 alpha propionate 1% cream (CB-03-01 1%)
  - Phase III trial underway
  - 12 weeks; BD application
  - Primary endpoints:
    - Reduction in inflammatory and non-inflammatory lesion count
    - ↓IGA

Oral sarecycline

- Novel tetracycline class antibiotic
- Narrow spectrum – potential for:
  - Improved efficacy
  - Fewer side effects
  - Less risk of antibiotic resistance/impact on GI flora?
- More limited activity against gram-negative GI organisms than minocycline/doxycycline
- Once daily

Leyden et al. Presented at AAD 75, Orlando, Fl. 2017

Late-breaking: Once-Daily Oral Sarecycline 1.5mg/kg/day for Moderate to Severe Acne Vulgaris: Pooled Data From Two Phase 3 Pivotal Studies

- 2002 patients; aged 9–45 years (mean age 19.9)
- Moderate to severe facial acne
  - (IGA ≥3, 20–50 inflammatory and ≤100 noninflammatory lesions, ≤2 nodules)
- 1:1 to sarecycline 1.5 mg/kg/day or placebo for 12 weeks
- Primary endpoints:
  - IGA success (≥2-grade improvement and score 0 [clear] or 1 [almost clear])
  - % change from baseline in inflammatory lesions
- At week 12:
  - IGA success rates were 22.2% vs. 13.0% (P<0.0001)
  - % reductions from baseline in inflammatory lesions were 50.4% vs. 34.7% (P<0.0001)

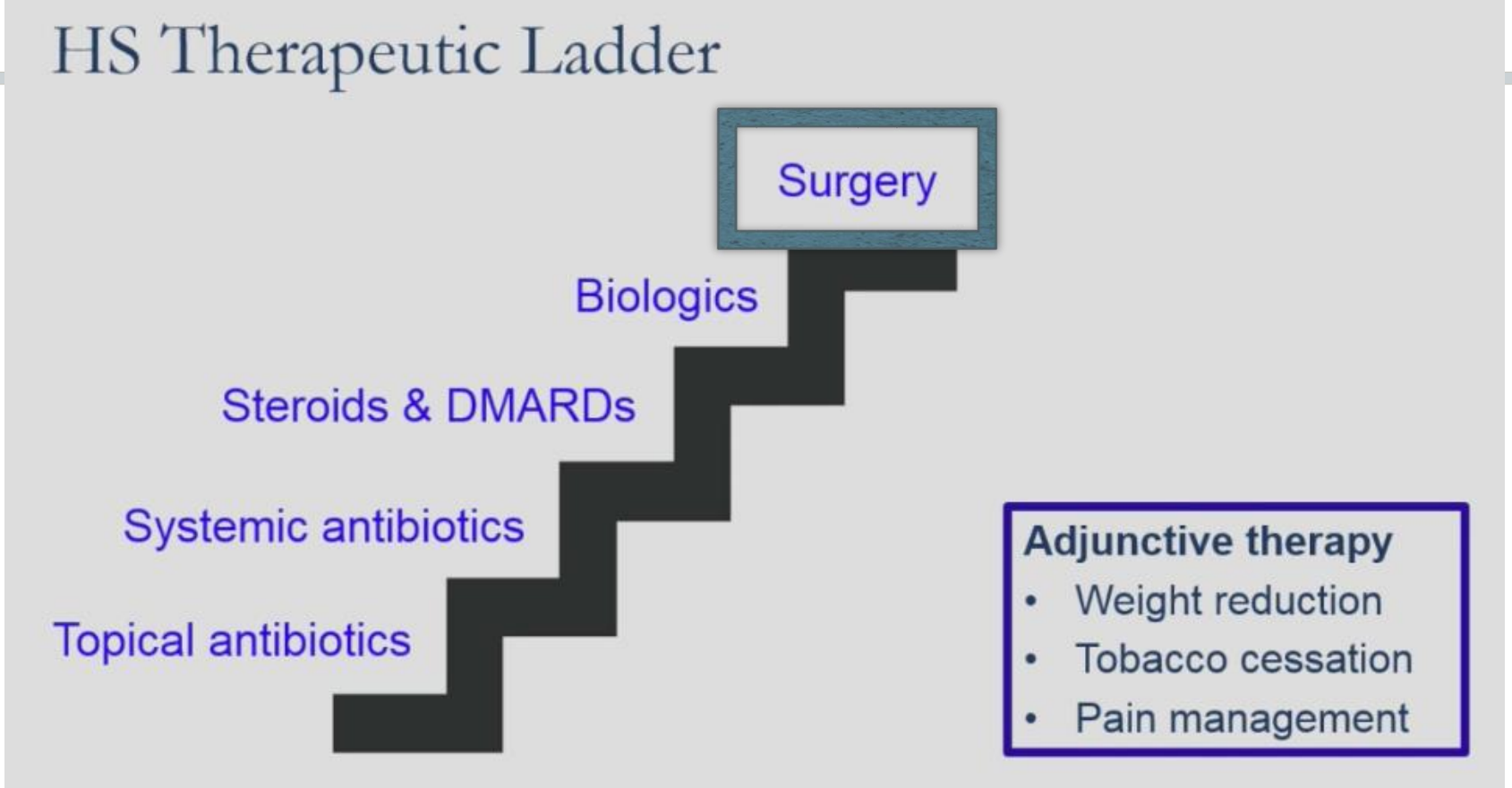
Late-breaking: Once-Daily Oral Sarecycline 1.5 mg/kg/day for Moderate to Severe Acne Vulgaris: Pooled Data From Two Phase 3 Pivotal Studies

