Addressing Gaps in Psoriasis 2025

Naiem T. Issa, MD, PhD

Director of Research & Academics
Forefront Dermatology, USA
Vienna, Virginia, USA

Assistant Professor of Dermatology
University of Miami Miller School of Medicine
Miami, Florida, USA

Clinical Assistant Professor of Dermatology
George Washington University School of Medicine
Washington, DC, USA

Leon Kircik, MD

Clinical Associate
Professor of Dermatology
Indiana University School of Medicine
Mount Sinai Medical Center, New York, NY
Physicians Skin Care, PLLC
Louisville, KY

Disclosures

Naiem T. Issa, MD, PhD

- Abbvie
- Bristol Myers Squibb
- Castle Biosciences
- Dermavant Sciences
- DermTech
- Galderma
- Incyte
- Journey
- LEO Pharma
- Lilly
- National Eczema Association
- Ortho Dermatologics
- Pfizer
- RBC Consultants
- Regeneron
- Sanofi
- SUN Pharma
- Verrica Pharmaceuticals

Leon Kircik, MD

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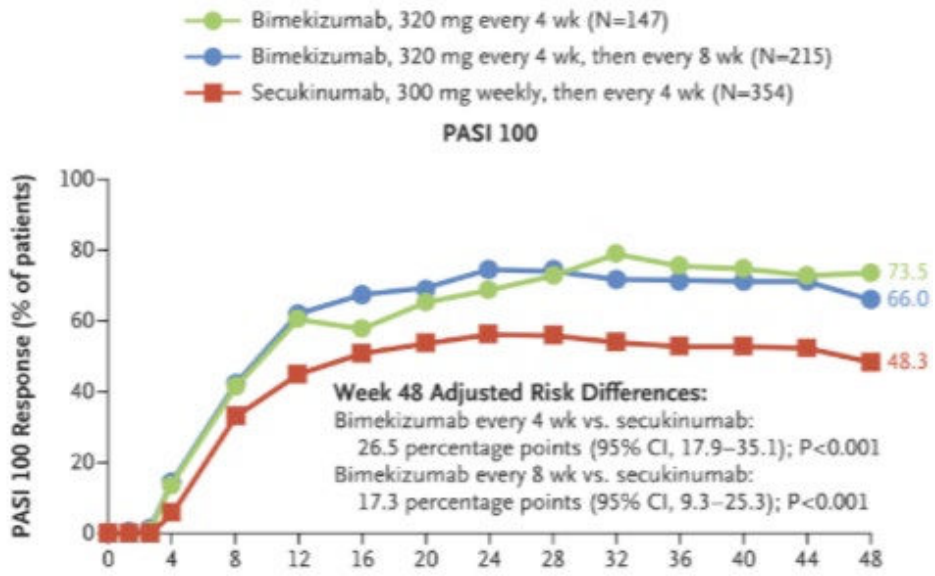
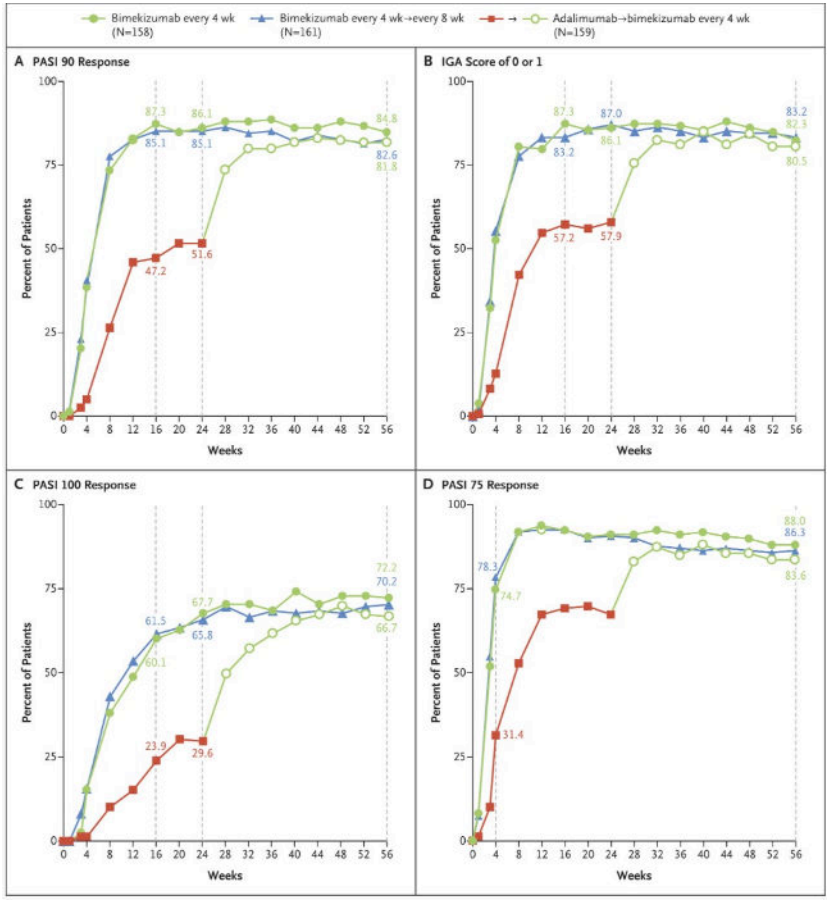
- QLT
- Quatrix
- Quinnova
- Serono
- SkinMedica
- Stiefel
- Sun Pharma
- Taro
- TolerRx
- Triax Pharmaceuticals
- UCB
- Valeant
- Warner & Chilcott
- Xenoport
- ZAGE

Speed

Does IL-17F Blockade Elicit the Most Rapid and Effective Clearance in Severe PsO?

- Bimekizumab PASI100 success greater than secukinumab (IL-17A) and adalimumab (TNFa) at Week #4





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SPECIALTIES TOPICS MULTIMEDIA CURRENT ISSUE LEARNING/CME AUTHOR CENTER PUBLICATIONS

ORIGINAL ARTICLE

Bimekizumab versus Secukinumab in Plaque Psoriasis

Authors: Kristian Reich, M.D., Ph.D., Richard B. Warren, M.D., Ph.D., Mark Lebwohl, M.D., Melinda Gooderham, M.D., Bruce Strober, M.D., Ph.D., Richard G. Langley, M.D., Carle Paul, M.D., Ph.D., +5, and Andrew Blauvelt, M.D. Author Info & Affiliations

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Bimekizumab versus Adalimumab in Plaque Psoriasis

Authors: Richard B. Warren, M.D., Ph.D., Andrew Blauvelt, M.D., Jerry Bagel, M.D., Kim A. Papp, M.D., Ph.D., Paul Yamauchi, M.D., Ph.D., April Armstrong, M.D., M.P.H., Richard G. Langley, M.D., +5, and Kristian Reich, M.D., Ph.D. Author Info & Affiliations

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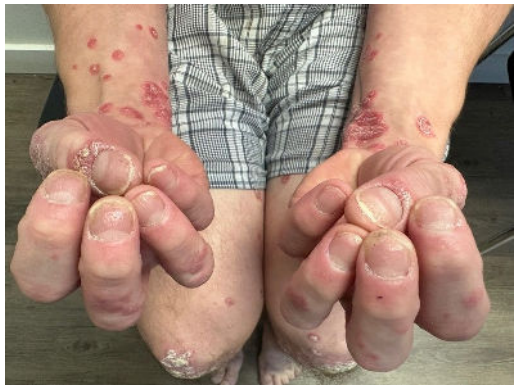
Speed

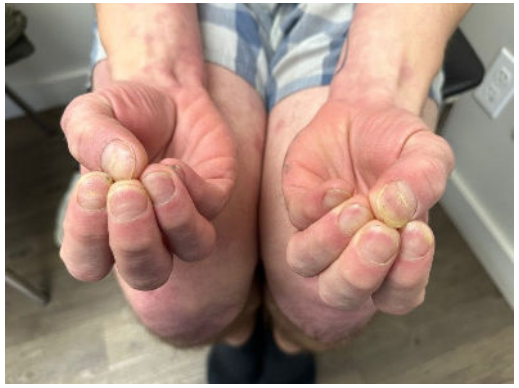
Does IL-17F Blockade Elicit the Most Rapid and Effective Clearance in Severe PsO?

- Anecdotal case reports of PASI90-100 achieved in <2 weeks with bimekizumab

Week 0



Week 2
PASI90



Courtesy: Ron Vender, MD, FRCPC
https://dermsquared.com/case-studies/rash-decisions-rapid-sustained-clearance-severe-psoriasis-il-17-inhibition

FIGURE 1. Psoriasis of the lower extremities at (A) day 0 (B) day 3 (72 hours after treatment with two subcutaneous injections of 160 mg bimekizumab into the arms), and (C) day 7.

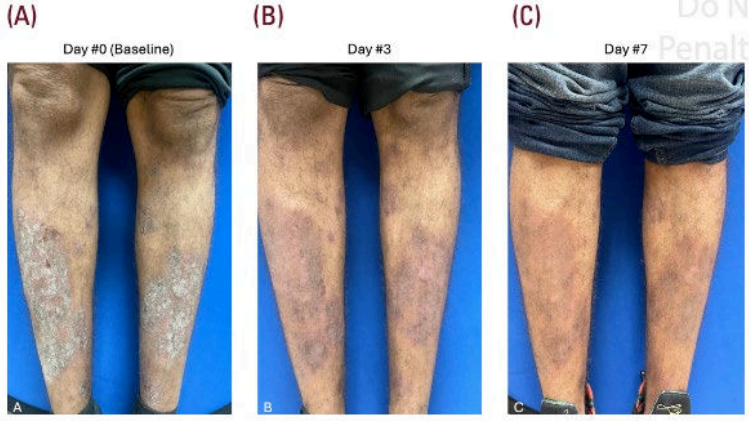
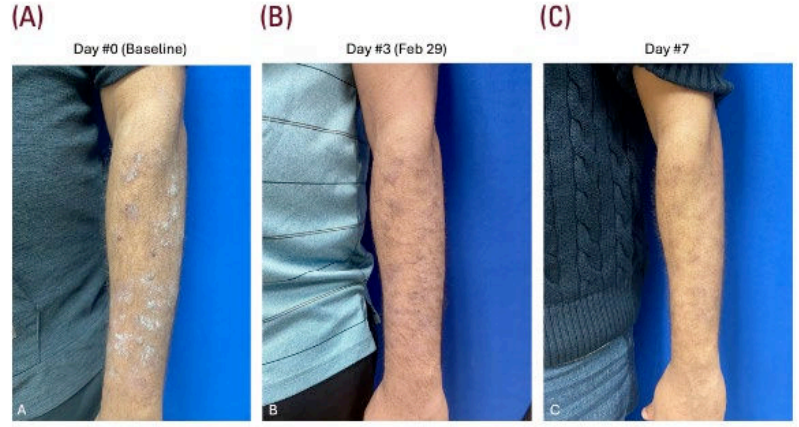


FIGURE 2. Psoriasis of the left forearm at (A) day 0 (B) day 3 (72 hours after treatment with two subcutaneous injections of 160 mg bimekizumab into the arms), and (C) day 7.



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Rapid Remission of Plaque Psoriasis With Bimekizumab Treatment

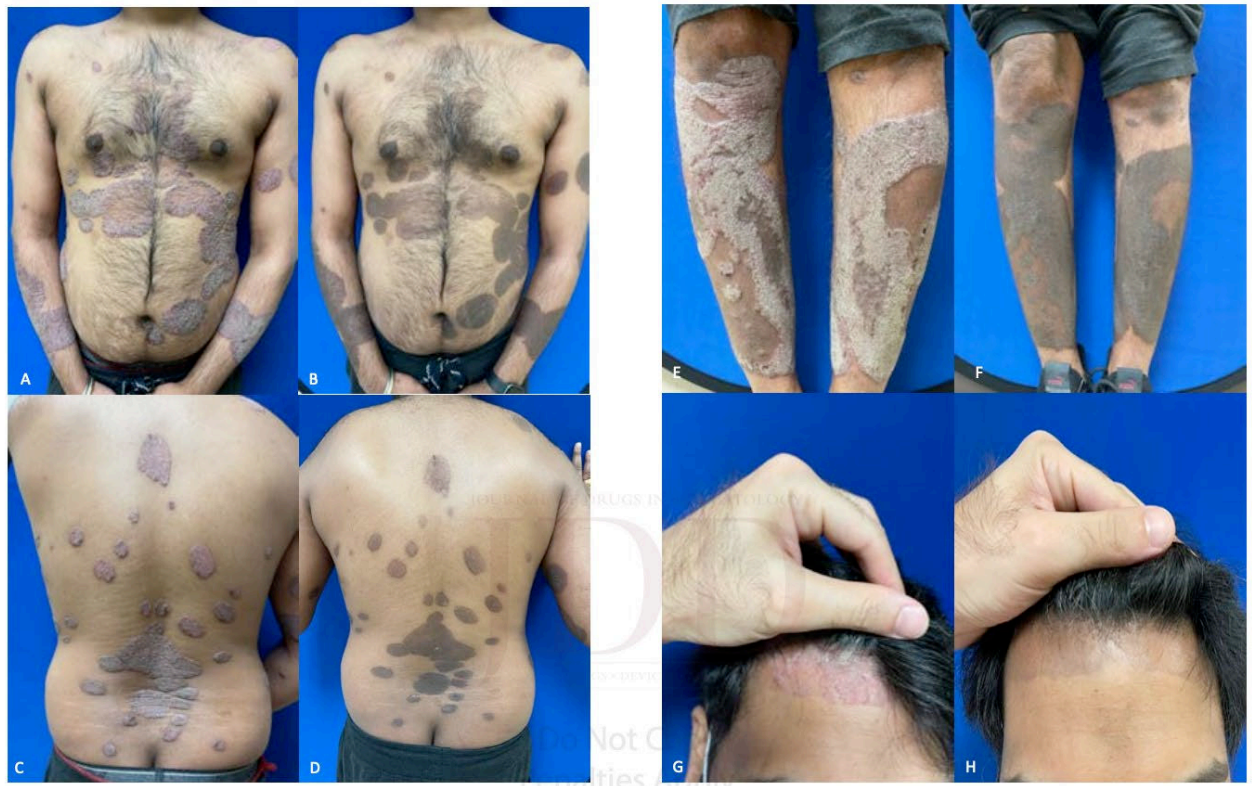
Rama Abdin BS,[a] Rola Gharib MD,[b,c] Christopher G. Bunick, MD PhD,[d] Naiem T. Issa MD PhD[e,f,g,h]

Combination

Combination Topical + Systemics

- Literature is sparse, but likely we are doing this in real-world treatment
- **NPF guidelines recommend topical treatment in combination with systemics for moderate-to-severe PsO**
- Make sure that the indication of your topical treatment aligns with the indication of systemic tx (i.e. topical is mild-mod, systemic mod-severe, so in chart disease you should say moderate for coverage)
- Case of rapid remission of severe PsO in 4 weeks using

FIGURE 1. (A, C, E, G) Generalized plaque psoriasis affecting the (A) trunk, (C) back, (E) legs, and (G) scalp. (B, D, F, H) Psoriasis-involved areas weeks after combination treatment with oral deucravacitinib 6 mg once daily and tapinarof cream 1% applied to affected areas once daily.



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First Use of Combination Oral Deucravacitinib With Tapinarof Cream for Treatment of Severe Plaque Psoriasis

Rama Abdin BS,[a] Leon Kircik MD,[b] Naiem T. Issa MD PhD[c,d*]

Combination

Combination Topical + Systemics

- Reduction in topical use over time due to systemic
- Complete clearance a/w less use

Table 3 Frequency of topical use at baseline and at 6 months.

Frequency (days/weeks)	Secukinumab (n = 39)	Ixekizumab (n = 26)	Brodalumab (n = 10)	Guselkumab (n = 37)	Ustekinumab (n = 26)
Baseline					
≥ 3-4	73.6%	80%	80%	70.3%	40.9%
1-2/Never	26.4%	20%	20%	29.7%	59.1%
6 months					
≥ 3-4	19.5%	17.4%	0%	29.5%	14.9%
1-2/never	80.5%	82.6%	100%	70.5%	85.1%

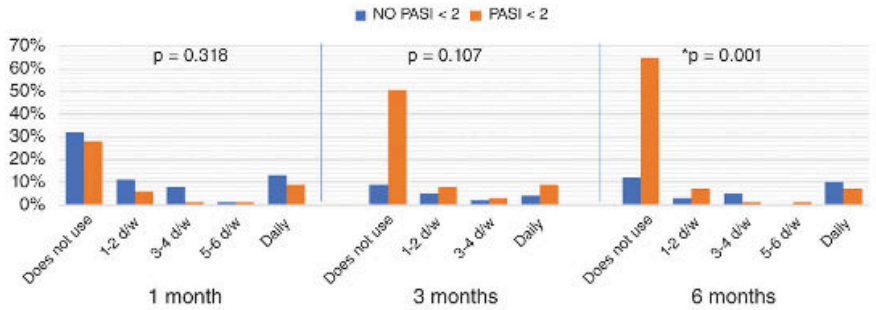


Figure 2 Bar chart. Topical use based on achieving absolute PASI < 2. d/w, days/week; PASI, Psoriasis Area Severity Index.

ACTAS Dermo-Sifiliográficas 115 (2024) T647–T653

ACTAS Dermo-Sifiliográficas

Full English text available at www.actasdermo.org

ORIGINAL ARTICLE

[Translated article] Comparing the Use of Topical Therapy Along with Anti-IL-17 and Anti-IL-23 to Treat Moderate-to-Severe Psoriasis in the Routine Clinical Practice

S. Berenguer-Ruiz[a], M. Romero-Dávila[b], M. Aparicio-Domínguez[a], M. Olivares-Guerrero[c], E. Daudén[a,b], M. Llamas-Velasco[a,b,*]

Combination

Systemic + Systemic

- Limited studies on combination systemic treatments, especially biologic+biologic
- Can help to reduce dosing of conventional immunosuppressives (i.e. Methotrexate)

› Br J Dermatol. 2024 Feb 16;190(3):355-363. doi: 10.1093/bjd/ljad382.

Safety of biologic therapy in combination with methotrexate in moderate to severe psoriasis: a cohort study from the BIOBADADERM registry

- **Combo Biologic (TNF, IL-17, IL-23) + MTX**
- 2829 patients and 5441 treatment cycles, a total of 12,853 PYS
- No increase in the total number of infections or serious infections in patients receiving combined therapy was observed for any group
- TNF inhibitor combined with MTX was associated with an increase in the incidence of gastrointestinal AEs (aIRR 2.50, 95% CI 1.57–3.98; P < 0.002).

Review › JAMA Dermatol. 2015 Apr;151(4):432-8. doi: 10.1001/jamadermatol.2014.3456.

Combining biologic therapies with other systemic treatments in psoriasis: evidence-based, best-practice recommendations from the Medical Board of the National Psoriasis Foundation

April W Armstrong [1], Jerry Bagel [2], Abby S Van Voorhees [3], Andrew D Robertson [4], Paul S Yamauchi [5]

- **UVB + Etanarcept/Adalimumab/Ustekinumab**
  - **Well tolerated**
- **MTX + Etanarcept**
- **Acitretin + Etanarcept**
- **Cyclosporine + Etanarcept/Adalimumab**
  - Helpful for transition (especially hospital setting) to prevent flares
  - Increased risk of malignancy*

› Indian J Dermatol. 2023 Jul-Aug;68(4):393-398. doi: 10.4103/ijd.ijd_813_22.

A Comparative Study of the Efficacy of Methotrexate versus Methotrexate with Apremilast in Moderate to Severe Chronic Plaque Psoriasis

Divyanshu Srivastava [1], Arvind Krishna [1], Abhinav David [1]

- **MTX 7.5mg weekly + Apremilast (PDE4i) vs MTX 7.5mg weekly**
- Prospective, 12 weeks, adult pts (N=40)

› J Eur Acad Dermatol Venereol. 2018 Feb;32(2):245-253. doi: 10.1111/jdv.14583. Epub 2017 Oct 17.

Biologics combined with conventional systemic agents or phototherapy for the treatment of psoriasis: real-life data from PSONET registries

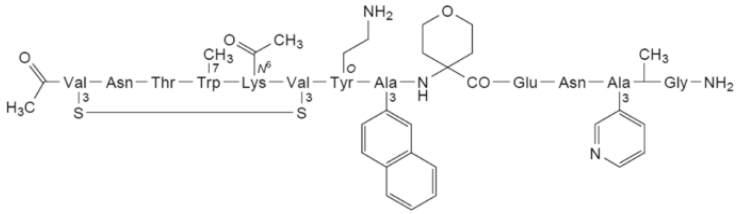
C I Busard [1], A D Cohen [2], P Wolf [3], S Gkalpakiotis [4], S Cazzaniga [5, 6], R S Stern [7], B A Hutten [8], I Feldhamer [2], F Quehenberger [9], R Lichem [3], M Kojanova [10], E Adenubiova [4], A Addis [11], L Naldi [5], P I Spuls [1]

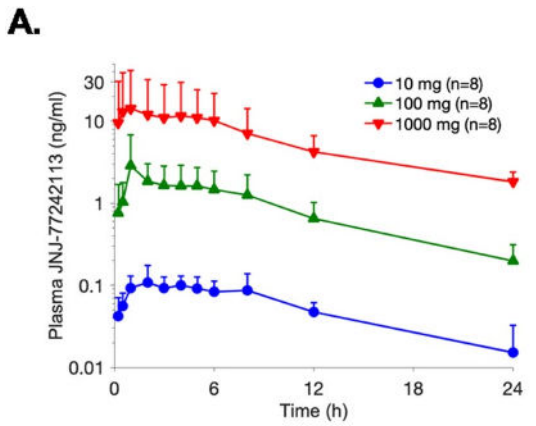
- **Biologic + MTX most commonly used**
- Termination due to safety issues infrequently reported
- Risk for tuberculosis reactivation seems higher when (anti-TNFα) biologics are combined with MTX
- Safety data for combinations with acitretin, UVB and cyclosporin extensive safety data are lacking

Oral Peptide

Development of Orally-Available PEPTIDE IL-23 RECEPTOR Antagonist

- JNJ-77242133
- **IL-23 RECEPTOR blocker** (extracellular domain), NOT cytokine blocker
- High Affinity
  - Kd (dissociation constant) – 7.1 nM
- Highly bioavailable
- Dose-dependent reduction in IFN-y induced by IL-23 in human whole blood assays
- Benefit: NO NEED FOR INJECTION





In vitro protein/cells	Binding affinity/IL-23–induced endpoint	JNJ-77242113 K_D or IC_{50} (pM)	K_D/IC_{50} range[c]	n[d]
Human IL-23R ECD (SPR in vitro)	Binding affinity (K_D)	7.1 ± 2.5	4–10	5
Human PBMC	IL-23–induced STAT3 phosphorylation	5.6 ± 1.2	4.3–6.6	3
Human PBMC	IL-12–induced STAT4 phosphorylation[a]	>2,000,000	–	2
Human NK cells	IL-23–induced IFNγ production	18.4 ± 6.2	12.4–28.3	5
Human (healthy) whole blood	IL-23–induced IFNγ production	11[b]	4–91	15
Human (psoriasis) whole blood	IL-23–induced IFNγ production	9[b]	0.5–35	4
Rat IL-23R ECD (SPR in vitro)	Binding affinity (K_D)	17.5 ± 7.8	12–23	2
Rat whole blood	IL-23–induced IL-17A production (20 ng/mL IL-23)	250 ± 62	160–340	6
Rat whole blood	IL-23–induced IL-17A production (4 ng/mL IL-23)	54 ± 34	12–110	8

Article | Open access | Published: 30 July 2024

JNJ-77242113, a highly potent, selective peptide targeting the IL-23 receptor, provides robust IL-23 pathway inhibition upon oral dosing in rats and humans

Anne M. Fourie, Xiaoli Cheng, Leon Chang, Carrie Greving, Xinyi Li, Beverly Knight, David Polidori, Aaron Patrick, Tripta Bains, Ruth Steele, Samantha J. Allen, Raymond J. Patch, Chengzao Sun, Sandeep Somani, Ashok Bhandari, David Liu, Keith Huie, Shu Li, Michael A. Rodriguez, Xiaohua Xue, Arun Kannan, Teddy Kosoglou, Jonathan P. Sherlock, Jennifer Towne, ... Nishit B. Modi
+ Show authors

Scientific Reports 14, Article number: 17515 (2024) | Cite this article

Oral Peptide

Development of Orally-Available PEPTIDE IL-23 RECEPTOR Antagonist

- FRONTIER-1 Phase 2 placebo-controlled 16-week dose-finding study in adults with PsO completed February 2024

The NEW ENGLAND JOURNAL of MEDICINE

RESEARCH SUMMARY

An Oral Interleukin-23–Receptor Antagonist Peptide for Plaque Psoriasis

Bissonnette R et al. DOI: 10.1056/NEJMoa2308713

CLINICAL PROBLEM

In patients with plaque psoriasis, there is a need for efficacious targeted therapies that can be taken orally. JNJ-77242113 is an oral agent that blocks the pathogenic effects of the cytokine interleukin-23, which is implicated in the pathologic process of this disease.

CLINICAL TRIAL

Design: A phase 2, dose-finding, double-blind, randomized, placebo-controlled trial assessed the efficacy and safety of JNJ-77242113 in patients with moderate-to-severe plaque psoriasis.

Intervention: 255 adults were randomly assigned to receive either JNJ-77242113 at a dose of 25 mg once daily, 25 mg twice daily, 50 mg once daily, 100 mg once daily, or 100 mg twice daily or placebo for 16 weeks. The primary end point was a reduction of ≥75% in the Psoriasis Area and Severity Index score (PASI 75 response; PASI scores range from 0 to 72, with higher scores indicating greater severity or extent of disease) at week 16.

RESULTS

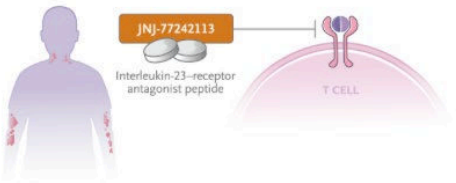
Efficacy: The percentages of patients who had a PASI 75 response were higher among those in the JNJ-77242113 groups than among those in the placebo group. A significant dose–response effect was observed.

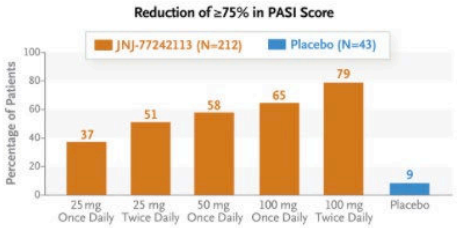
Safety: The incidence of adverse events was generally similar across the groups and did not seem to increase with higher doses of JNJ-77242113.

LIMITATIONS AND REMAINING QUESTIONS

- The number of patients in each trial group was small, and the duration of treatment was short.
- The results cannot be used to infer definitive effects of JNJ-77242113 for particular dose groups or for secondary end points.
- Phase 3 trials are needed to confirm the magnitude and durability of the clinical response to JNJ-77242113.

Links: Full Article | NEJM Quick Take | Editorial





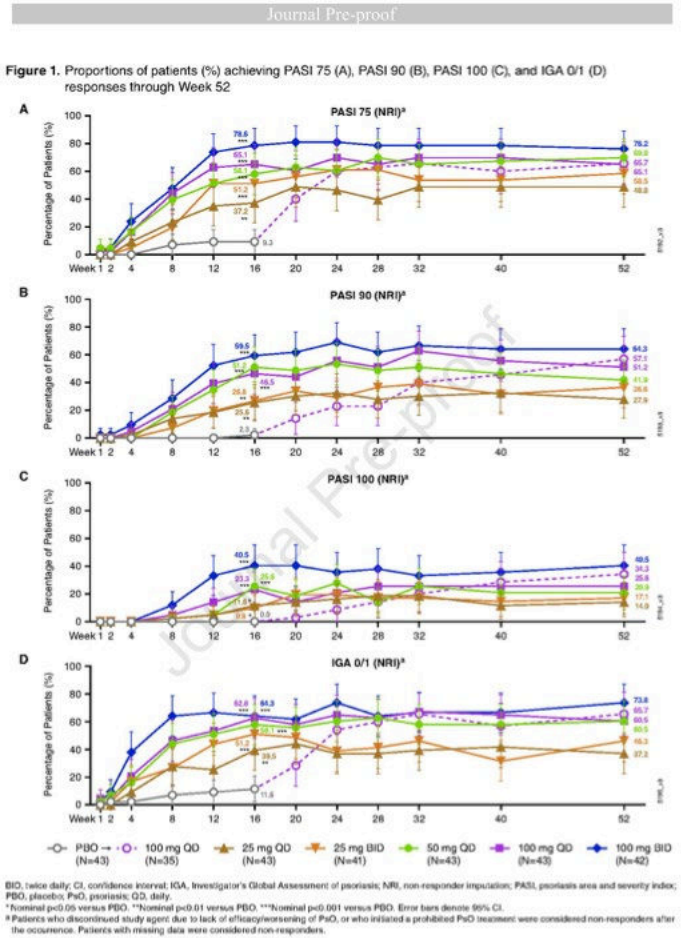
CONCLUSIONS

In patients with moderate-to-severe plaque psoriasis, 16 weeks of treatment with the oral interleukin-23–receptor antagonist peptide JNJ-77242113 showed a dose–response relationship and greater efficacy than placebo.

Oral Peptide

Development of Orally-Available PEPTIDE IL-23 RECEPTOR Antagonist

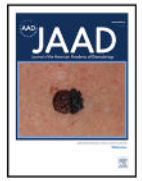
- FRONTIER-2 Phase 2b long-term extension of FRONTIER-1 (adults, weeks 16-52)
- Skin clearance maintained through week 52
- No evidence of dose-dependent AEs
- Most frequent AEs: nasopharyngitis, URI, COVID-19



BID, twice daily; CI, confidence interval; IGA, Investigator's Global Assessment of psoriasis; NRI, non-responder imputation; PASI, psoriasis area and severity index; PBO, placebo; PsO, psoriasis; QD, daily.
*Nominal p<0.05 versus PBO. **Nominal p<0.01 versus PBO. ***Nominal p<0.001 versus PBO. Error bars denote 95% CI.
[a] Patients who discontinued study agent due to lack of efficacy/worsening of PsO, or who initiated a prohibited PsO treatment were considered non-responders after the occurrence. Patients with missing data were considered non-responders.

FRONTIER-2: A phase 2b, long-term extension, dose-ranging study of oral JNJ-77242113 for the treatment of moderate-to-severe plaque psoriasis

Laura K. Ferris, MD, PhD, Jerry Bagel, MD, Yu-Huei Huang, MD, PhD, Andrew E. Pink, PhD, Stephen K. Tyring, MD, PhD, Georgios Kokolakis, MD, PhD, Amy M. DeLozier, DrPH, Shu Li, PhD, Yaung-Kaung Shen, PhD, Charles Iaconangelo, PhD, Takayuki Ota, MD, PhD, Robert Bissonnette, MD



Oral Peptide

Development of Orally-Available PEPTIDE IL-23 RECEPTOR Antagonist

- Upcoming Phase 3 trials

Active, not recruiting

A Study of JNJ-77242113 in Adolescent and Adult Participants With Moderate to Severe Plaque Psoriasis (ICONIC-LEAD)

ClinicalTrials.gov ID NCT06095115

>= 12 years old
Co-primary Endpoint: PASI-90 & IGA 0/1
Contains WITHDRAWAL arm

Active, not recruiting

A Study of JNJ-77242113 for the Treatment of Participants With Plaque Psoriasis Involving Special Areas (Scalp, Genital, and/or Palms of the Hands and the Soles of the Feet) (ICONIC-TOTAL)

ClinicalTrials.gov ID NCT06095102

>= 12 years old
Special Sites*

Active, not recruiting

A Study of JNJ-77242113 for the Treatment of Participants With Moderate to Severe Plaque Psoriasis (ICONIC-ADVANCE 2)

ClinicalTrials.gov ID NCT06220604

>= 18 years old
Deucravacitinib active comparator**

Active, not recruiting

A Study of JNJ-77242113 for the Treatment of Participants With Generalized Pustular Psoriasis or Erythrodermic Psoriasis

ClinicalTrials.gov ID NCT06295692

>= 12 years old
GPP

Modification

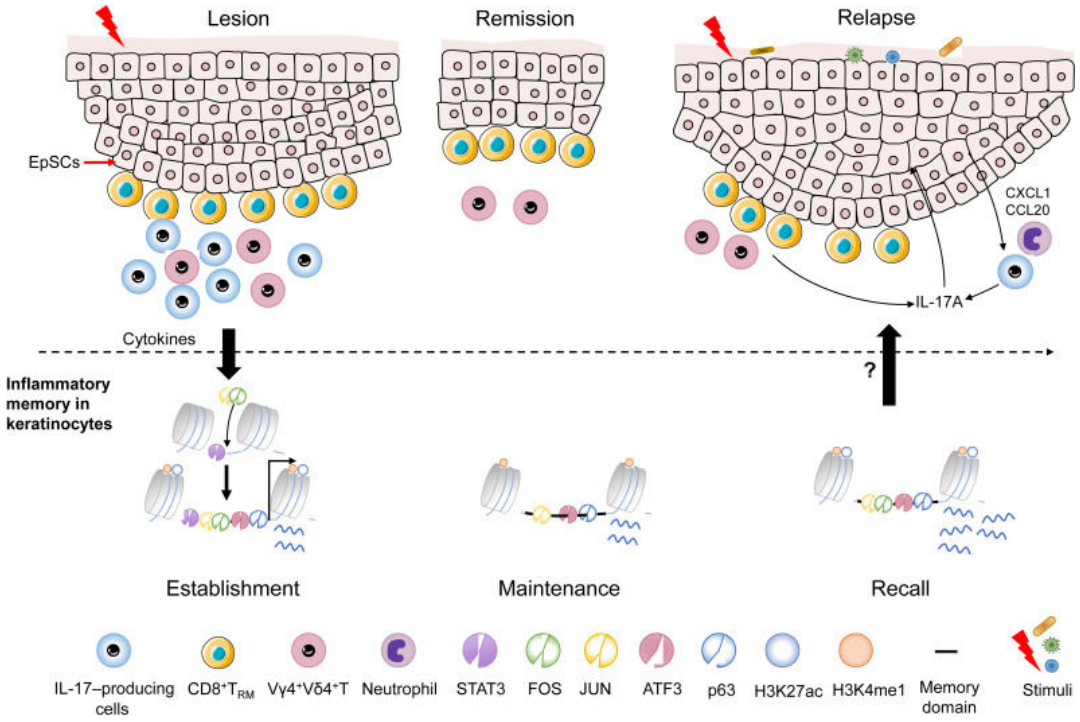
Disease Modification in PsO

- Recent efforts to defined “disease modification” internationally
- Delphi consensus in 2023 developed following definition and measurement criteria:
    - ***A sustained improvement in the disease course of plaque psoriasis resulting from a change in pathophysiology that minimizes the need for treatment***
    - In patients with moderate-to-severe plaque psoriasis, in the absence of precise biomarkers, disease modification may be evaluated by sustained BSA <1% / PGA 0-1 for >12 months *following treatment cessation*

Modification

Disease Modification in PsO

- Mounting evidence shows that resolved psoriatic skin lesions contain a population of **resident memory T cells (Trm)** that are responsible for local relapse of psoriasis
- **Skin epithelial stem cells (EpSCs)** that give rise to keratinocytes also exhibit inflammatory memory
  - Can mount robust inflammatory reaction upon challenge (i.e. Koebner effect)
  - Imiquimod mouse model of PsO showed that EpSCs were long lived in the inflamed skin after the resolution of inflammation
  - Exhibit chromatin epigenetic changes that lead to memory*




REVIEW · Volume 2, Issue 3, 100116, May 2022 · Open Access Download Full Issue

The Relapse of Psoriasis: Mechanisms and Mysteries

Danning Tian[1] · Yuping Lai[1,2]

Affiliations & Notes Article Info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Perspective | Published: 13 July 2023

Disease modification in inflammatory skin disorders: opportunities and challenges

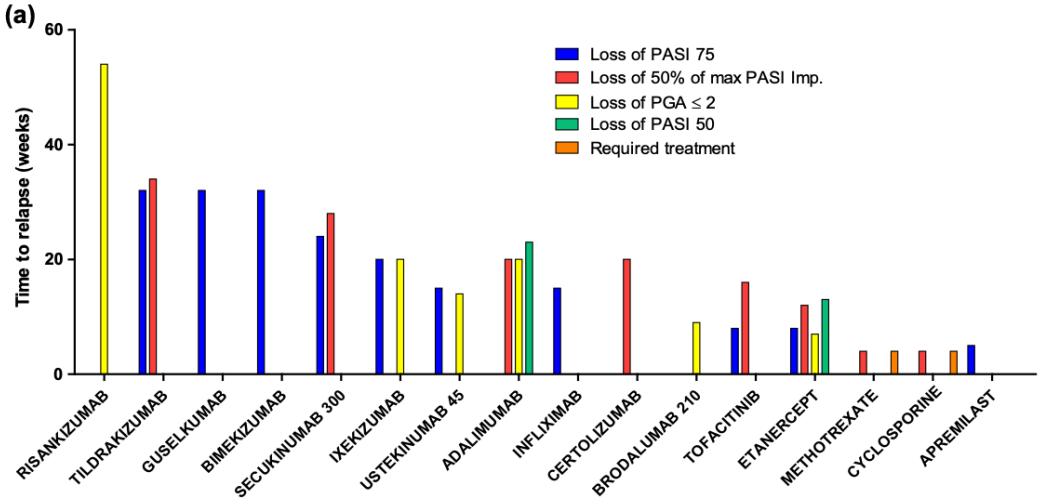
Thomas Bieber

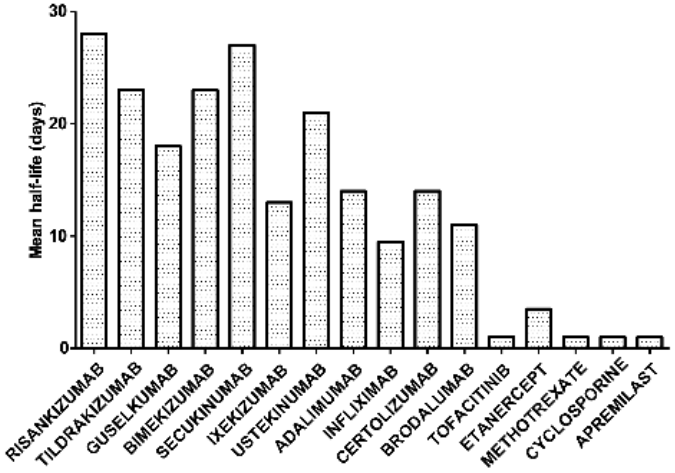
Nature Reviews Drug Discovery 22, 662–680 (2023) | Cite this article

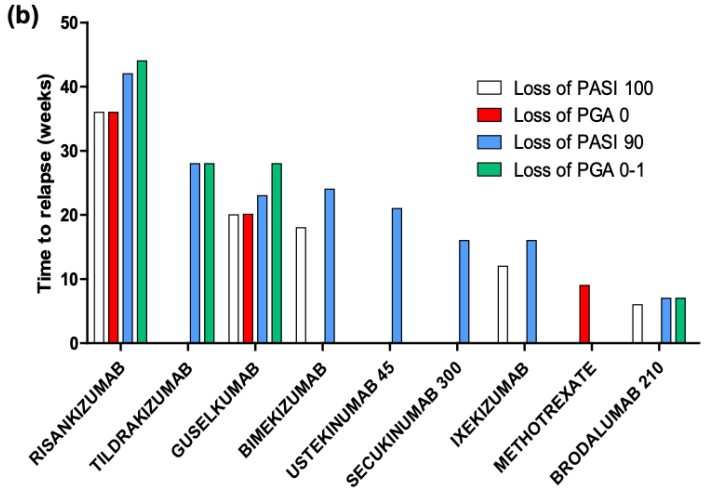
Modification

Time to Relapse After PsO Biologic Discontinuation

- General pattern that IL-23 & IL-17 inhibition >>> TNFa, oral small molecules, PDE4i
- Longer median time to relapse overall seems to be related to biologics with greater half-lives