- TEAEs:
  - Nausea (3.2% vs. 1.7%)
  - Headache (2.8% vs. 3.8%)
  - Nasopharyngitis (2.8% vs. 2.3%)
- Vulvovaginal candidiasis and vulvovaginal mycotic infection, sunburn, dizziness, photosensitivity, and urticaria, each occurred in <1% of sarecycline patients

- Sarecycline is a novel, tetracycline-class antibiotic representing the first narrow spectrum, targeted therapy for acne
- Sarecycline was safe, well tolerated, and effective for moderate to severe acne

Hidradenitis suppurativa

1. Treatment options including emerging treatment options
2. Late-breaking abstracts



Adalimumab remains only FDA approved biologic for treatment of HS

J Invest Dermatol. 2017 Nov 10. pii: S0022-202X(17)33147-0. doi: 10.1016/j.jid.2017.10.030. [Epub ahead of print]

MABp1 Targeting IL-1α for Moderate to Severe Hidradenitis Suppurativa Not Eligible for Adalimumab: a Randomized Study.

Kanni T[1], Argyropoulou M[1], Spyridopoulos T[1], Pistiki A[1], Stecher M[2], Dinarello CA[3], Simard J[2], Giamarellos-Bourboulis EJ[4].

- Double-blind, placebo controlled
- 20 patients, ≥18 years; HS II/III
- Primary end point (HiSCR) assessed at 12 weeks
- Concomitant antibiotic allowed
- HiSCR achieved in 60% vs. 10%
- US improvements in treated patients
- Well-tolerated

Secukinumab

- IL17A monoclonal antibody
  - 300mg weekly for 1 month, then q4 weeks
  - Case reports of 2 patients, both improved

Schuch et al. Acta Derm Venereol. 2018
Thorlacius et al. Br J Dermatol. 2017

- Clinical trial
  - Recruiting
  - Open label
  - 21 patients; HS II/III
  - Treatment x 24 weeks
    - 300mg 0,1,2,3, then every 4 weeks

Phase two open label single centre study to evaluate the efficacy of apremilast for the treatment of hidradenitis suppurativa

Kerdel F, Azevedo F, Lynn A, Don FA, Kerdel Don C, Fabbrocini G, Kerdel FA – unpublished to date

- 20 patients; HS I and II
- Primary endpoint (HiSCR 30) week 16
- Active treatment 24 weeks, follow-up to 28 weeks
- 65% achieved HiSCR 30 week 16 and 24
- 55% achieved HiSCR 50 week 16 and 60% week 24
- Improvements PGA, DLQI, modified sartorius, pain VAS
- Flares following withdrawal of treatment at week 24

Original Article

Complement activation in hidradenitis suppurativa: a new pathway of pathogenesis?