American Journal of Clinical Dermatology (2022) 23:433–447
https://doi.org/10.1007/s40257-022-00679-y

SYSTEMATIC REVIEW

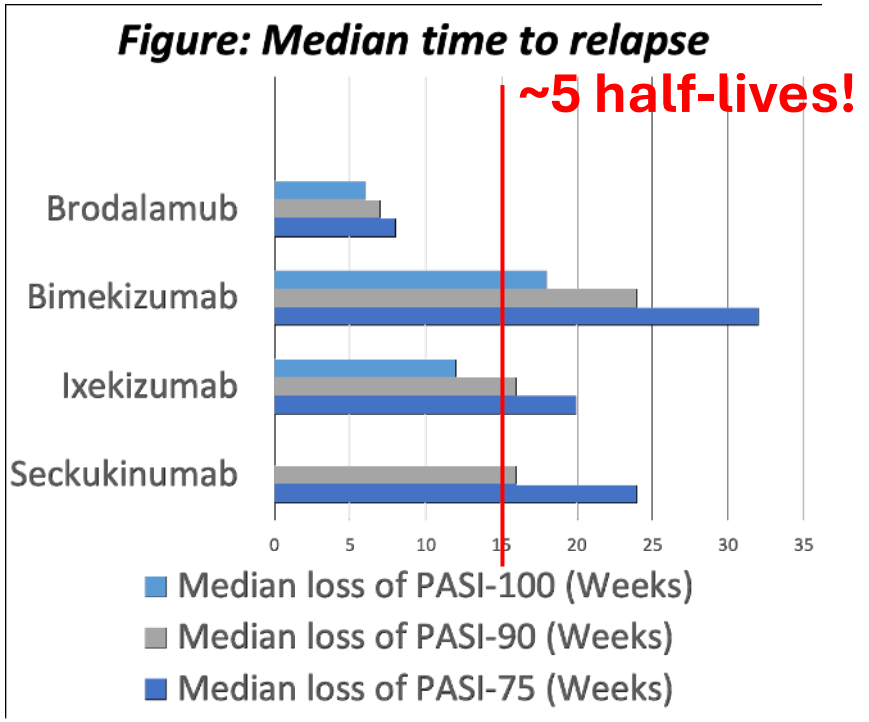
Time to Relapse After Discontinuing Systemic Treatment for Psoriasis: A Systematic Review

Marie Masson Regnault[1] · Jason Shourick[2] · Fatma Jendoubi[3] · Marie Tauber[3] · Carle Paul[3]

Modification

Pharmacokinetic Explanations for Differences Among IL-17 Class?

- Brodalumab has the quickest relapse time and the shortest half-life, bioavailability and lowest binding affinity for its target (IL-17 receptor)
  - However, efficacy of Brodalumab is ~ to other IL-17 inhibitors and half-life is ~ to Ixekizumab so difference in time to relapse remains elusive
  - Perhaps explained by the relatively low binding affinity for its target resulting in increased clearance or diminished sustained efficacy
  - IL-17 cytokines still in milieu and may signal through alternate pathways
- Half-life appears to be a major factor in determining time to relapse given the ~40-fold difference in binding affinity between Secukinumab and Ixekizumab and similar bioavailability
- **Differences in target binding association (Kon) & dissociation constants (Koff) may explain the longest time to relapse seen with Bimekizumab among the IL-17 family**
  - **Bimekizumab has LOWEST Koff (<1.0 x 10^{-6} nM) amongst the IL-17A inhibitors means it binds the tightest**
- **Targeting IL-17F is also a unique variable to bimekizumab**



Drug	Half-life (Days)	Bioavailability (%)	Binding Affinity (Kd) (nM)		Binding affinity (K_{on}) ($M^{-1}S^{-1}$)		Binding affinity (K_{off}) (S^{-1})	
Secukinumab	27	73	IL-17A = 0.060		IL-17A = 4.3 x 10^5		IL-17A = 2.6 x 10^{-5}	
Ixekizumab	13	72	IL-17A = 0.0018		IL-17A = 7.5 x 10^6		IL-17A = 1.3 x 10^{-5}	
Bimekizumab	23	70.1	IL-17A = 0.003	IL-17F = 0.023	IL-17A = 9.21 x 10^5	IL-17F = 7.23 x 10^5	IL-17A = < 1.0 x 10^{-6}	IL-17F = 1.01 x 10^{-4}
Brodalumab	11	54.8	IL-17RA = 0.239		NA		NA	

Al-Tariq, K., Bunick, CG., **Issa, N.T.** (*In Preparation*)

Modification

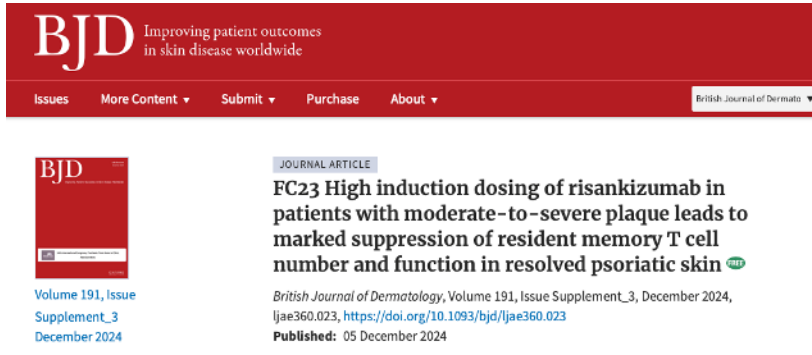
Does High Biologic Induction Dose Modify Disease Course?

- Effort by Dr. Andy Blauvelt
- Phase 2, double-blind, single-center KNOCKOUT study
- N = 20 (16 completed 52 wks)
- **Tx: Risankizumab 300mg or 600mg at Weeks 0, 4 and 16 *without further dosing***
  - **FDA approved dosing = 150 mg***
- Primary Endpoint: sPGA at weeks 16 & 52
- Exploratory: scRNA-seq of biopsy samples at week 0 & 52

Modification

Does High Biologic Induction Dose Modify Disease Course?

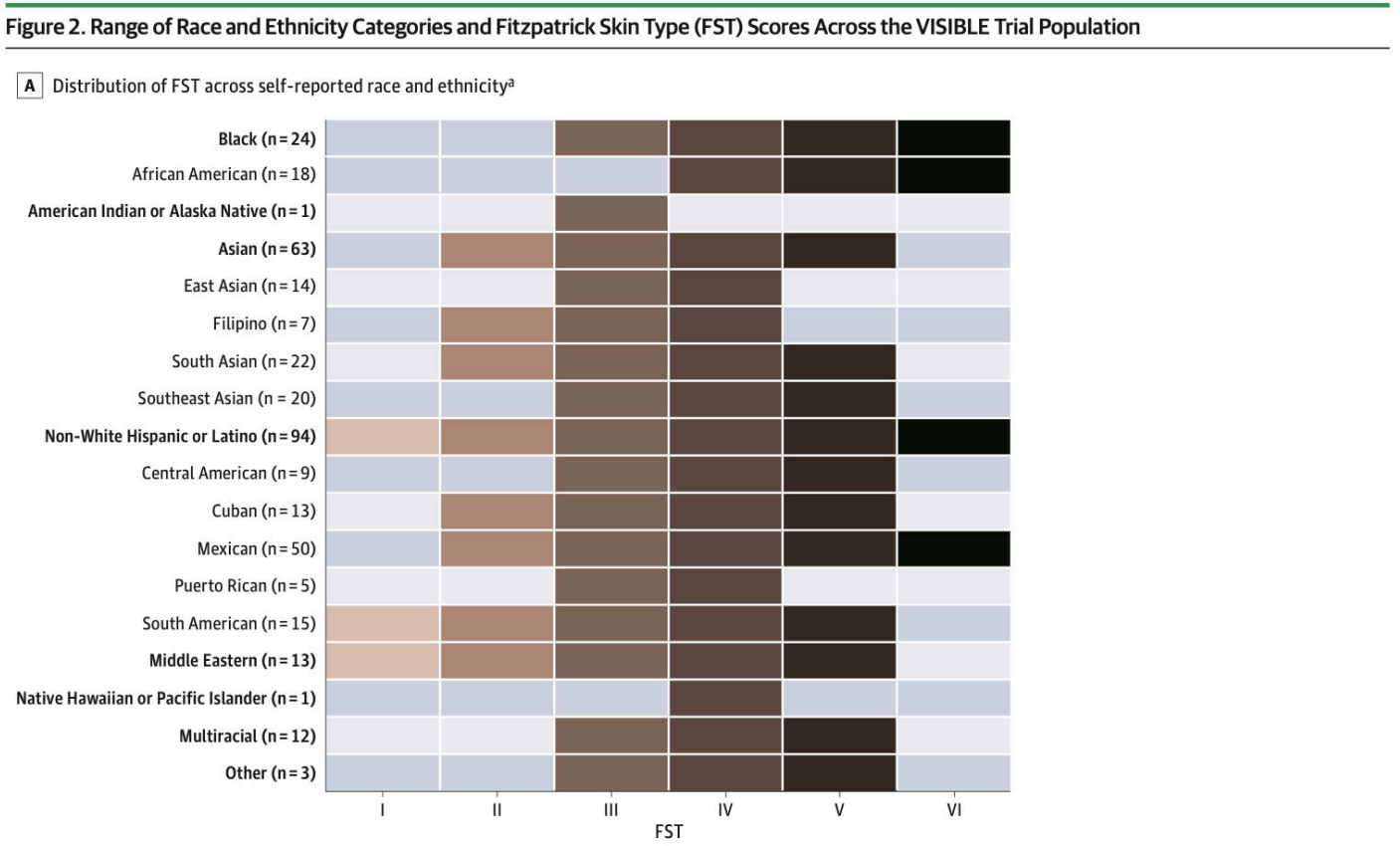
- At Week 16, sPGA 0/1 and sPGA 0 responses were achieved by **94.4% and 66.7%** of all patients, respectively
- At Week 52, 36 weeks after the last dose, sPGA 0/1 and sPGA 0 responses were achieved by **61.1% and 44.4%** of all patients, respectively.
- In lesions of patients receiving the higher dose (600 mg) of risankizumab, the **number of CD8+ tissue-resident memory T (TRM) cells was markedly reduced**, with more marked suppression of the intercellular communication network between TRM and keratinocytes compared with the lower dose (300 mg) group.



SOC

Updates in Studies Focusing on Skin of Color Patients

- Diverse racial and ethnic representation in clinical trials has been limited
- Limited primary data on clinical response, genetics, and quality of life in populations with psoriasis and skin of color (SoC).
  - SoC = race and/or ethnicity other than White
  - Lack of correlation b/w race/ethnicity (social constructs) & FST
    - **Race/ethnic groups can contain spectrum of FST**
  - FST (propensity to tan/burn) cannot be reliably approximated from skin tone
- Varying Skin Tones in Body and Scalp Psoriasis: Guselkumab Efficacy and Safety trial (VISIBLE)
  - **First large-scale, Phase 3b RCT dedicated to evaluating psoriasis and treatment outcomes in participants with SoC, including all skin tones, using a combination of objective and patient-reported parameters.**



Original Investigation

December 11, 2024

Improving Diversity in a Novel Psoriasis Study

VISIBLE as a Framework for Clinical Trial Quality Improvement

Andrew Alexis, MD, MPH[1]; Amy McMichael, MD[2]; Neelam Vashi, MD[3]; et al

Author Affiliations | Article Information

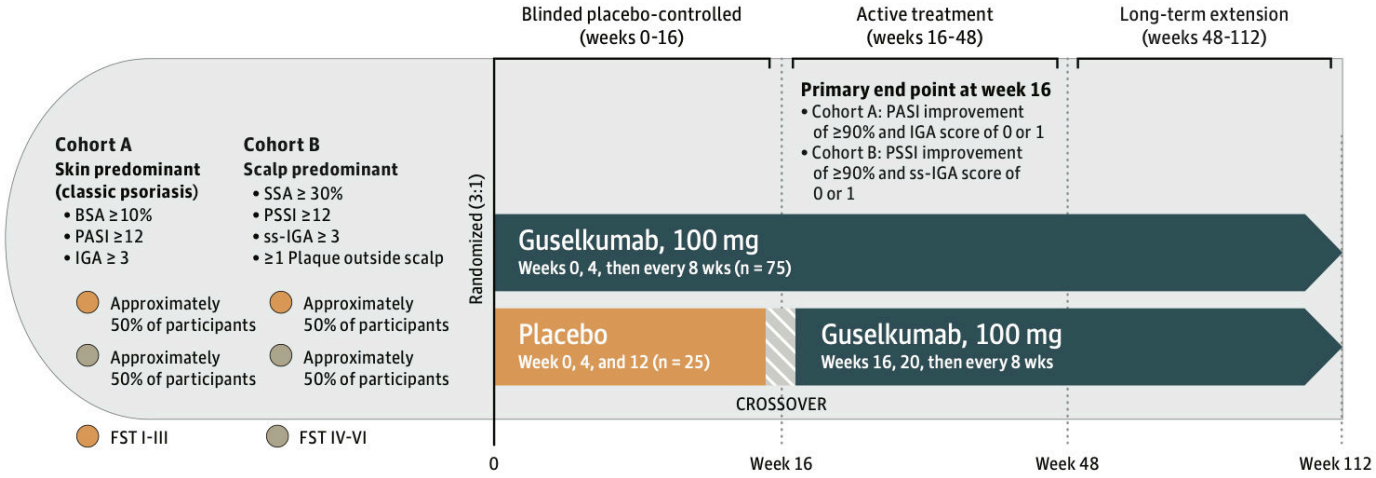
JAMA Dermatol. Published online December 11, 2024. doi:10.1001/jamadermatol.2024.5103

SOC

Updates in Studies Focusing on Skin of Color Patients

- Classic psoriasis and scalp predominant cohorts
- In both cohorts, PASI/PSSI 90 and IGA/ss-IGA 0/1 achieved by 57.1%/65.8% and 68.4%/74.0%, respectively (data available by Janssen Immunology*)

Figure 1. The VISIBLE Study Design



BSA indicates body surface area; FST, Fitzpatrick skin type; IGA, Investigator's Global Assessment; PASI, Psoriasis Area and Severity Index; PSSI, Psoriasis Scalp Severity Index; SSA, scalp surface area; and ss-IGA, scalp-specific IGA.

Original Investigation
December 11, 2024

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VISIBLE as a Framework for Clinical Trial Quality Improvement

Andrew Alexis, MD, MPH[1]; Amy McMichael, MD[2]; Neelam Vashi, MD[3]; et al
Author Affiliations | Article Information
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Special Sites

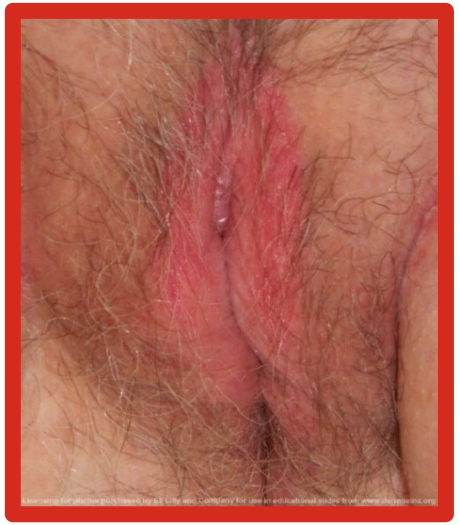
Updates in Studies Focusing on PsO Involving High-Impact Sites

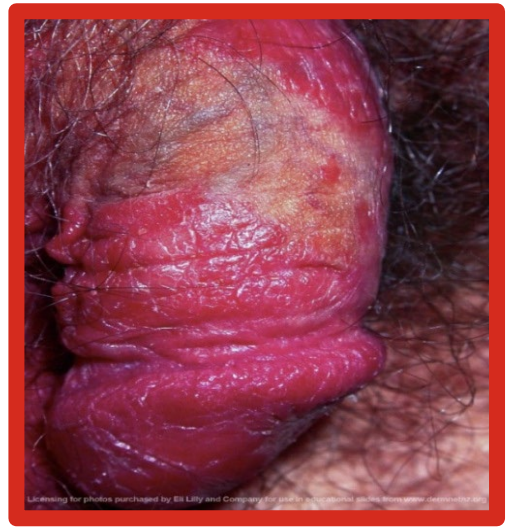
- **Genital**
- Palmoplantar
- Scalp
- Nails
- Intertriginous

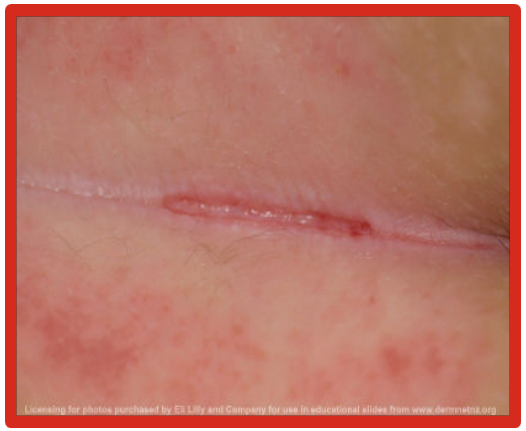
Genital

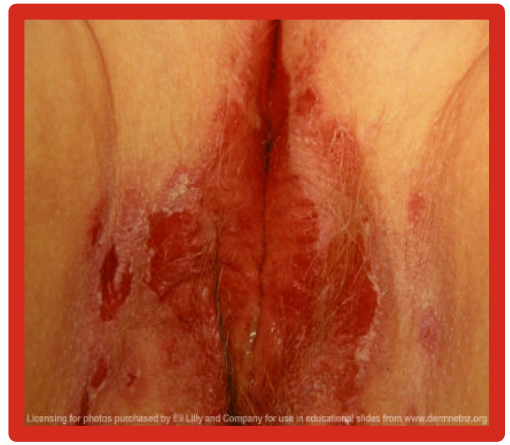
Large Burden on QoL

- Current therapies for genital psoriasis have limitations[3,4]
  - Risk of adverse reactions to topical treatments
  - Limited options for patients who fail topical treatment
  - Absence of published data and controlled studies
- Severe pruritus may lead to scratching, significant excoriations (abrasions), and lichenification (diffuse thickening of the epidermis)
- **There is a need for dedicated trials examining the efficacy of treatments, including biologics, specifically in genital psoriasis**









1. Buechner SA. *BJU Int* 2002;90:498-506
2. Welsh BM et al. *Med J Aust* 2003;178:391-5
3. Meeuwis KA et al. *Acta Derm Venereol* 2015;95:211-6
4. Meeuwis KA et al. *Acta Derm Venereol* 2011;91:5-11

Genital

Studies

Randomized, Double-Blind, Placebo-Controlled

- Apremilast – DISCREET (2024)
- Ixekizumab – IXORA-Q (2018/2020)
- Guselkumab – SPECTREM (2024)


ORIGINAL ARTICLES

Efficacy and safety of apremilast in patients with moderate-to-severe genital psoriasis: Results from DISCREET, a phase 3 randomized, double-blind, placebo-controlled trial

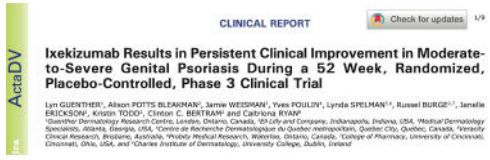
Joseph F Merola, MD, MMSc,[1] Lawrence Charles Parish, MD, MD (Hon),[2] Lyn Guenther, MD,[3] Charles Lynde, MD,[4,5] Jean-Philippe Lacour, MD,[6] Petra Staubach, MD,[7] Sue Cheng, MD, PhD,[8] Maria Paris, MD,[1] Hernan Picard, MD, PhD,[8] Cynthia Deignan, PhD,[1] Shauna Jardon, PharmD,[1] Mindy Chen, MS,[8] and Kim A. Papp, MD, PhD[9,10]


CLINICAL TRIAL

British Journal of Dermatology

Efficacy and safety of ixekizumab in a randomized, double-blinded, placebo-controlled phase IIIb study of patients with moderate-to-severe genital psoriasis*

C. Ryan,[1] A. Menter,[2] L. Guenther,[3] A. Blauvelt,[4] R. Bissonnette,[5] K. Meeuwis,[6] J. Sullivan,[7] J.C. Cather,[8] G. Yosipovitch,[9] A.B. Gottlieb,[10] J.F. Merola,[11] K. Callis Duffin,[12] S. Fretzin,[13] O.O. Osuntokun,[14] R. Burge,[14] A.N. Naegeli,[14] F.E. Yang,[14] C.-Y. Lin,[14] K. Todd[14] and A. Potts Bleakman[14] on behalf of the IXORA-Q Study Group


ActaDV

CLINICAL REPORT

Ixekizumab Results in Persistent Clinical Improvement in Moderate-to-Severe Genital Psoriasis During a 52 Week, Randomized, Placebo-Controlled, Phase 3 Clinical Trial


SPECTREM: Guselkumab Demonstrates Consistent Complete Clearance at Week 16 Across Special Sites in Participants with Low Body Surface Area, Moderate Psoriasis

SPECTREM: Guselkumab Demonstrates Significant Clearance at Week 16 Across Special Sites in Participants with Low Body Surface Area, Moderate Psoriasis

Retrospective or Observational


Australasian Journal of Dermatology

REVIEW ARTICLE | Open Access

JEADV

Adult genital psoriasis: An updated review for clinicians

Michelle Wu BMed, MD, Gayle Fischer MD, FACD

First published: 28 February 2024 | https://doi.org/10.1111/ajd.14227 | Citations: 1

ORIGINAL ARTICLE

Effectiveness of guselkumab in patients with facial and/or genital psoriasis: Interim analysis results at Week 12 from the GULLIVER study

C. Bonifati, S. Lembo, A. G. Richetta, M. Romanelli, F. Satolli, M. Corazza, L. Atzori, C. Lasagni, C. Potenza, P. Savoia, F. Bardazzi, V. G. Di Lernia, L. Bianchi, G. Fabbrocini, C. Giofrè, L. Zichichi ... See all authors

First published: 26 June 2024 | https://doi.org/10.1111/jdv.20187

Dermatology Practical & Conceptual

A Real-Life 208 Week Single-Centred, Register-Based Retrospective Study Assessing Secukinumab Survival and Long-Term Efficacy and Safety Among Greek Patients with Moderate to Severe Plaque Psoriasis, Including Difficult-to-Treat Manifestations Such as Genitals and Scalp

Effectiveness of ixekizumab for the treatment of moderate-to-severe plaque psoriasis with involvement of difficult-to-treat areas: A 52-week multicenter retrospective study

Dermatology Practical & Conceptual

Bimekizumab for the Treatment of Plaque Psoriasis with Involvement of Genitalia: A 16-Week Multicenter Real-World Experience — IL PSO (Italian Landscape Psoriasis)

Dermatology and Therapy

Adis

Dermatol Ther (Heidelb). 2024 Mar 27;14(4):907–918. doi: 10.1007/s13555-024-01134-y

Effectiveness of Ixekizumab in Chinese Patients with Moderate-Severe Plaque Psoriasis with Special Area Involvement: Subanalysis of a Prospective, Multicenter, Observational Real-World Study


Research Article

Effectiveness of tildrakizumab 200 mg: an Italian multicenter study

Annunziata Dattola, Nicoletta Bernardini, Francesca Svara, Anna Balato, Giacomo Caldarola, Domenico D'Amico, ...show all

Article: 2420825 | Received 16 Sep 2024, Accepted 14 Oct 2024, Published online: 27 Oct 2024

Cite this article | https://doi.org/10.1080/09546634.2024.2420825

Journal of Clinical Medicine

MDPI

J Clin Med. 2024 Jan 16;13(2):495. doi: 10.3390/jcm13020495

Effectiveness, Tolerability, and Drug Survival of Risankizumab in a Real-World Setting: A Three-Year Retrospective Multicenter Study—IL PSO (ITALIAN LANDSCAPE PSORIASIS)

Comparative Study | Dermatol Ther. 2020 Jan;33(1):e13110. doi: 10.1111/dth.13110. Epub 2019 Dec 4.

Biological therapy in genital psoriasis in women

Martina Burlando [1], Astrid Herzum [1], Luca Carmisciano [2], Emanuele Cozzani [1], Aurora Parodi [1]

JOURNAL ARTICLE | ACCEPTED MANUSCRIPT

Long-term effectiveness and safety of deucravacitinib in psoriasis: A 52-week real-world study of genital, scalp, and nail lesions

Get access

Teppei Hagino, Hidehisa Saeki, Eita Fujimoto, Naoko Kanda

Clinical and Experimental Dermatology, llae530, https://doi.org/10.1093/ced/llae530

Published: 06 December 2024 **Article history**


DOI: 10.1111/dde.13974

ORIGINAL ARTICLE

DERMATOLOGIC THERAPY WILEY

Efficacy and safety of adalimumab in difficult-to-treat psoriasis

Review | Dermatol Pract Concept. 2023 Jul 1;13(3):e2023245. doi: 10.5826/dpc.1303a245.

Brodalumab in the Treatment of Plaque Psoriasis Localized in Difficult-to-Treat Areas: A Narrative Review

Maria Vittoria Cannizzaro [1], Giulia Coscarella [1, 2], Andrea Chiricozzi [1, 2]

Genital

Apremilast DISCREET Trial

- Significantly greater response in apremilast group for modified genital PGA as early as week 4

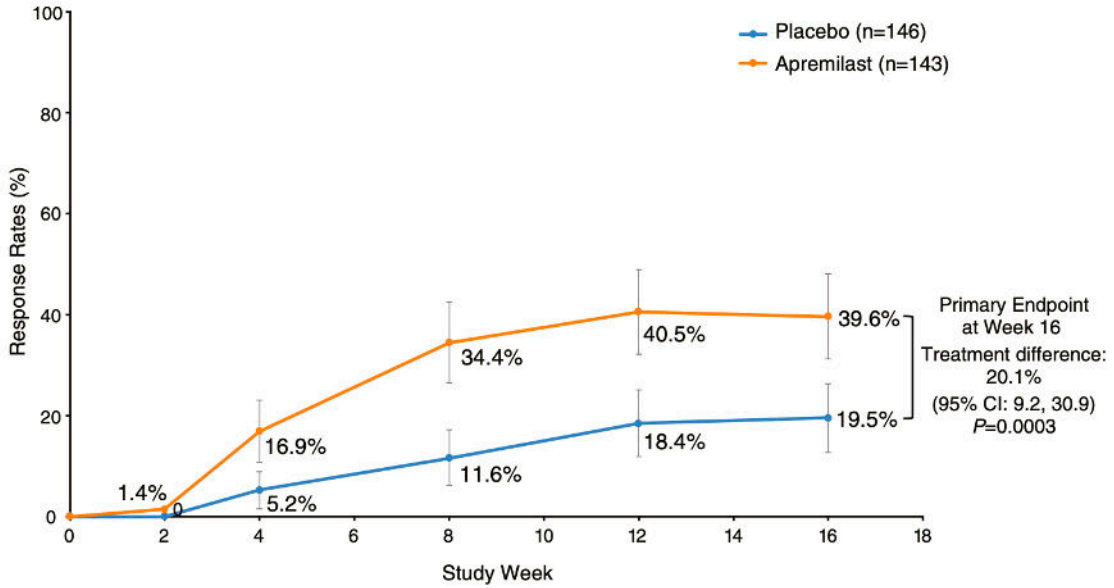


Fig 1. Proportion of patients with modified genital PGA response over 16 weeks (clear or almost clear with ≥2-point reduction). Error bars represent 95% CI. Multiple imputations used for missing data. Modified genital PGA response is defined as a score of 0 (clear) or 1 (almost clear) with a ≥2-point reduction from baseline. Includes patients in the intent-to-treat population. *Genital PGA*, static Physician Global Assessment of Genitalia.

ORIGINAL ARTICLES

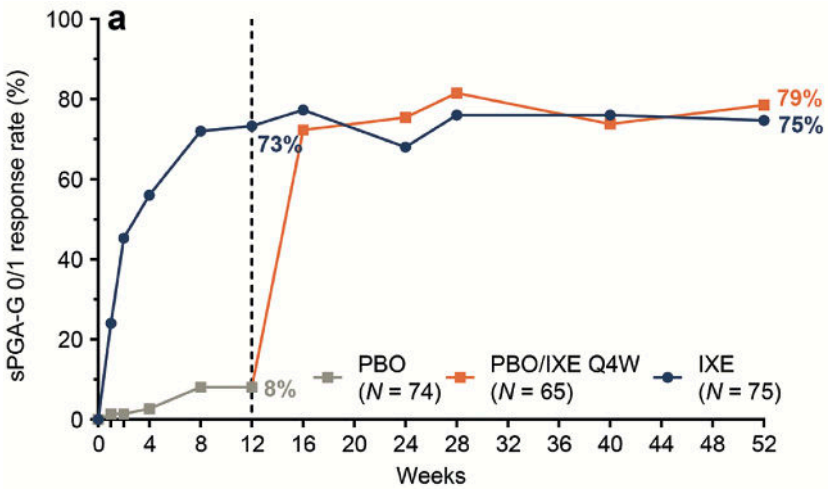
Efficacy and safety of apremilast in patients with moderate-to-severe genital psoriasis: Results from DISCREET, a phase 3 randomized, double-blind, placebo-controlled trial

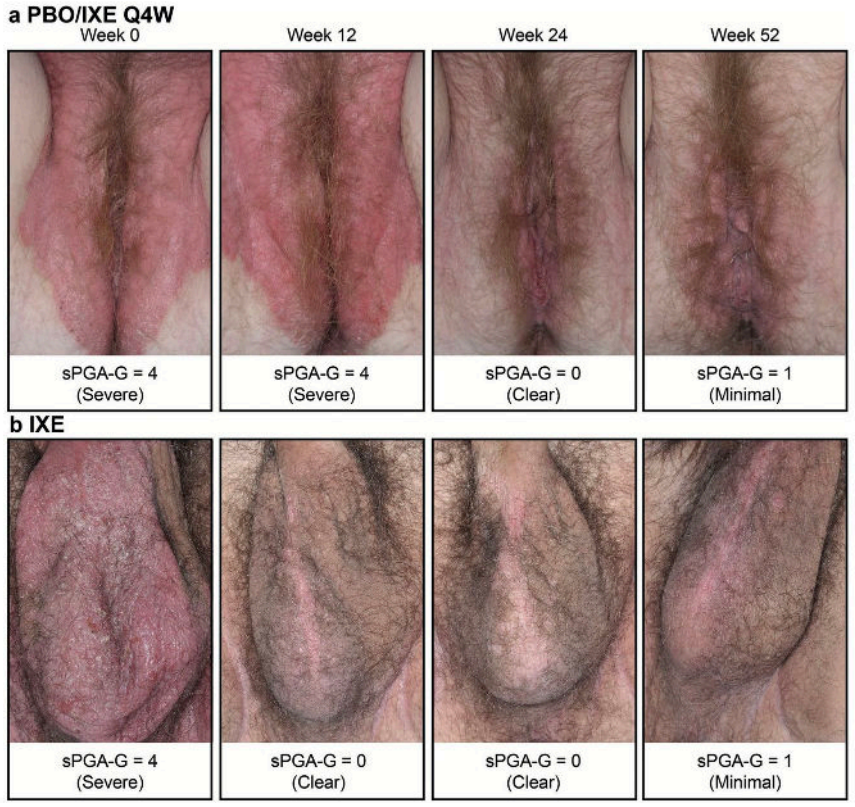
Joseph F. Merola, MD, MMSc,[a] Lawrence Charles Parish, MD, MD (Hon),[b] Lyn Guenther, MD,[c] Charles Lynde, MD,[d,e] Jean-Philippe Lacour, MD,[f] Petra Staubach, MD,[g] Sue Cheng, MD, PhD,[h] Maria Paris, MD,[i] Hernan Picard, MD, PhD,[h] Cynthia Deignan, PhD,[j] Shauna Jardon, PharmD,[j] Mindy Chen, MS,[h] and Kim A. Papp, MD, PhD[k,l]

Genital

Ixekizumab IXORA-Q Trial

- Inclusion criteria:
  - sPGA >= 3
  - sPGA-G >=3
  - BSA >= 1%
  - Confirmation of plaque psoriasis in a non-genital area
  - Failed or intolerant to >= 1 topical tx
- Significantly greater response in ixekizumab group for static Physician's Global Assessment of Genitalia (sPGA-G) as early as week 1
- Effects persisted through Week 52





CLINICAL TRIAL

BJD British Journal of Dermatology

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C. Ryan,[1] A. Menter,[2] L. Guenther,[3] A. Blauvelt,[4] R. Bissonnette,[5] K. Meeuwis,[6] J. Sullivan,[7] J.C. Cather,[8] G. Yosipovitch,[9] A.B. Gottlieb,[10] J.F. Merola,[11] K. Callis Duffin,[12] S. Fretzin,[13] O.O. Osuntokun,[14] R. Burge,[14] A.N. Naegeli,[14] F.E. Yang,[14] C.-Y. Lin,[14] K. Todd[14] and A. Potts Bleakman[14] on behalf of the IXORA-Q Study Group

ActaDV

CLINICAL REPORT

Check for updates 1/9

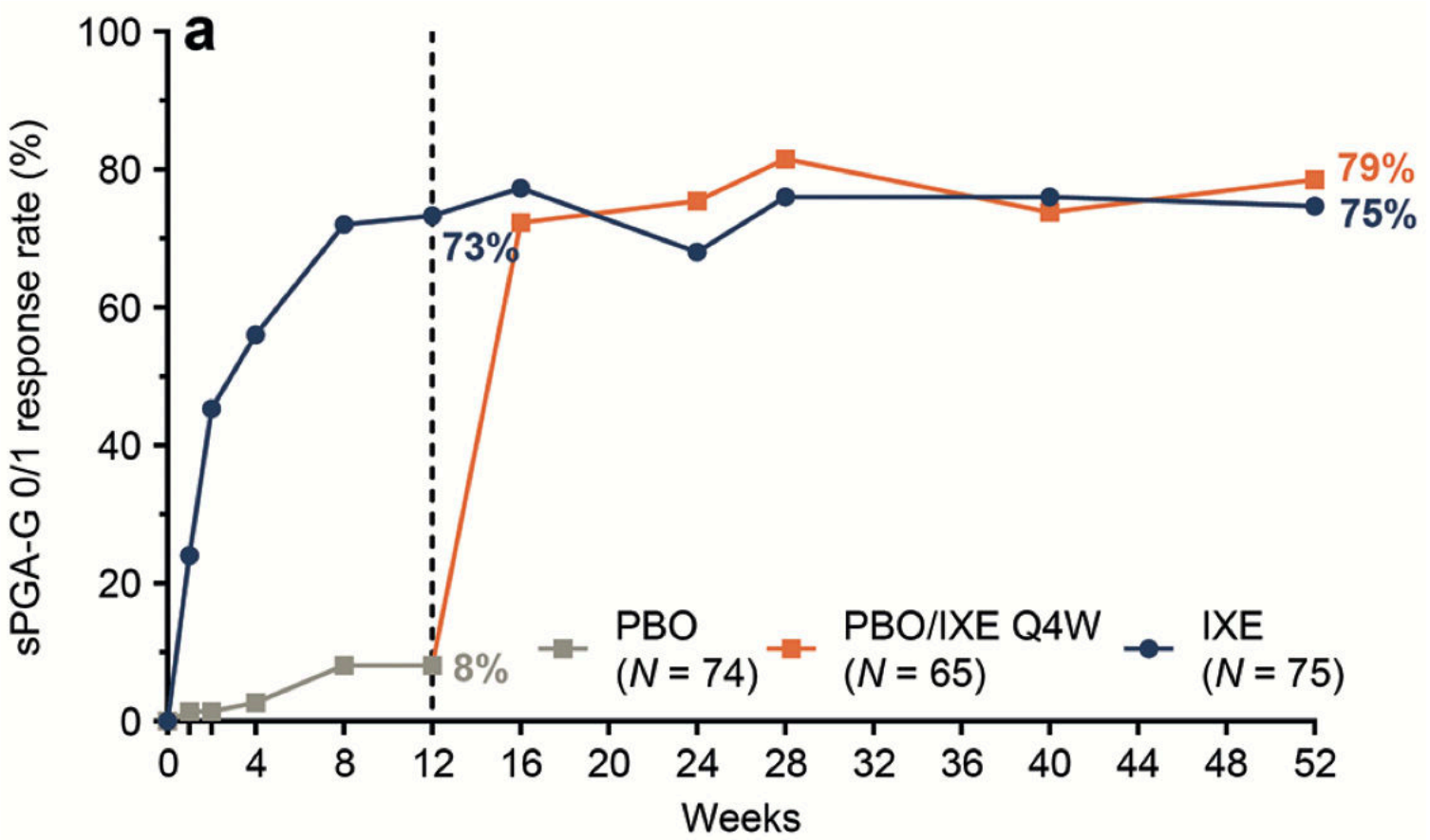
Ixekizumab Results in Persistent Clinical Improvement in Moderate-to-Severe Genital Psoriasis During a 52 Week, Randomized, Placebo-Controlled, Phase 3 Clinical Trial

Lyn GUENTHER[1], Alison POTTS BLEAKMAN[2], Jamie WEISMAN[3], Yves POULIN[4], Lynda SPELMAN[5,6], Russel BURGE[2,7], Janelle ERICKSON[2], Kristin TODD[2], Clinton C. BERTRAM[2] and Caitriona RYAN[8]
[1]Guenther Dermatology Research Centre, London, Ontario, Canada, [2]Eli Lilly and Company, Indianapolis, Indiana, USA, [3]Medical Dermatology Specialists, Atlanta, Georgia, USA, [4]Centre de Recherche Dermatologique du Quebec metropolitain, Quebec City, Quebec, Canada, [5]Veracity Clinical Research, Brisbane, Australia, [6]Probity Medical Research, Waterloo, Ontario, Canada, [7]College of Pharmacy, University of Cincinnati, Cincinnati, Ohio, USA, and [8]Charles Institute of Dermatology, University College, Dublin, Ireland

Genital

Ixekizumab IXORA-Q Trial

- Significantly greater response in ixekizumab group for static Physician's Global Assessment of Genitalia (sPGA-G) as early as week 1
- Effects persisted through Week 52



Genital

Guselkumab SPECTREM Trial

Methods

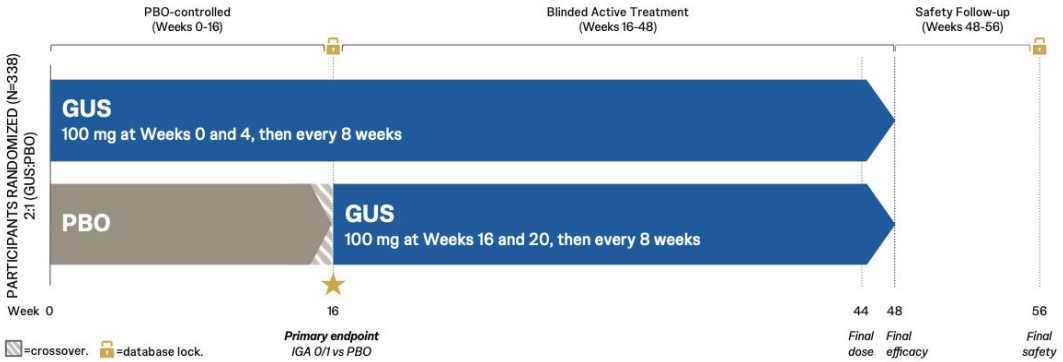
A total of 338 participants were randomized to receive GUS (N=225) or PBO (N=113)