T. Kanni, O. Zenker, M. Habel, N. Riedemann, E. J. Giamarellos-Bourboulis

Accepted manuscript online: 6 February 2018 Full publication history

- First study of complement activation in HS
- 54 treatment naïve patients, 14 healthy controls
- Circulating C5a and C5b-9 were significantly greater in patient than control plasma
- C5a stimulates over-production of TNFα
  - May be a future therapeutic target

EFFICACY AND SAFETY OF IFX-1, AN ANTI-C5A MONOCLONAL ANTIBODY, IN AN OPEN-LABEL, PHASE 2A STUDY IN PATIENTS WITH SEVERE HIDRADENITIS SUPPURATIVA NOT ELIGIBLE FOR ADALIMUMAB

Evangelos J. Giamarellos-Bourboulis[1], Maria Argyropoulou[1], Theodora Kanni[1], Isabell Kopka[2], Othmar Zenker[2]

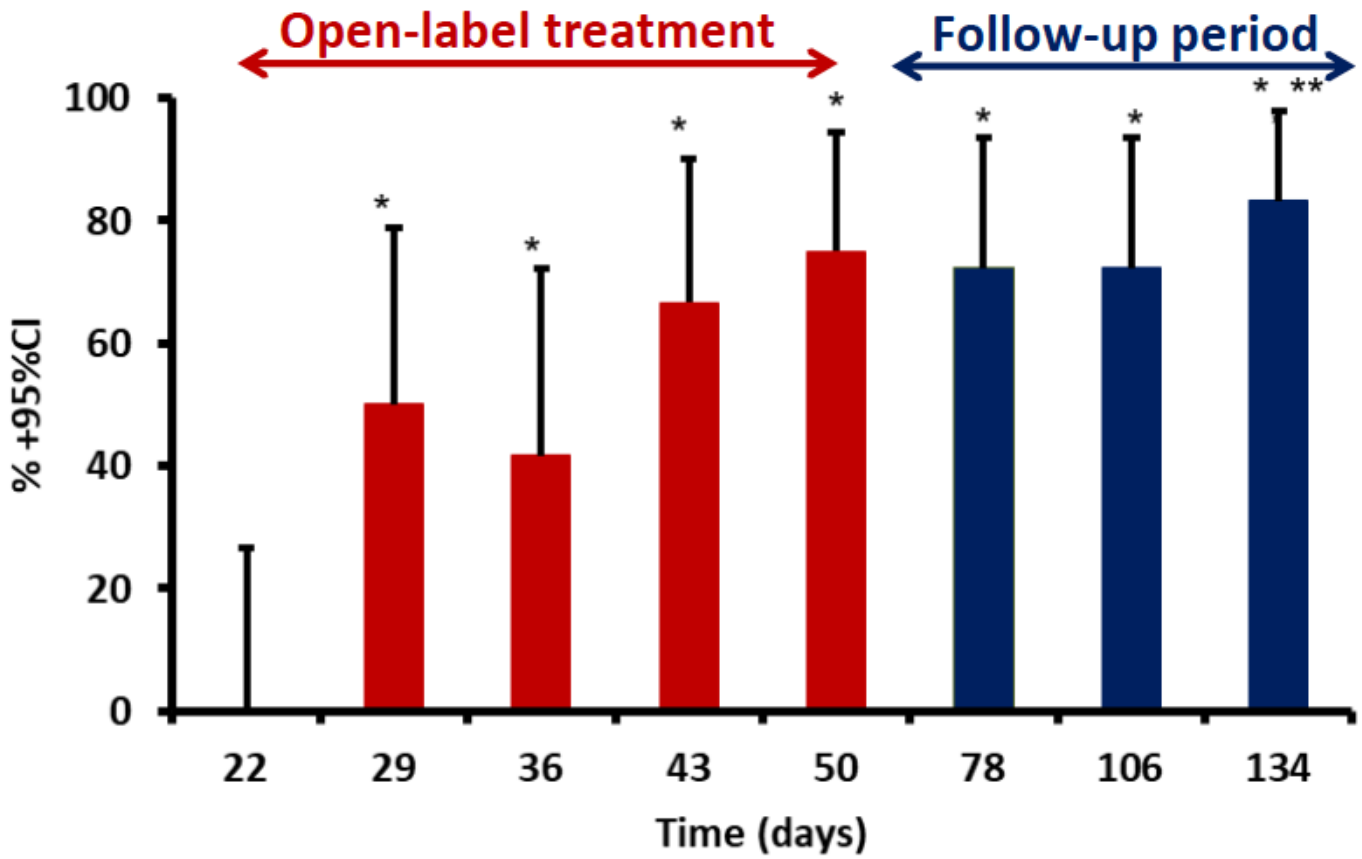
[1] Fourth Department of Internal Medicine, National and Kapodistrian University of Athens, Medical School, Greece
[2] InflaRx GmbH, Jena, Germany