Key Inclusion Criteria

- IGA=3
- BSA=2-15% with ≥1 plaque outside of special sites
- ≥1 special site with at least moderate severity (scalp, face, intertriginous, genital)

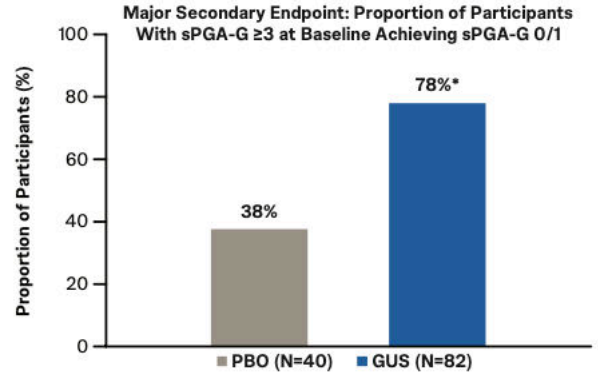
Endpoints presented at Week 16 included:

- Key major secondary endpoints:
  - Proportions of participants achieving ss-IGA 0/1, f-IGA 0/1, i-IGA 0/1, and sPGA-G 0/1



78% of GUS-randomized participants achieved sPGA-G 0/1 at Week 16

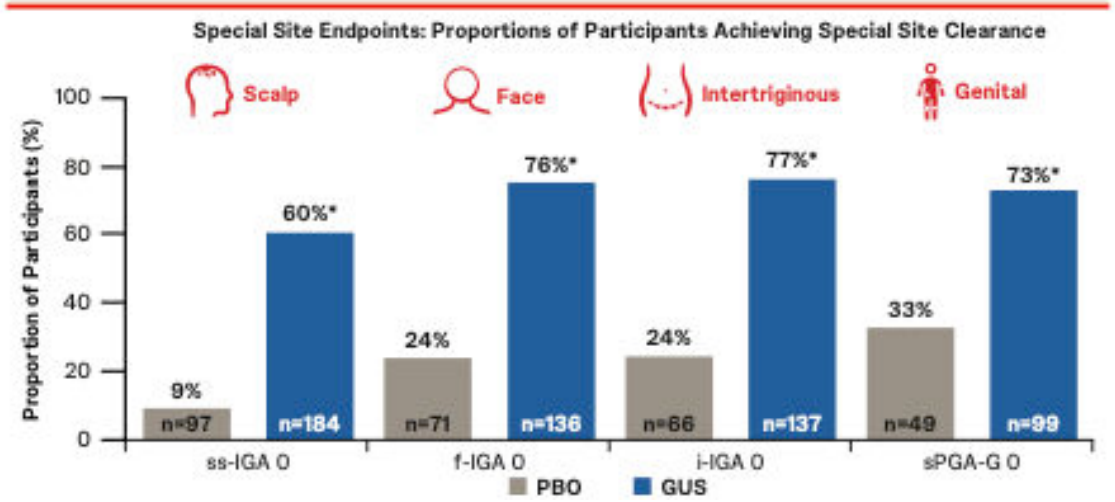
Genital



*p<0.001 GUS vs PBO; p-value is based on the chi-squared test, not adjusted for baseline stratification factor. NRI was used: participants who discontinued study agent due to lack of efficacy, worsening of PsO, or use of a prohibited PsO treatment prior to designated visit were considered nonresponders from that point forward. Participants with missing data were considered nonresponders.

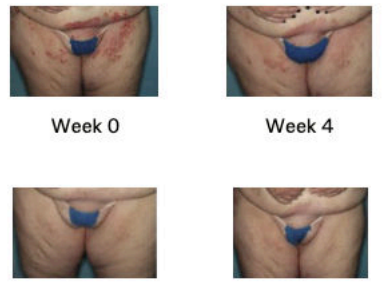
>70% achieved sPGA-G 0 (complete clearance) by week 16

≥60% of GUS-randomized participants achieved complete clearance of assessed special sites at Week 16



GUS-randomized participant with sPGA-G ≥3 at baseline who achieved sPGA-G 0/1 at Week 16

Genital



SPECTREM: Guselkumab Demonstrates Significant Clearance at Week 16 Across Special Sites in Participants with Low Body Surface Area, Moderate Psoriasis

SPECTREM: Guselkumab Demonstrates Consistent Complete Clearance at Week 16 Across Special Sites in Participants with Low Body Surface Area, Moderate Psoriasis

Genital

Ixekizumab vs Secukinumab

- 2021 small-scale 1:1 randomized trial over 24 weeks
- Similar sPGA-G outcome between ixekuzmab and secukinumab (IL-17A inhibitors)
- No placebo control

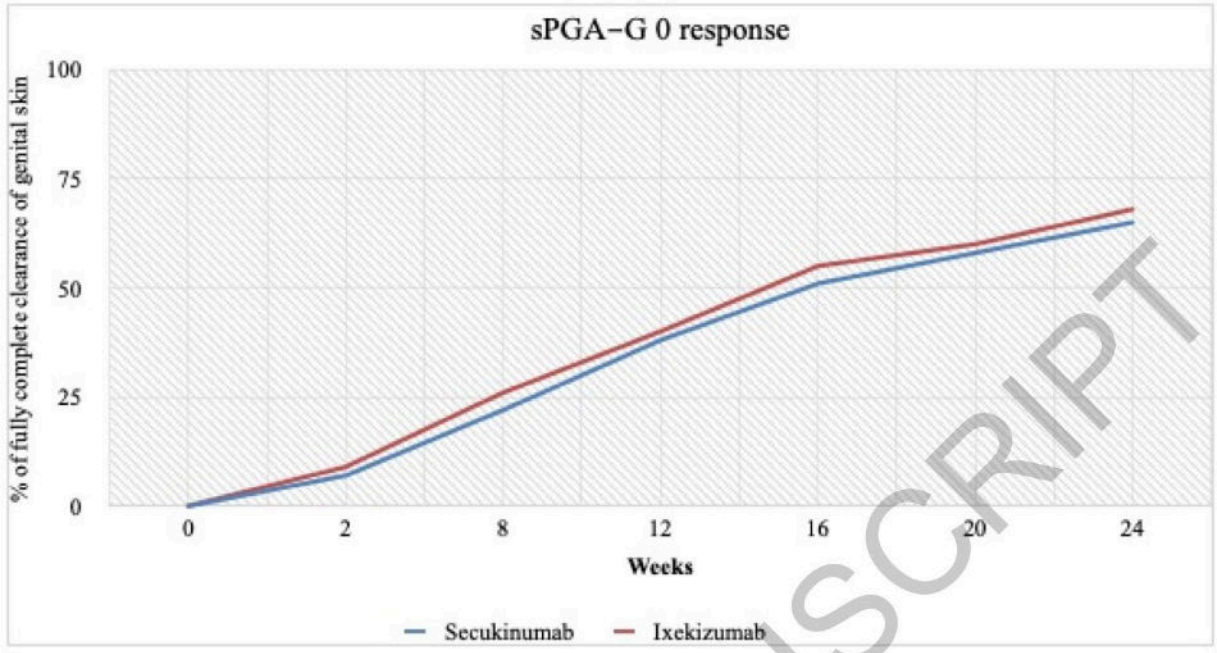


Figure 2. sPGA?G 0 response throughout 24 weeks

Original Research

A Randomized Controlled Ixekizumab Vs Secukinumab Trial to Study the Impact on Sexual Activity in Adult Patients with Genital Psoriasis

Nawaf AlMutairi & Bayoumy Ibrahim Eassa

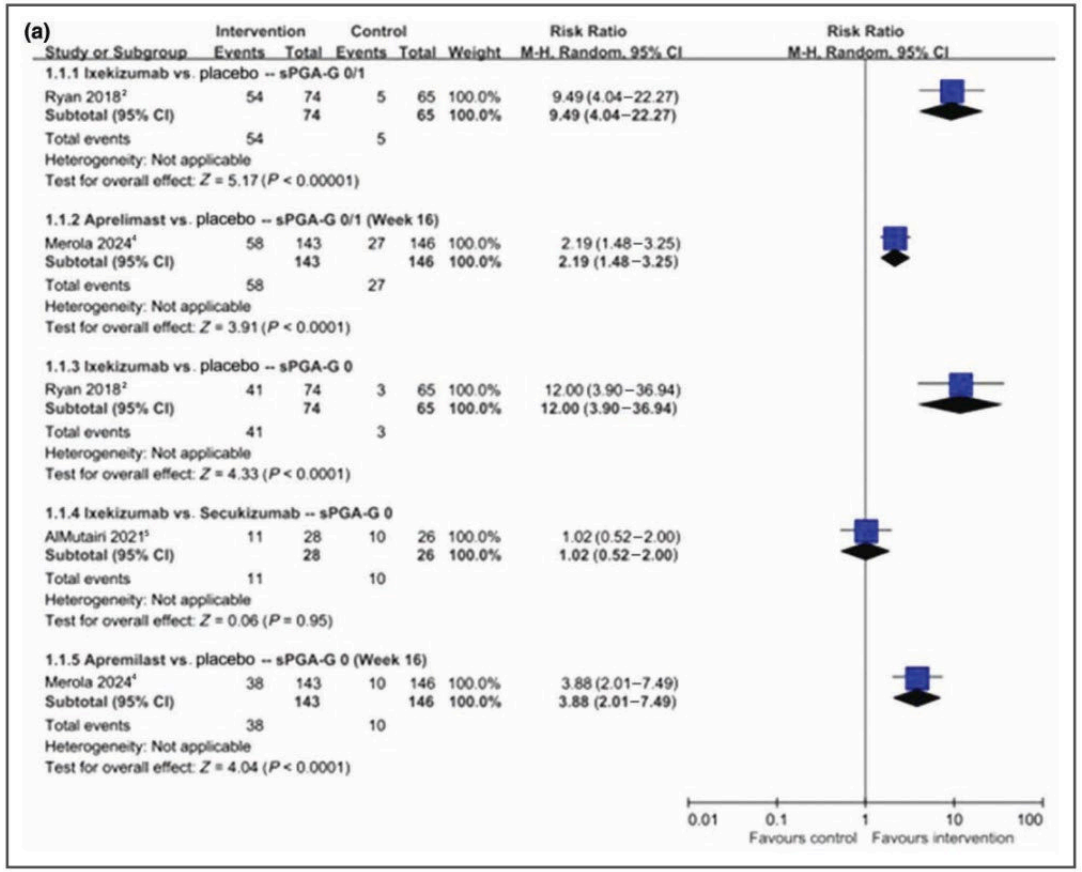
Pages 297-298 | Received 07 Sep 2020, Accepted 26 Oct 2020, Published online: 09 Nov 2020

Cite this article https://doi.org/10.1080/14712598.2021.1843629

Genital

Systematic Review of RCTs (2024)

- Ixekizumab and apremilast were effective in alleviating genital psoriasis and improving sexual function
- Ixekizumab and secukinumab did not differ in efficacy or improvement of sexual dysfunction.



JOURNAL ARTICLE CORRECTED PROOF

Efficacy and safety of biologics and small-molecule inhibitors in treating genital psoriasis: a systematic review of randomized controlled trials Get access

Chien-Cheng Lai, Shih-Chieh Shao, Ethan T K Tsai, Ching-Chi Chi

British Journal of Dermatology, ljae370, https://doi.org/10.1093/bjd/ljae370
Published: 30 September 2024 **Article history**

Genital

Ixekizumab vs Risankizumab

- 2022 small-scale 1:1 randomized trial over 24 weeks
- N = 36
- Similar sPGA-G outcome between ixekizumab (IL-17A, 93.8%) and Risankizumab (IL-23, 95.0%)
- No placebo control

JEADV JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

Letter to the Editor

A head-to-head comparison of risankizumab and ixekizumab for genital psoriasis: a real-life, 24-week, prospective study

E. Sotiriou, K. Bakirtzi, I. Papadimitriou, A. Tsentemeidou, P. Eftychidou, V. Eleftheriadis, A. Lallas, D. Ioannides, E. Vakirlis

First published: 19 December 2021 | https://doi.org/10.1111/jdv.17880 | Citations: 7

Viral Reactivation

HBV Reactivation

Risk with Biologics?

- 2023 meta-analysis
- Patients with psoriasis carried a similar risk of HBVr with all types of cytokine inhibitors
- Among HBsAg+ patients without antiviral prophylaxis, the HBVr rate was 25%. ***However, this risk could be effectively eliminated with antiviral prophylaxis.***
- Hepatitis B virus reactivation typically occurs with immune reconstitution and therefore antiviral therapy should continue for 6-12 months after stopping immunosuppression.

TABLE 1 Analysis of the pooled incidence of HBVr in patients with psoriasis who were treated with cytokine inhibitors

	No. of studies	No. of included patients	Incidence rate (%)	95% CI	I^2 (%)
Patient group					
HBsAg+ without prophylaxis	3	17	25.3	10.4–49.7	0
HBsAg−/HBcAb+ without prophylaxis	8	138	5.0	2.3–10.8	0
Drug catalogue					
Interleukin-12/-23 inhibitor	5	92	4.0	1.3–11.8	0
Interleukin-17 inhibitor	4	63	6.6	1.9–20.5	0
Interleukin-23 inhibitor	1	11	5.0	0.3–47.5	0
Study region					
Asian	3	91	3.7	0.9–13.7	0
Non-Asian	5	75	5.9	2.2–14.7	0
HBsAb status					
HBsAb positive	6	67	7.2	2.0–17.9	0
HBsAb negative	3	19	9.1	2.3–30.1	0

Abbreviations: HBcAb, hepatitis B core antibody; HBsAb, hepatitis B surface antibody; HBsAg, hepatitis B surface antigen; HBV, hepatitis B virus; HBVr, hepatitis B virus reactivations.

Interpreting Hepatitis B Blood Test Results

Interpretation & Action Needed	HBsAg Hepatitis B Surface Antigen	HBsAb (anti-HBs) Hepatitis B Surface Antibody	HBcAb (anti-HBc) Hepatitis B Core Antibody
Not Immune - Not Protected Has not been infected, but still at risk for possible hep B infection. Vaccine is needed.	−	−	−
*Immune Controlled - Protected Surface antibodies present due to natural infection. Has recovered from a prior hep B infection. Cannot infect others. No vaccine is needed.	−	+	+
Immune - Protected Has been vaccinated. Does not have the virus and has never been infected. No vaccine is needed.	−	+	−
Infected Positive HBsAg indicates hep B virus is present. Virus can spread to others. Find a doctor who is knowledgeable about hep B for further evaluation. More Testing Needed.	+	−	+
*Could be Infected Result unclear - possible past or current hep B infection. Find a doctor who is knowledgeable about hep B for further evaluation. More Testing Needed.	−	−	+

AP&T Alimentary Pharmacology and Therapeutics

LETTER TO THE EDITOR | Free Access

Letter: Incidence of hepatitis B virus reactivation in patients with psoriasis treated with cytokine inhibitors

Meng-Hsuan Kuo, Chih-Wei Tseng, Shih-Chieh Shao

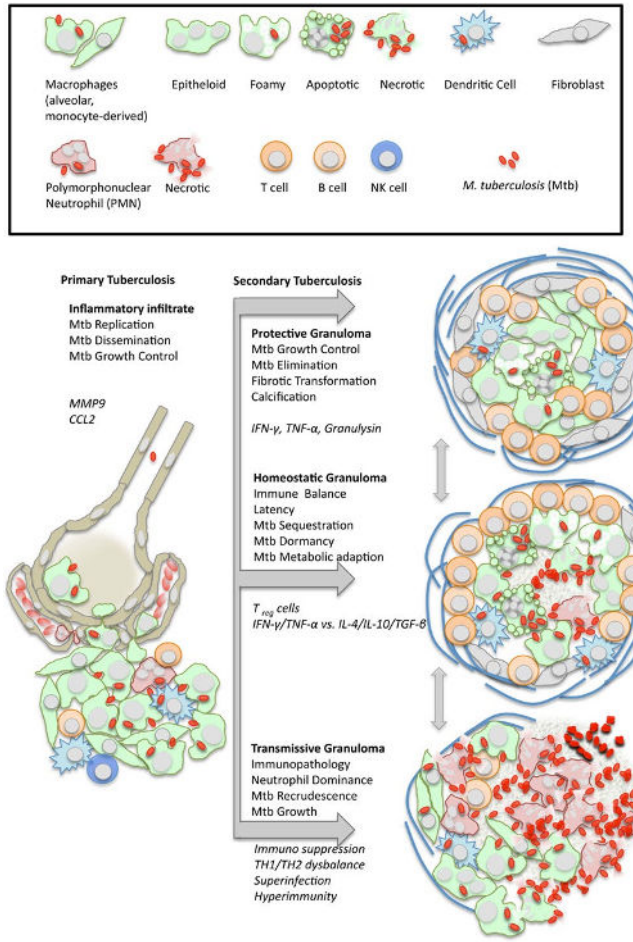
First published: 28 September 2023 | https://doi.org/10.1111/apt.17682

Tuberculosis

T B

Overview of Tuberculosis

- TB infection controlled via granuloma formation resulting in latent TB infection (LTBI)
  - **Th1 (TNF, IFN-gamma) process**
- 25% of world population has LTBI
- 5-10% of immunocompetent patients with LTBI will develop active infection
- Risk factors for reactivation:
  - Medical Conditions (i.e. HIV, diabetes, malignancy, organ transplant)
  - Immunosuppressive/immunomodulatory treatments (i.e. TNF inhibitors)
- **Testing for LTBI:**
  - **Interferon Gamma Release Assay (IGRA)**
    - **Preferred method if >= 5 yrs of age who received BCG vaccine (less likely to produce false positives)***
  - **Tuberculin Skin Test (TST, PPD)**
    - **False positives in BCG-vaccinated patients**
  - **CXR**
    - **Required for pts with +IGRA/+PPD to assess for active pulmonary TB**



frontiers in IMMUNOLOGY
REVIEW ARTICLE
published: 07 January 2013
doi: 10.3389/fimmu.2012.00411

The granuloma in tuberculosis: dynamics of a host–pathogen collusion

Stefan Ehlers[1,2]* and Ulrich E. Schaible[1,3]

TB

Factors A/W Higher Risk for AEs *with Anti-Tuberculosis Drugs*

- Advanced age >60yrs
- Liver disease
  - Pre-existing liver disease (i.e. HBV/HCV, cirrhosis)
  - Liver disease risk factors (i.e. alcoholism, diabetes, obesity, hepatotoxic drugs)
- HIV infection
- Chronic renal disease
  - Increases risk of isoniazid toxicity
- Pregnancy
- Polypharmacy
  - Drug-drug interactions

- Isoniazid:
  - Cutaneous & GI AEs
  - Peripheral neuropathy
  - Hepatotoxicity (cases of fulminant hepatitis requiring liver transplantation)
- Rifampicin
  - Many drug-drug interactions to consider
  - Thrombocytopenia

JEADV Journal of the European Academy of Dermatology & Venereology

Review Article

Risk of tuberculosis reactivation with interleukin (IL)-17 and IL-23 inhibitors in psoriasis – time for a paradigm change

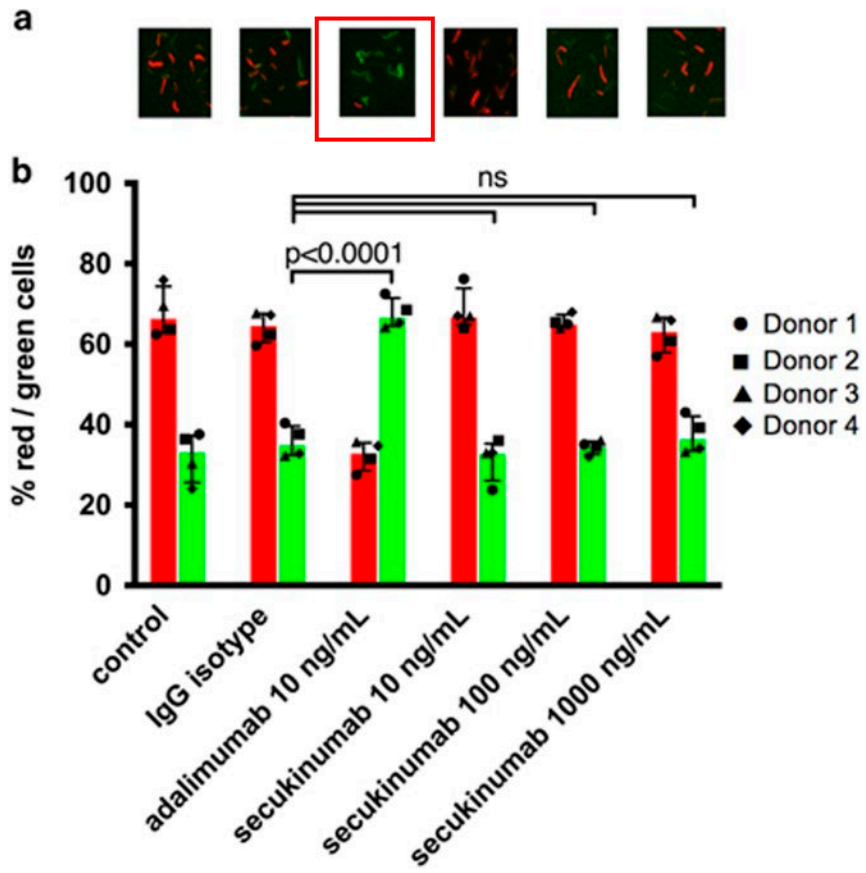
M. Nogueira, R.B. Warren, T. Torres

First published: 12 August 2020 | https://doi.org/10.1111/jdv.16866 | Citations: 58

TB

IL-17A and IL-23 are Dispensable for IFN-gamma response against Mycobacterium in Models

- Absence of IL-23 p19 subunit has little effect on mycobacterial disease progression in early and chronic infection
- In vitro study examined the effect of the anti-tumor necrosis factor-α (TNFα) antibody adalimumab and secukinumab on dormant M. tuberculosis H37Rv in a novel human three-dimensional microgranuloma model.
  - Anti-TNFα treatment showed increased staining for Auramine-O, decreased Nile red staining and decreased rifampicin resistance, indicative of mycobacterial reactivation.
  - In contrast, secukinumab treatment was comparable to control indicating a lack of effect on *M. tuberculosis* dormancy.



RESEARCH ARTICLE | JULY 15 2005

IL-23 Compensates for the Absence of IL-12p70 and Is Essential for the IL-17 Response during Tuberculosis but Is Dispensable for Protection and Antigen-Specific IFN-γ Responses if IL-12p70 Is Available[1] FREE

Shabaana A. Khader; John E. Pearl; Kaori Sakamoto; Leigh Gilmartin; Guy K. Bell; Dawn M. Jelley-Gibbs; Nico Ghilardi; Fred deSauvage; Andrea M. Cooper

+ Author & Article Information

J Immunol (2005) 175 (2): 788–795.

> Clin Transl Immunology. 2017 Aug 25;6(8):e152. doi: 10.1038/cti.2017.34. eCollection 2017 Aug.

Inhibition of IL-17A by secukinumab shows no evidence of increased *Mycobacterium tuberculosis* infections

Michael Kammüller [1], Tsen-Fang Tsai [2], Christopher Em Griffiths [3], Nidhi Kapoor [4], Pappachan E Kolattukudy [4], Dominique Brees [1], Salah-Dine Chibout [1], Jorge Safi Jr [5], Todd Fox [6]

Affiliations + expand

PMID: 28868144 PMCID: PMC5579471 DOI: 10.1038/cti.2017.34

TB

Risk of Latent TB Reactivation Among PsO Pts on Biologics

- Majority of prior clinical trials excluded patients with active TB or untreated LTBI**
- 2024 meta-analysis of PsO studies showed:
  - No statistically significant difference in the LTBI reactivation rate after treatment with biologics, regardless of whether patients received prophylactic therapy or not
  - Consistent with previous findings, **TNF-α inhibitors had a higher reactivation rate of LTBI compared with IL-17 inhibitors and IL-23 inhibitors**, which had a lower or zero risk of triggering LTBI reactivation.

Table 1
Subgroup analysis of LTBI reactivation rates based on characteristics of included studies.

Characteristic	No. of studies	LTBI reactivation	95% CI	Heterogeneity (I^2), %	*p* value
Prophylaxis					
Receive treatment	17	0.0000	0.0000-0.0009	10.10	0.336
Did not receive treatment	12	0.0000	0.0000-0.0040	0.00	0.975
Types of biologics					
IL-17 inhibitors	10	0.0000	0.0000-0.0000	0.00	0.997
IL-23 inhibitors	4	0.0000	0.0000-0.0038	0.00	0.935
TNF-α inhibitors	5	0.0127	0.0000-0.0579	40.57	0.151
Study design					
Retrospective	17	0.0000	0.0000-0.0005	3.32	0.415
Prospective	3	0.0087	0.0000-0.0350	NA	NA
Geographic region					
Europe	8	0.0000	0.0000-0.0074	16.42	0.301
Asia	6	0.0011	0.0000-0.0128	0.00	0.722
South America	2	0.0162	0.0162-0.0474	NA	NA

IL-17, interleukin-17; IL-23, interleukin-23; TNF-α, tumor necrosis factor-α; NA, not available.

LETTER TO THE EDITOR · Volume 89, Issue 3, 106226, September 2024 · Open Access · Download Full Issue

Risk for latent tuberculosis infection reactivation among patients with psoriasis on biologics treatment: A meta-analysis

Xinyu Zhu · Xiaoyuan Pan · Meihong Da · Fei Wang · Zhengbang Dong
Affiliations & Notes · Article Info

TB

Risk of Latent TB Reactivation Among PsO Pts on Biologics

- 2024 real-world LTBI reactivation outcomes in multinational, multicenter study
- IL-17 & IL-23 inhibitors
- N = 405 patients
- Complete, incomplete, no chemoprophylaxis was administered in 62.2%,10.1% and 27.7% of patients, respectively
- Mean duration of biological treatment was 32.87 ± 20.95 months
- ***Only one case*** **of active tuberculosis infection (ATBI) was observed, after 14 months of treatment with ixekizumab.**
  - **Extrapulmonary TB (intestinal)**
  - **Proportion of patients treated with ixekizumab who developed ATBI was 1.64%**

Characteristics of the population	Values
Current biologic therapy, *n* (%)	
Guselkumab	58 (14.3)
Risankizumab	101 (24.9)
Tildrakizumab	30 (7.4)
Secukinumab	121 (29.9)
Ixekizumab	61 (15.1)
Brodalumab	34 (8.4)

American Journal of Clinical Dermatology (2024) 25:333–342
https://doi.org/10.1007/s40257-024-00845-4

ORIGINAL RESEARCH ARTICLE

Treatment of Psoriasis Patients with Latent Tuberculosis Using IL-17 and IL-23 Inhibitors: A Retrospective, Multinational, Multicentre Study

Tiago Torres[1,2] · Andrea Chiricozzi[3,4] · Luis Puig[5] · Ana Maria Lé[1] · Angelo Valerio Marzano[6,7] · Paolo Dapavo[8] · Esteban Dauden[9] · Jóse-Manuel Carrascosa[10] · Elizabeth Lazaridou[11] · Gleison Duarte[12] · André V. E. Carvalho[13] · Ricardo Romiti[14] · Natalia Rompoti[15] · Laetitia Teixeira[2,16] · Miguel Abreu[2,17] · Elena Ippoliti[3,4] · Carlo Alberto Maronese[6,7] · Mar Llamas-Velasco[9] · Eva Vilarrasa[5] · Elena del Alcázar[10] · Athina-Ioanna Daponte[11] · Marina Papoutsaki[15] · Andrea Carugno[18] · Francesco Bellinato[19] · Paolo Gisondi[19]

TB

Risk of Latent TB Reactivation Among PsO Pts on Biologics

- 129 PsO patients on IL-17A inhibitors secukinumab & ixekizumab
- 75% did not received TB preventive treatment
- 235 person-years of follow-up
- **NO active TB cases identified among the 129 patients**

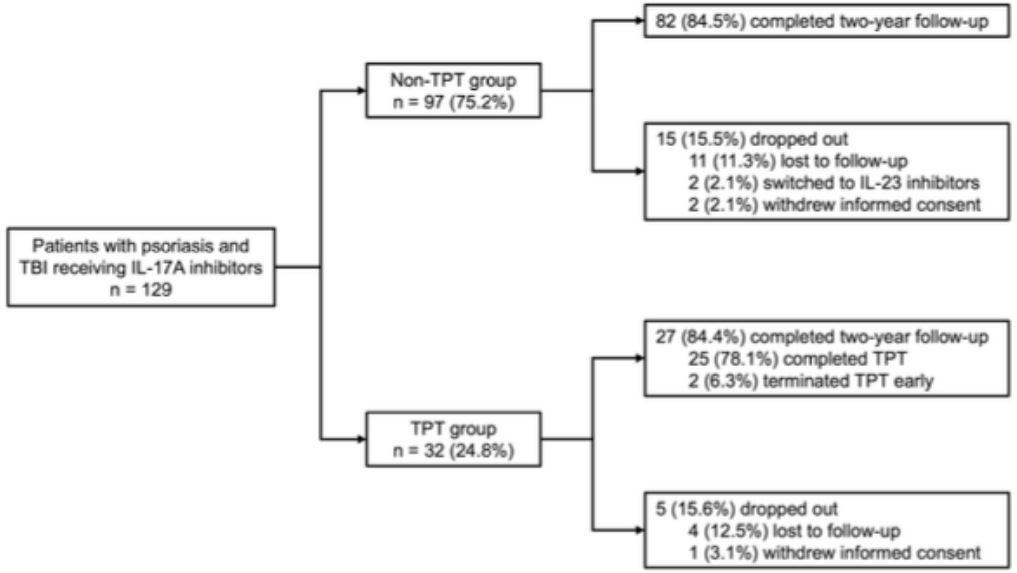


Fig. 1 Participant flow diagram for the study. *IL* interleukin, *TBI* tuberculosis infection, *TPT* tuberculosis preventive treatment

Dermatol Ther (Heidelb) (2024) 14:893–906
https://doi.org/10.1007/s13555-024-01130-2

ORIGINAL RESEARCH

Interleukin-17A Inhibitors in Patients with Psoriasis and Tuberculosis Infection: A 2-Year Prospective Study on Safety Without Preventive Treatment

Chun-Xia He · Chao Wu · Li Zhang · Hong-Zhong Jin

TB

Summary

- Avoid TNF-a inhibitors in LTBI who have NOT been adequately initiated/treated

- Consider IL-17 and IL-23 inhibitors in PsO patients with LTBI who may not undergo chemoprophylaxis due to risk factors and/or patient preference

Malignancy

Malignancy

Conceptualization

No Prior Hx

- Increased risk of developing **NEW** malignancy?

+Prior Malig

- Increased risk of malignancy **RECURRENCE**?
- Increase risk of **NEW** malignancy?

Active Malig

- Affect on **METASTASIS** and **PROGRESSION-FREE SURVIVAL**?
- Affect on chemotherapy, XRT, targeted therapeutics, and immunotherapy?

Malignancy

Conceptualization

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- Increased risk of developing **NEW** malignancy?

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- Increased risk of malignancy **RECURRENCE**?
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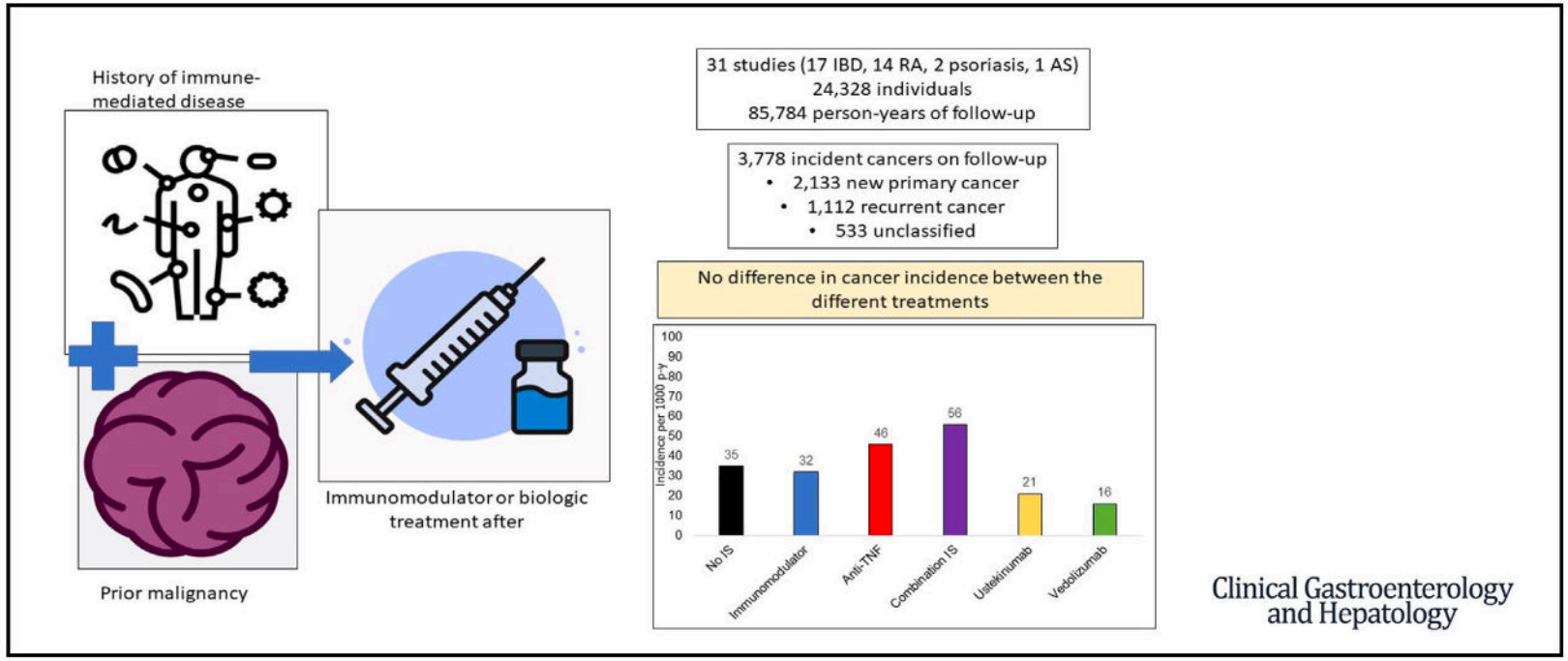
Active Malig

- Affect on **METASTASIS** and **PROGRESSION-FREE SURVIVAL**?
- Affect on chemotherapy, XRT, targeted therapeutics, and immunotherapy?

Malignancy | +Prior Malig

Risk of New/Recurrence?

- 2024 meta-analysis
- Studies address new or recurrence of cancer
- 31 studies (17 inflammatory bowel disease, 14 rheumatoid arthritis, 2 psoriasis, and 1 ankylosing spondylitis) contributing 24,328 persons and 85,784 person-years (PY) of follow-up evaluation.
- Median time to initiation of tx after index cancer = 5 years
  - **<u>Comparison b/w initiation >5 yrs and <5 yrs showed no difference</u>**



***Rates of cancer recurrence were similar among: NO immunosuppression (IS), anti-TNF, immunomodulators, combination IS**

***Patients receiving ustekinumab and vedolizumab had numerically lower rates of cancer**

Clinical Gastroenterology and Hepatology 2024;22:499–512

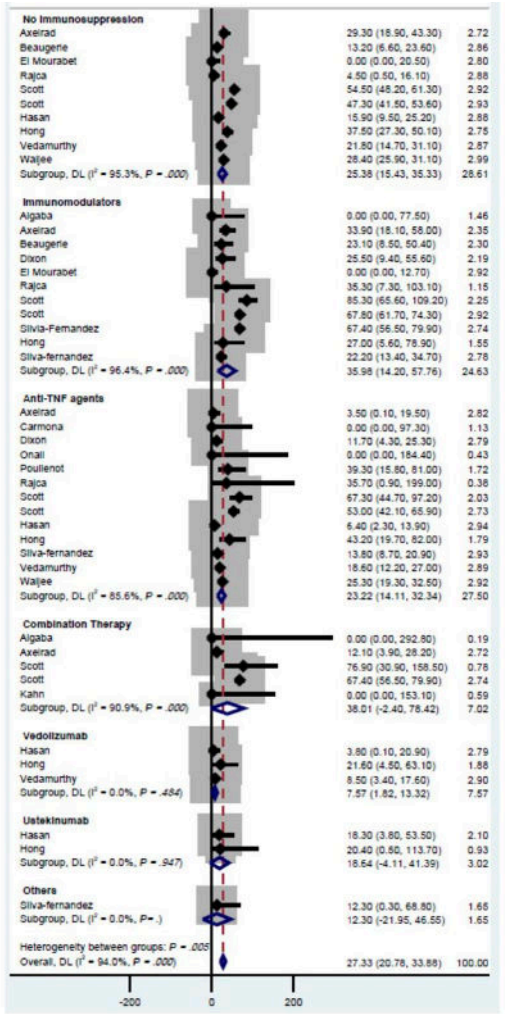
Risk of Cancer Recurrence in Patients With Immune-Mediated Diseases With Use of Immunosuppressive Therapies: An Updated Systematic Review and Meta-Analysis

Akshita Gupta,[1] Laurent Peyrin-Biroulet,[2,3] and Ashwin N. Ananthakrishnan[1,4]

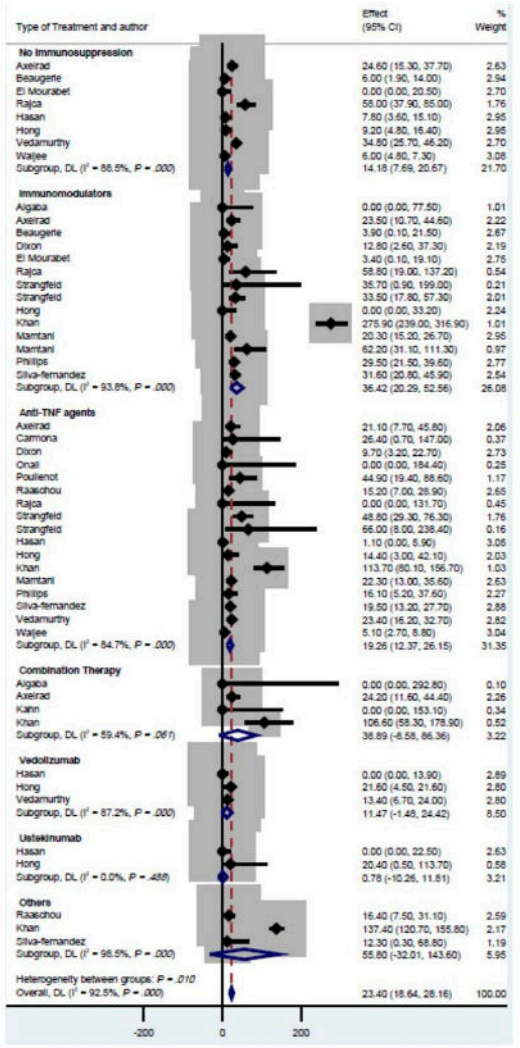
Malignancy | +Prior Malig

Risk of New/Recurrence?

- No increased risk of NEW incident malignancy
- No increased risk of malignancy RECURRENCE



Supplementary Figure 1. Forest plot of risk of new primary cancer by type of immunosuppression in individuals with a prior history of cancer. DL, Der-simonian Laird.