ΕΛΛΗΝΙΚΗ ΔΗΜΟΚΡΑΤΙΑ
Εθνικόν και Καποδιστριακόν Πανεπιστήμιον Αθηνών
ΙΔΡΥΘΕΝ ΤΟ 1837

Late breaking: Efficacy and safety of IFX-1, an anti-C5a monoclonal antibody, in an open-label, phase 2a study in patients with severe HS not eligible for adalimumab

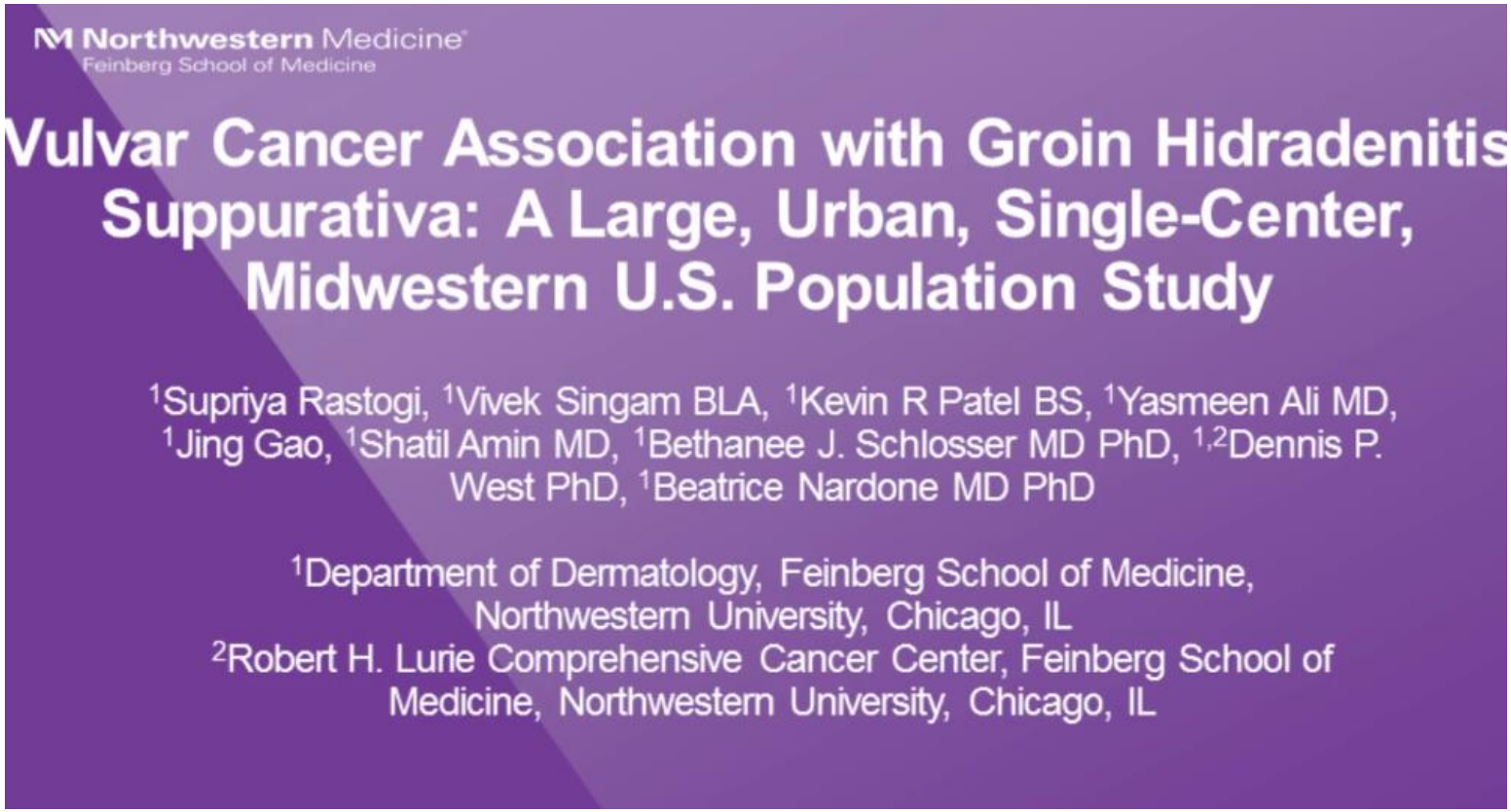
- Humanised monoclonal IGG4K antibody that specifically binds to the soluble human complement split product C5a
- Open label
- 12 patients; ≥18 years
- 8 weeks treatment, 12 weeks follow-up
- Primary endpoints:
  1. Safety and tolerability
  2. Adverse effects
- Secondary endpoint:
  1. Efficacy – PGA/HiSCR/VAS
- TEAE: 50% of patients
  - None related to medication
  - 1 patients stopped medication