Supplementary Figure 2. Forest plot of risk of recurrence of prior cancer by type of immunosuppression in individuals with a prior history of cancer. DL, Der-simonian Laird.

Risk of Cancer Recurrence in Patients With Immune-Mediated Diseases With Use of Immunosuppressive Therapies: An Updated Systematic Review and Meta-Analysis

Akshita Gupta,[1] Laurent Peyrin-Biroulet,[2,3] and Ashwin N. Ananthakrishnan[1,4]

Malignancy

+Prior Malig

Risk of New/Recurrence?

- No increased risk of malignancy RECURRENCE when separated by HIGH-RISK vs. LOW-RISK malignancy types

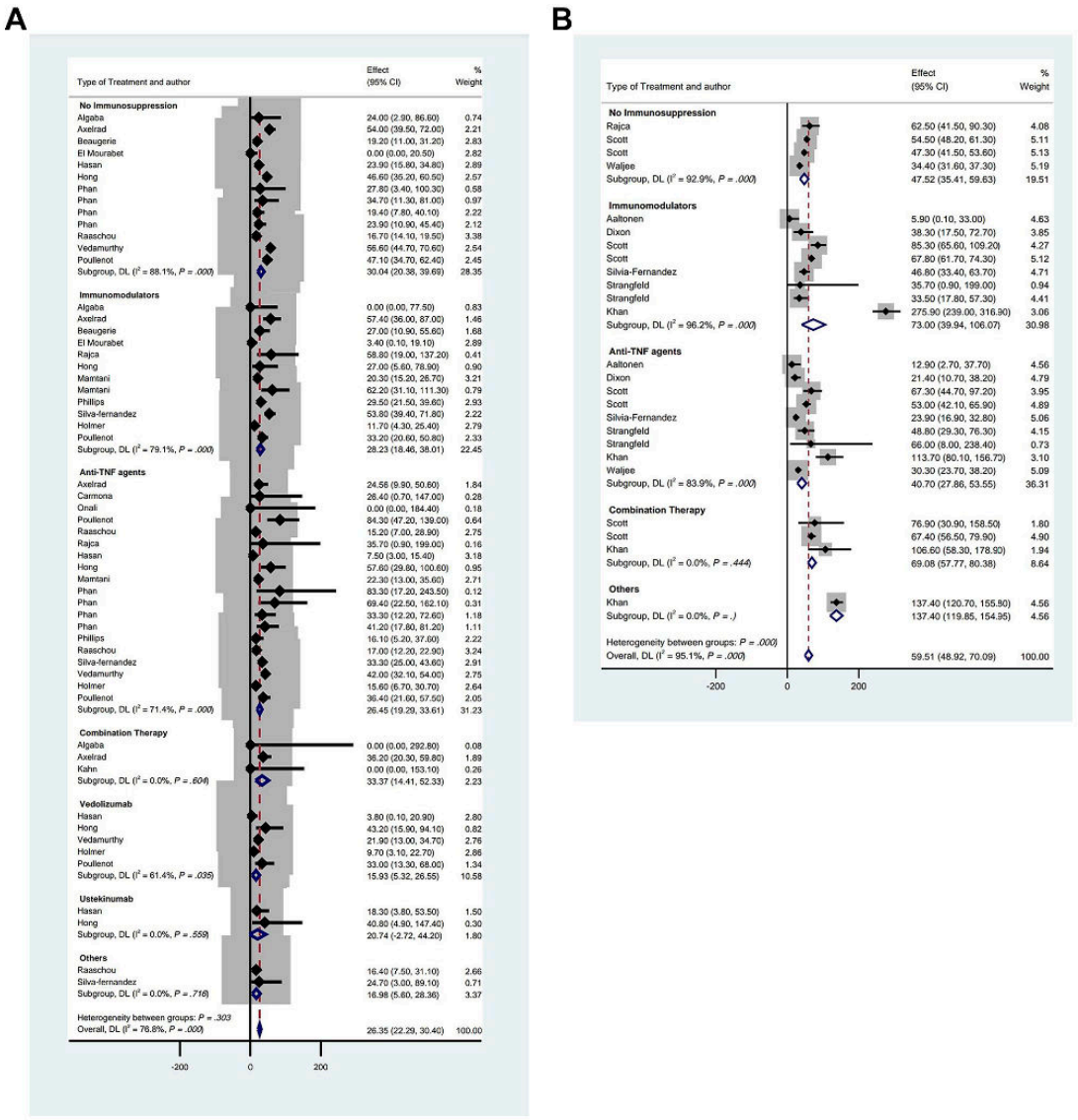


Figure 4. (*A*) Forest plot of risk of cancer recurrence by type of immunosuppression in studies with a proportion of high-risk index cancer of less than 50%. (*B*) Forest plot of risk of cancer recurrence by type of immunosuppression in studies with a proportion of high-risk index cancer ≥50%. DL, Der-simonian Laird.

Clinical Gastroenterology and Hepatology 2024;22:499–512

ıtients With
ı Use of Immunosuppressive
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and Ashwin N. Ananthakrishnan[1,4]

Malignancy

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Biologics in Malignancy (Real-World)

Table 1. In this table are reported demographic data of the analyzed population.

Patient n°	Age	Sex	Cancer Diagnosis	Biologic therapy start date	Biologic type	Biologic therapy duration (weeks)	Comorbidities	PsA	Basal PASI	PASI response
1	87	F	Sep-11	Nov-18	ixekizumab	96	arterial hypertension (AH), hypotiroidism	no	18	100
2	86	F	Oct-12	Nov-18	ixekizumab	96	AH	no	25	90
3	54	F	Jun-16	Jul-17	secukinumab	164	None	yes	12	90
4	65	F	Nov-14	Nov-18	Ustekinumab	96	Hypercolesterolemia, obesity	no	16	100
5	70	F	May-13	Nov-18	ixekizumab	96	AH, overweight	no	13	90
6	78	M	Apr-12	Nov-17	ixekizumab	192	AH, gout, obesity	No	15	100
7	68	M	Jul-16	Apr-17	etanercept	168	blindness	yes	14	90
8	32	F	Jan-11	Mar-17	ustekinumab	144	None	No	12	100
9	58	M	Dec-11	Nov-18	ixekizumab	96	Coronary artery disease, hepatitis B (HBV)	yes	10	100
10	55	M	May-13	Nov-18	secukinumab	96	AH	yes	15	100
11	50	M	May-15	Nov-16	secukinumab	192	None	yes	12	100
12	78	M	Dec-10	Oct-16	etanercept	196	AH, CVD, HBV	yes	25	100
13	49	M	Feb-12	Nov-18	guselkumab	96	Sipple syndrome	no	20	90
14	50	M	Jun-12	Nov-17	ustekinumab	144	None	no	10	100
15	78	M	Jun-18	Aug-18	risankizumab	96	AH, gout	no	35	100
16	46	F	Jul-12	Nov-18	ustekinumab	96	None	no	26	90

- 2021 single-center Italian study, N=16 (**5 dx with cancer in previous 5 years**)
- >= 96 weeks (some 144 wks) of biologic therapy
- TNF, IL-12/23, IL-23, IL-17A inhibitors
- **NO cancer recurrence or new malignancy noted**

JOURNAL OF DERMATOLOGICAL TREATMENT
https://doi.org/10.1080/09546634.2021.1886231

Taylor & Francis
Taylor & Francis Group

ORIGINAL ARTICLE

Check for updates

Biologic therapies for plaque type psoriasis in patients with previous malignant cancer: long-term safety in a single- center real-life population

M. Valenti[a,b], G. Pavia[a,b], L. Gargiulo[a,b], P. Facheris[a,b], F. Sanna[a], R. G. Borroni[a,b], A. Costanzo[a,b] and A. Narcisi[a]

[a]Dermatology Unit, Humanitas Clinical and Research Center - IRCCS, Rozzano, Italy; [b]Dermatology Unit, Department of Biomedical Sciences, Humanitas University, Milan, Italy

Malignancy

+Prior Malig

Secukinumab (IL-17Ai) in Malignancy (Real-World)

- Italian real-world study in PsO patients with malignancy history within 10 years with median interval between cancer diagnosis and initiation of secukinumab of 3.5 years
- **Absence of recurrence and progression over a mean of 56 ± 31.7 weeks of secukinumab treatment**
- Three patients developed a second malignancy during treatment, in two cases unrelated to the previous neoplasm. In all three patients, we were able to recognize high-risk factors for cancer development, such as a strong family or personal history of cancer and exposure to environmental risk factors.

Dermatol Ther (Heidelb). 2022 Sep 28;12(11):2613–2626. doi: 10.1007/s13555-022-00797-9

Secukinumab in Patients with Psoriasis and a Personal History of Malignancy: A Multicenter Real-Life Observational Study

Malignancy

+Prior Malig

IL-17A Inhibitors in Malignancy (Real-World)

- Observational retrospective analysis in pts with prior malignancy in clinical remission (N=9) or advanced/metastatic disease (N=3) at University Hospital of Verona
- Median time between the diagnosis of malignancy and the initiation of IL-17A inhibitor was **15 months**, IQR 13.5-22.5.
- **No cancer recurrence was found within a median of 46 months follow up (IQR 36-48) in the patients with history of malignancy in clinical remission (n = 9)**
- **Cancer progression was observed in two out three patients with advanced/metastatic disease.**

TABLE 2 Characteristics of the patients with history of malignancy and treated with an IL-17A inhibitor for psoriasis

Age, sex	Malignancy	Stage	Age at malignancy onset	Time between malignancy diagnosis and IL-17A inhibitor, months	IL-17A inhibitor	Follow up, months	Therapy for malignancy	Disease recurrence or progression
68, M	Urothelial bladder carcinoma	In situ	65	20	Secukinumab	6	Surgery	No
48, F	Breast ductal carcinoma	In situ	45	14	Secukinumab	28	Surgery	No
58, M	Prostate acinar adenocarcinoma	I	55	16	Ixekizumab	22	Surgery	No
49, F	Melanoma	IA	45	36	Secukinumab	18	Surgery	No
52, M	Prostate acinar adenocarcinoma	I	50	22	Secukinumab	13	Surgery	No
65, M	Colon adenocarcinoma	II	62	14	Ixekizumab	9	Surgery	No
71, M	Prostate acinar adenocarcinoma	II	70	14	Ixekizumab	24	Surgery + radiotherapy	No
44, M	Thyroid medullary carcinoma	II	40	24	Ixekizumab	36	Surgery	No
58, F	Uterus adenocarcinoma	III	50	24	Secukinumab	48	Surgery	No
69, M	Lung microcitoma	IV	68	12	Secukinumab	12	Chemotherapy	No
80, M	Colon adenocarcinoma	IV	76	12	Ixekizumab	48	Surgery + chemotherapy	Yes
77, M	Lung adenocarcinoma	IV	76	6	Secukinumab	8	Radiotherapy + chemotherapy	Yes

Abbreviations: F, female; M, male.

ORIGINAL ARTICLE

DERMATOLOGIC THERAPY WILEY

IL-17A inhibitors in patients with chronic plaque psoriasis and history of malignancy: A case series with systematic literature review

Francesco Bellinato | Paolo Gisondi | Martina Maurelli | Giampiero Girolomoni

Malignancy | +Active Malig

IL-23/IL-23R Axis and Tumor Microenvironment

- Milestone 2024 Nature paper
- ***Unexpected immunosuppressive property of IL-23*** which is an otherwise proinflammatory cytokine
- **IL-23 signaling stabilizes effector Treg, which reduce anti-tumor immunity**

nature immunology

Article

https://doi.org/10.1038/s41590-024-01755-7

IL-23 stabilizes an effector T_{reg} cell program in the tumor microenvironment

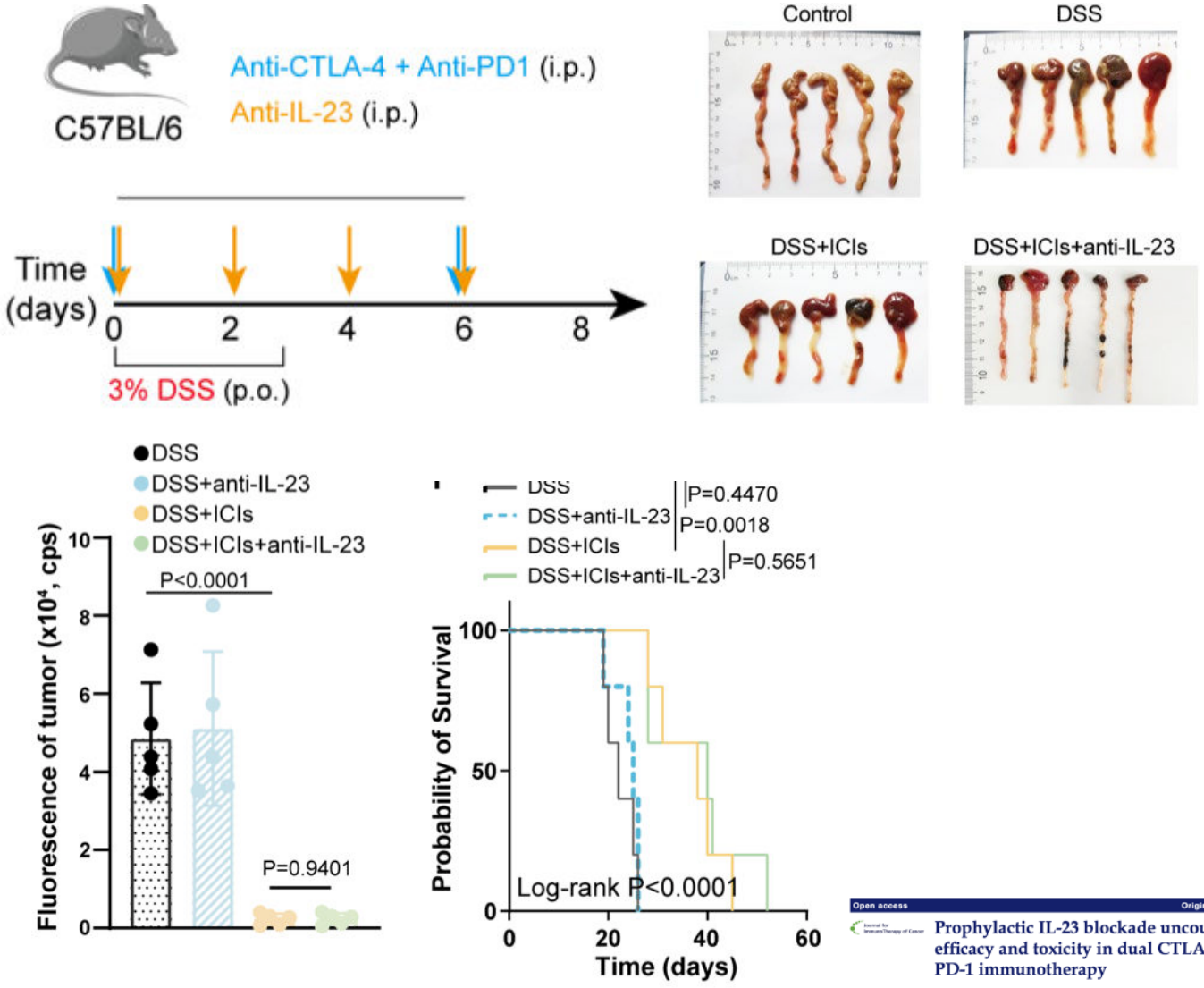
Received: 20 January 2023

Tobias Wertheimer[1,8], Pascale Zwicky[1,8], Lukas Rindlisbacher[1], Colin Sparano[1],

Malignancy | +Active Malig

IL-23/IL-23R Axis and Tumor Microenvironment

- **Interleukin (IL)-23 concentrations were markedly elevated** in the serum of patients with irAEs compared with those without.
- Prophylactic blockade of IL-23 ameliorated hepatitis, myocarditis, splenitis, and lung inflammation colitis induced by dual cytotoxic T-lymphocyte associated protein 4 and programmed cell death protein-1 immunotherapy in irAEs murine models, and moreover, **did not impair the antitumor effects.**
- **IL-23 blockade may dissociate efficacy and toxicity in combined ICI*****



Open access Original research

Prophylactic IL-23 blockade uncouples efficacy and toxicity in dual CTLA-4 and PD-1 immunotherapy

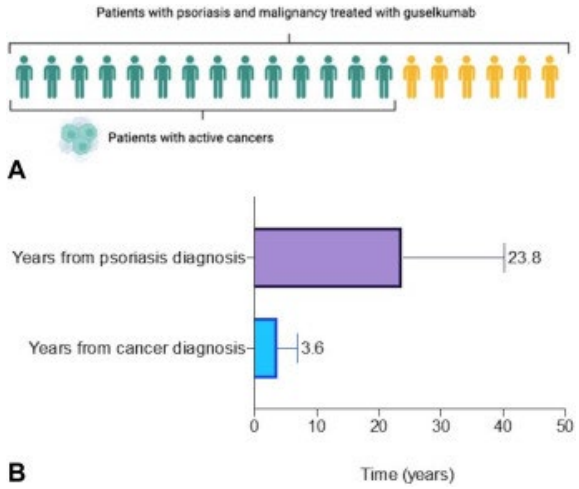
Mingyi Ju, Jiaojiao Zhang, Zhuoyuan Deng, Minjie Wei, Lianghua Ma, Ting Chen, Lin Zhao

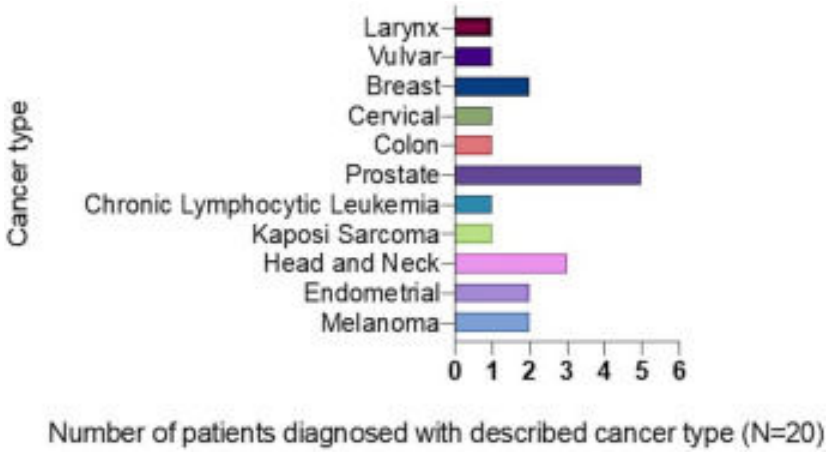
Malignancy

+Active Malig

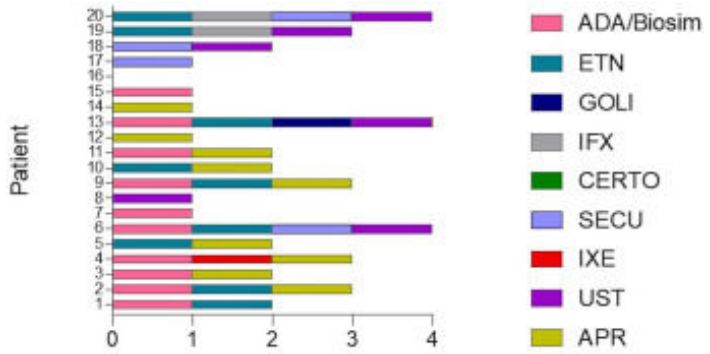
IL-23 Inhibitor Guselkumab in Malignancy (Real-World)

- Multicenter, retrospective study
- Target population was patients >18 years of age who came to the dermatology clinic and were being treated with guselkumab and had a **diagnosis of neoplasm in the last ≤5 year**
- 14 out of 20 pts had ACTIVE cancers
- **No AEs, neither serious AEs nor dropouts related to guselkumab safety profile, were detected in the nonactive cancer group or in the active-cancer group of patients**





Number of patients diagnosed with described cancer type (N=20)



Number of previous treatments before initiating guselkumab

Case Reports > Eur J Dermatol. 2020 Oct 1;30(5):609-611. doi: 10.1684/ejd.2020.3860.