HS CLINICAL RESPONSE (HiSCR)

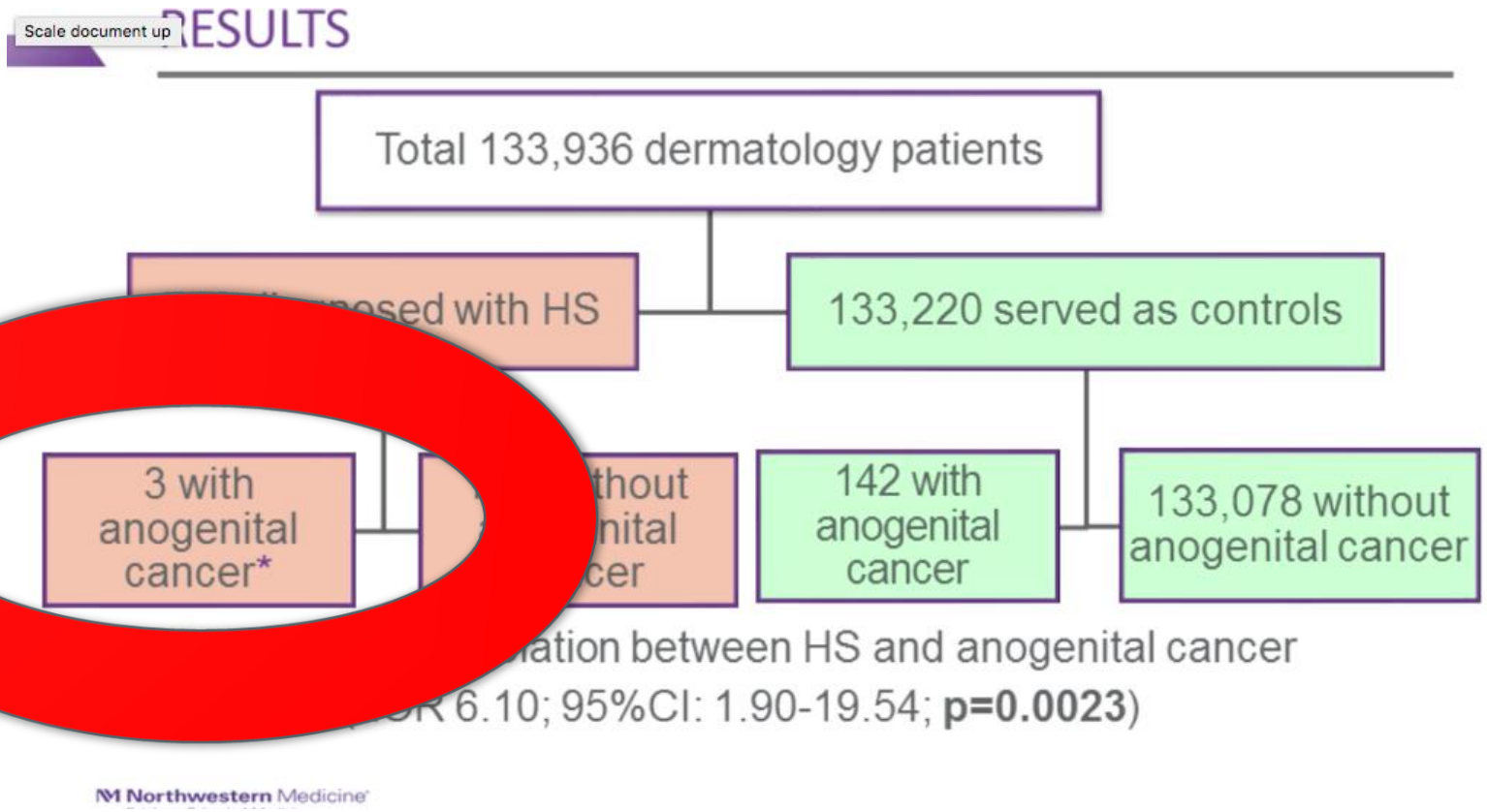


* $p < 0.05$ compared with day 22 ** $p = 0.09$ compared with day 50

Late breaking abstract



Late breaking: Vulvar cancer association with groin hidradenitis suppurativa: A large urban single center mid-western US population study



Late breaking: Vulvar cancer association with groin hidradenitis suppurativa: A large urban single center mid-western US population study

RESULTS

Northwestern incidence of vulvar cancer among adult females with HS	2.6/10,000 persons per year
SEER incidence of vulvar cancer among general adult female population	0.3/10,000 persons per year

Our findings represent an 8-fold greater incidence of vulvar cancer among adult female HS patients compared to adult females in the general population.

Pyoderma gangrenosum

1. Co-morbitidies in PG
2. Surgical procedures in patients with PG
3. Emerging treatment options

JAMA Dermatology | Original Investigation

The Association of Age With Clinical Presentation and (

Hovik J. Asl
William G. T
Misha Rose

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      -
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Table 4. Age-Focused Initial Evaluation for Pyoderma Gangrenosum

Age Group	Recommended Workup
All patients	• A thorough history and physical examination focused on associated comorbidities and symptoms • Skin biopsy with tissue culture (bacterial, fungal, and mycobacterial) • CBC with differential • Age-appropriate malignancy screening
Targeted evaluation based on history and physical examination	• Inflammatory arthritis evaluation including anti-CCP and/or RF • Autoimmune and vasculitis evaluation including ANA and ANCA
Age <65 y	• A thorough history and physical examination to evaluate for IBD • Low threshold for referral to gastroenterology for evaluation of IBD (including endoscopy and colonoscopy)
Age ≥65 y	• A thorough history and physical examination to evaluate for malignant neoplasms and hematologic disorders • Blood smear • Monoclonal gammopathy evaluation including SPEP, UPEP, and IFE • Low threshold for referral to hematology and oncology for consideration of bone marrow biopsy

atologic malignancies 9.7% vs 4.1%; *P* = .04, **and hematologic disorders** (MGUS, MDS, and PV) 10.6% vs 2.1%; *P* < .001

J Am Acad Dermatol. 2018 Feb;78(2):310-314.e1. doi: 10.1016/j.jaad.2017.09.040. Epub 2017 Sep 22.

Risk of developing pyoderma gangrenosum after procedures in patients with a known history of pyoderma gangrenosum-A retrospective analysis.

Xia FD[1], Liu K[2], Lockwood S[3], Butler D[4], Tsiaras WG[2], Joyce C[5], Mostaghimi A[6].

- Retrospective study
  - Patients with history of PG who underwent surgical procedures at Brigham & Women's Hospital and Massachusetts General Hospital from 2000-2015
- 166 patients; 601 surgeries
  - Mean age 52.8 years; 80.1% women
- 33 cases post-surgical PG in 25 patients
  - 5.5% recurrence by procedure (33/601)
  - 15.1% recurrence by patients (25/166)
- Exacerbation/recurrence rate significantly association with:
  1. Procedure type (p=0.022)
     - More invasive procedures such as small and large open surgeries, mohs surgery/skin excision and debridement were more likely to be associated with PG recurrence
  2. Having chronically present PG (>1 year) at the time of procedure (p=0.041)

Clinical trials in PG

- STOP GAP trial
  - Prednisolone 0.75mg/kg/d vs. Ciclosporin 4mg/kg/d
  - 112 pts in 39 centers over 4 years
  - Primary outcome: speed of healing over 6/52
  - No statistical difference in outcomes
  - AE similar for 2 groups, but more serious AE (infection) in prednisolone group
- Infliximab
  - Only randomised placebo-controlled trial for therapy in PG
  - Infliximab 5mg/kg vs placebo
  - Week 2: 46% infliximab improved, 6% placebo
  - 29 patients infliximab – 69% beneficial repsonse

Other treatment options – **limited evidence**

- TNFα antagonists
  - Adalimumab
  - Etanercept
- IL-1 antagonists
  - Canakinumab
  - Anakinra
    - Rapid response – within days
    - Beware risk pathergy with daily injection
- IL12/23 antagonists
  - Ustekinumab
    - High doses
- *IL17 antagonist*
  - *Secukinumab – clinical trial ongoing*
- Rifampicin 600mg/day and Clindamycin 600mg/day
- Apremilast

Thank you