Treatment of psoriasis vulgaris with guselkumab in a patient with non-small cell lung cancer

Koji Kamiya [1], Hiroyoshi Yamauchi [2], Mamitaro Ohtsuki [1]

> Dermatol Reports. 2022 Mar 17;14(3):9282. doi: 10.4081/dr.2022.9282. eCollection 2022 Sep 14.

Seven cancer patients receiving guselkumab for treatment of moderate-to-severe psoriasis

Luca Mastorino [1], Niccolò Siliquini [1], Gianluca Avallone [1], Michela Ortoncelli [1], Pietro Quaglino [1], Paolo Dapavo [1], Simone Ribero [1]

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PSORIASIS · Volume 16, P66-71, September 2024 · Open Access · Download Full Issue

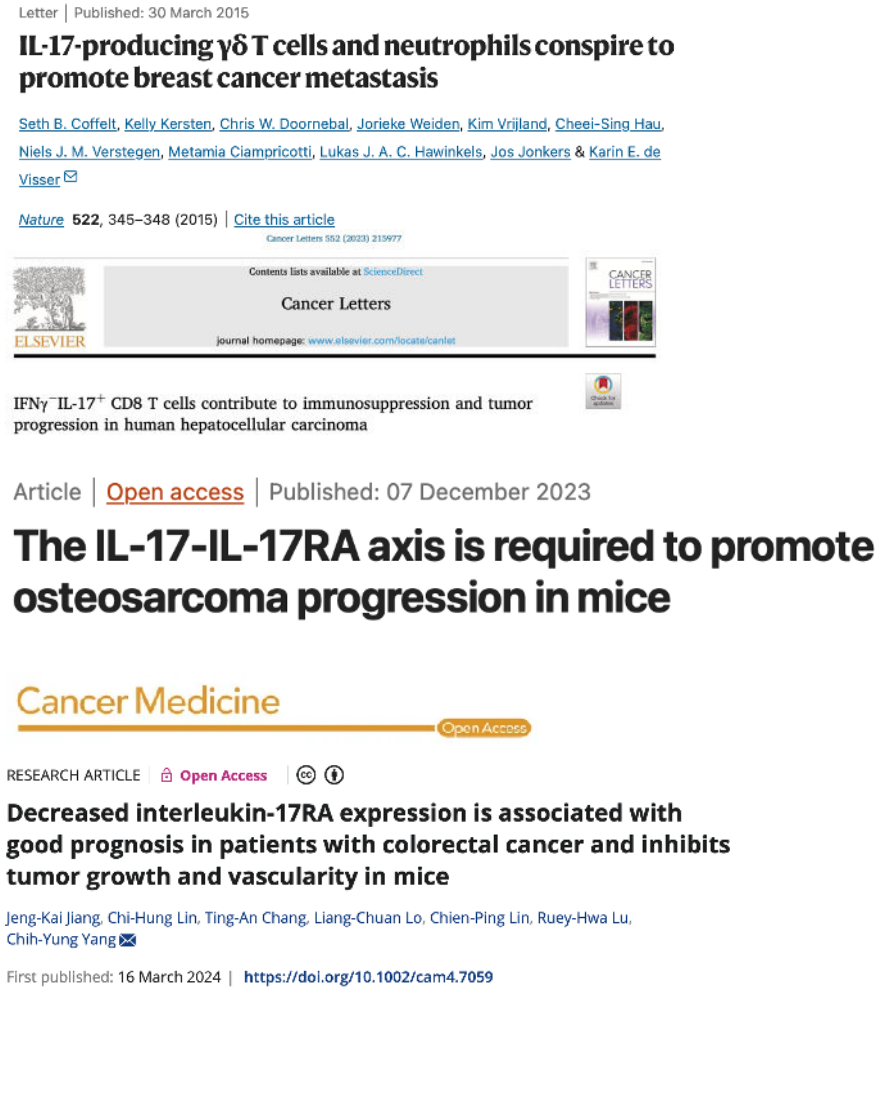
Real-world outcomes in patients with malignancy and moderate-to-severe psoriasis treated with guselkumab

Tamara Gracia Cazaña, MD, PhD [a] [✉] · Josep Riera Monroig, MD [b] · Rosa Izu, MD, PhD [c] · ... · Victoria Fuentelsaz, MD, PhD [i] · Ana Morales Callaghan, MD, PhD [a] · Mariano Ara-Martín, MD, PhD [e] ... Show more

Malignancy | +Active Malig

IL-17 Promotes Malignancy/Metastasis in Some Cancers

- **Breast** tumor-induced, IL-17-producing gd-T cells drive expansion of neutrophils that SUPPRESS CD8+ T cells → subsequent distant-organ metastasis
- **Hepatocellular** Carcinoma: IL-17-producing CD8+ T cells infiltrated Treg cells (immunosuppressive), higher density correlated with poorer prognosis
- **Osteosarcoma**: IL-17 essential to maintain cells in undifferentiated state; IL-17 deficient mice with human xenograft osteosarcoma transplanted exhibited prolonged survival, but NOT IL-17RA deficient mice (this is b/c osteosarcoma cells exhibited IL-17RA+)
- **Colon** cancer: IL-17RA expression elevated in CRC cells vs adjacent normal tissues, correlated with Stage (i.e. IL-17RA expression highest in Stage IV vs Stages I & II). Mouse Knock-down experiments of IL-17RA significantly repressed tumor growth, vascularity, and infiltrating Tregs



Letter | Published: 30 March 2015

IL-17-producing γδ T cells and neutrophils conspire to promote breast cancer metastasis

Seth B. Coffelt, Kelly Kersten, Chris W. Doornebal, Jorieke Weiden, Kim Vrijland, Cheei-Sing Hau, Niels J. M. Verstegen, Metamia Ciampricotti, Lukas J. A. C. Hawinkels, Jos Jonkers & Karin E. de Visser

Nature **522**, 345–348 (2015) | Cite this article

Cancer Letters 552 (2023) 215977

Contents lists available at ScienceDirect

Cancer Letters

journal homepage: www.elsevier.com/locate/canlet

ELSEVIER

CANCER LETTERS

IFNγ⁻IL-17⁺ CD8 T cells contribute to immunosuppression and tumor progression in human hepatocellular carcinoma

Article | Open access | Published: 07 December 2023

The IL-17-IL-17RA axis is required to promote osteosarcoma progression in mice

Cancer Medicine

Open Access

RESEARCH ARTICLE | Open Access

Decreased interleukin-17RA expression is associated with good prognosis in patients with colorectal cancer and inhibits tumor growth and vascularity in mice

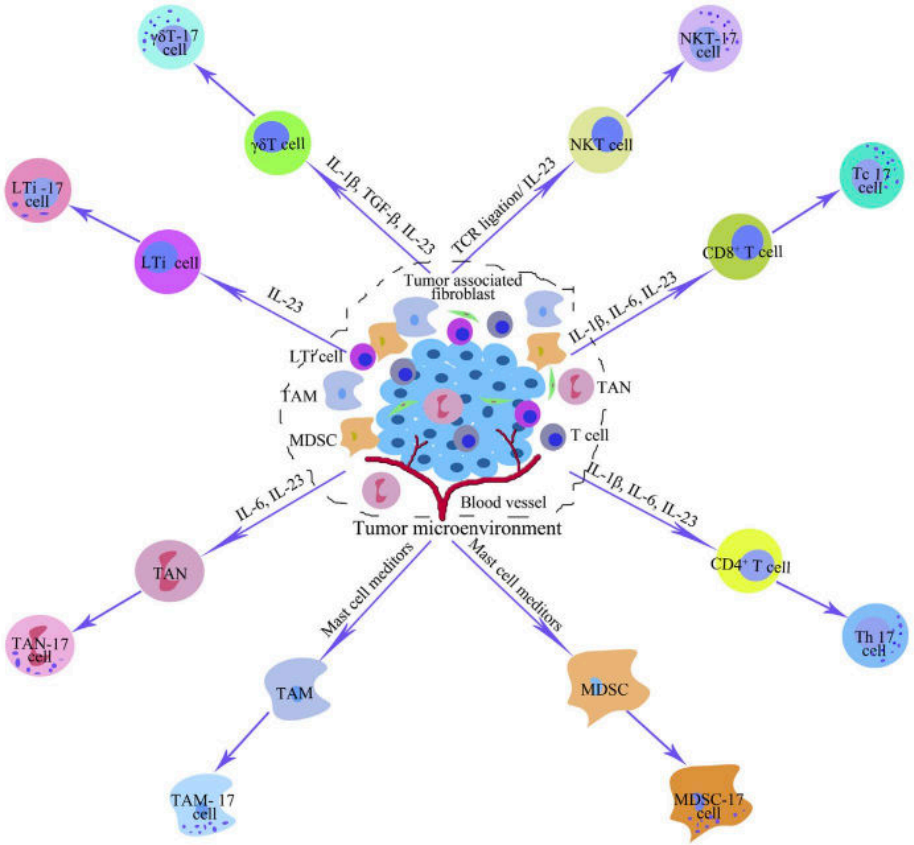
Jeng-Kai Jiang, Chi-Hung Lin, Ting-An Chang, Liang-Chuan Lo, Chien-Ping Lin, Ruey-Hwa Lu, Chih-Yung Yang

First published: 16 March 2024 | https://doi.org/10.1002/cam4.7059

Malignancy | +Active Malig

IL-17 May Have Anti-Tumor Effects in some Cancers

- Increased IL-17 expression correlated with higher 5-year survival rate for:
  - Gastric adenocarcinoma
  - Esophageal squamous cell carcinoma
  - Ovarian cancer
  - Chronic lymphocytic leukemia
  - Cervical adenocarcinoma
- IL-17 expression expression inversely proportional to depth of tumor invasion in cervical adenocarcinoma and esophageal cancer
- Ovarian tumor cells implanted in normal mice transfected with IL-17 cDNA resulted in tumor growth
- **Observations indicate that IL-17 exerts antitumor immunity by recruiting T lymphocytes.**
  - **IL-17 can induce tumor cells to release chemokines CXCL9 and CXCL10 to attract effector CD8+ T cells and NK cells**
- IL-17 also recruits/promotes neutrophil infiltration
- Whether IL-17 promotes or inhibits tumorigenesis likely depends on the cell or tumor type and the nature of the cytokines present at the tumor site



Cytokine xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.journals.elsevier.com/cytokine

Review article

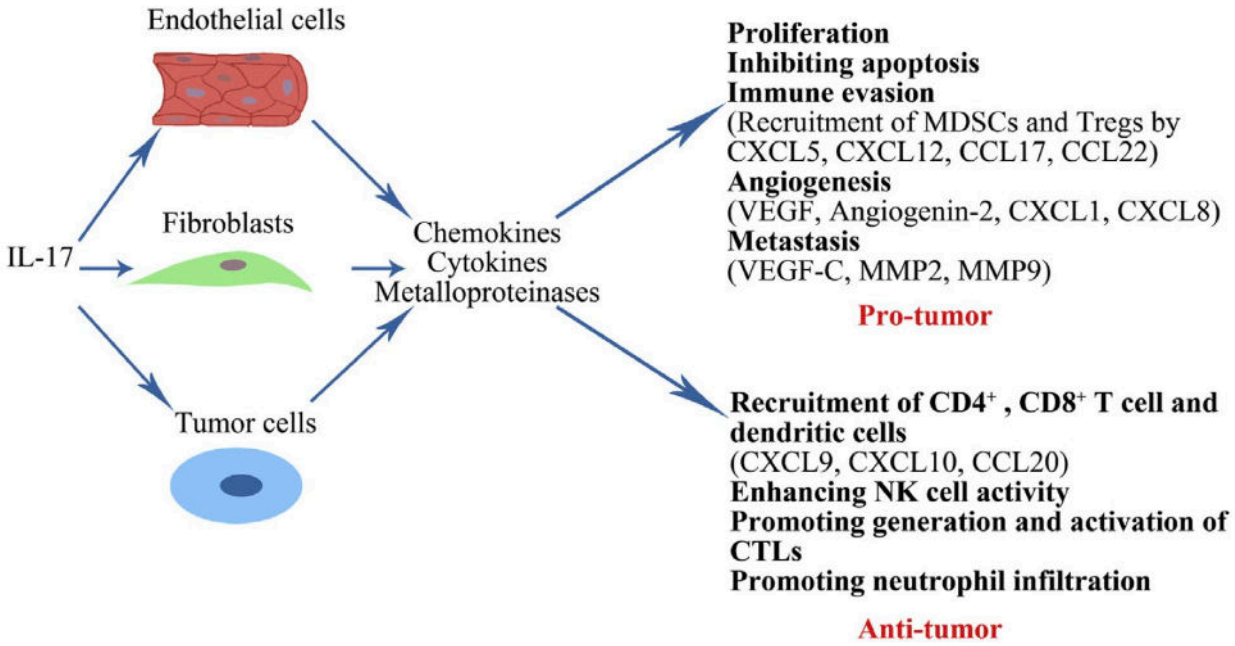
Interleukin-17 acts as double-edged sword in anti-tumor immunity and tumorigenesis

Xin Qian[a,1], Hankui Chen[b,1], Xiaofeng Wu[a], Ling Hu[c], Qi Huang[d], Yang Jin[d,*]

Malignancy | +Active Malig

IL-17 Malignancy Summary: Controversial

- Double-edged cytokine that acts in a cancer-type depending manner as an anti- or pro-tumor cytokine
- Controversial role of IL-17 in cancer comes from the heterogeneity in how the IL-17 is measured in the different reports: as IL- 17 mRNA or protein levels by western blotting and/or ELISA, as the presence of Th17 tumor-infiltrating T cell.
- Role of IL-17 in different human cancers has been studied mostly in in vitro cell models and human xenografts
  - Much more complex study models needed




Autoimmunity Reviews 19 (2020) 102429
Contents lists available at ScienceDirect
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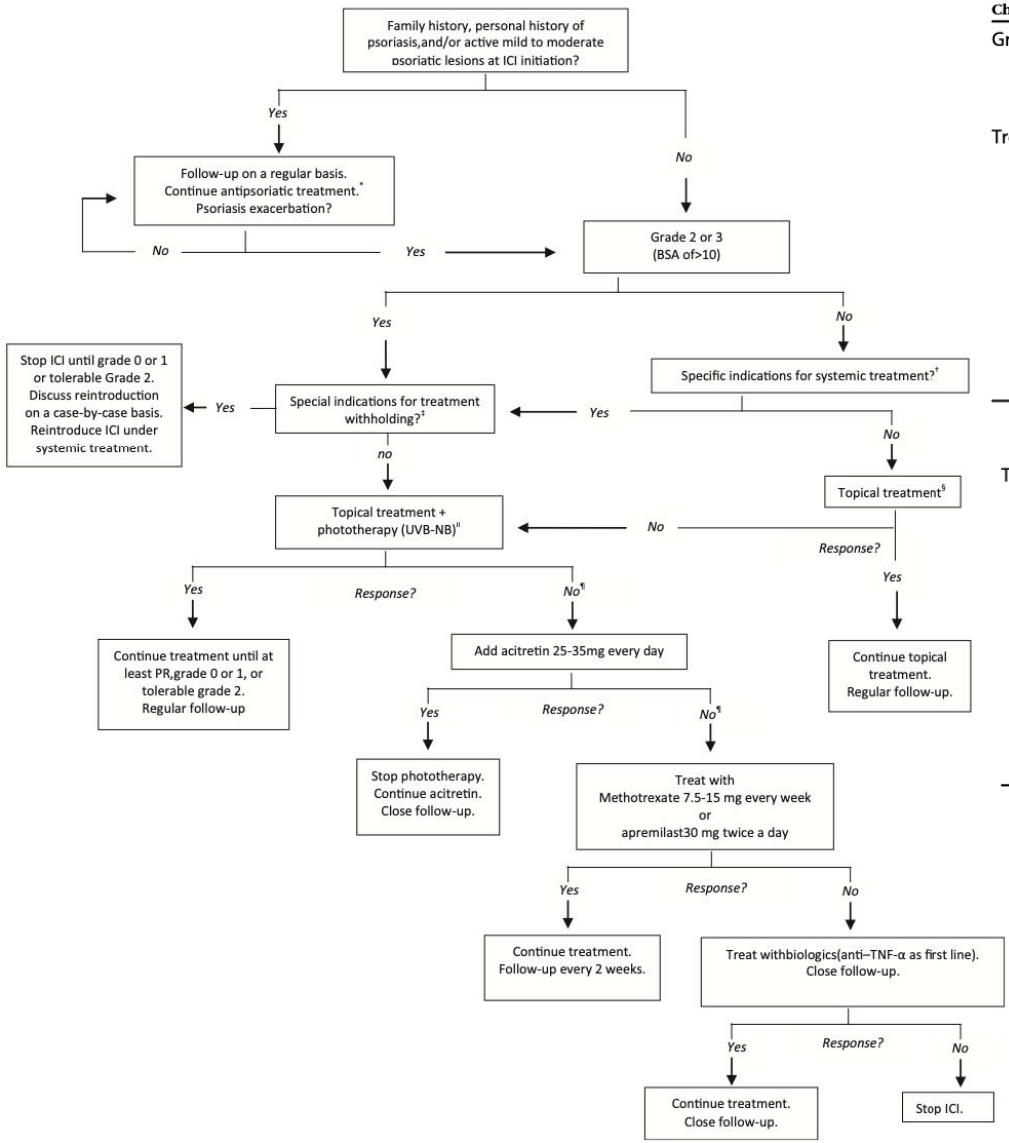
ELSEVIER
Review

Critical role of interleukin (IL)-17 in inflammatory and immune disorders: An updated review of the evidence focusing in controversies

Malignancy | +Active Malig

ICI-Induced PsO Treatment (Real-World)

- 2020 multi-center retrospective study focusing on ICI-driven PsO
  - Anti-PD1 or anti-PD-L1
- Psoriasis affecting more than 10% of the body surface area as well as pustular psoriasis increase the risk of treatment modification/interruption.
- Treatments: phototherapy, orals, biologics
- No unpredicted adverse events*
- Acitretin does not harbor immunosuppressive properties thus does not interfere with ICI treatment
- **Algorithmic approach for systemics in ICI-induced PsO**
  - **nbUVB → Acitretin → Apremilast/MTX → Biologics**



Characteristics	Value
Grade (first visit), n (%)	
1 (<10% BSA, mild)	60 (57.1)
2 (10%-30% BSA, moderate)	34 (32.4)
3 (>30% BSA, severe)	11 (10.5)
Treatment, n (%)	
Topicals monotherapy	68 (59.1)
Acitretin	21 (18.3)
Apremilast	7 (14.8)
Methotrexate	5 (4.3)
Steroids	8 (7)
Anti—TNF-α	2 (1.7)
Ustekinumab	1 (0.9)
Acitretin + guselkumab	1 (0.9)
Acitretin followed by methotrexate	1 (0.9)
Acitretin followed by apremilast	1 (0.9)

Type of cancer		.773
NSCLC	9.87 (10.4)	
Melanoma	20.8 (29.3)	
Head and neck SCC	6.5 (5.24)	
Renal cell carcinoma	7.33 (4.63)	
Urothelial carcinoma	15.3 (18.3)	
Hodgkin lymphoma	6.5 (0.70)	
Merkel cell carcinoma	18	
Hepatocellular carcinoma	7 (5.00)	
Gastric cancer	5 (4.24)	
Mesothelioma	5	
Ovarian cancer	9	
Pulmonary neuroendocrine	4	

Immune checkpoint-mediated psoriasis: A multicenter European study of 115 patients from the European Network for Cutaneous Adverse Event to Oncologic Drugs (ENCADO) group

Vasiliki Nikolaou, MD,[a] Vincent Sibaud, MD,[b] Davide Fattore, MD,[c] Pietro Sollena, MD,[d,e] Ariadna Ortiz Brugues, MD,[f] Damien Giacchero, MD,[g] Maria Concetta Romano, MD,[h] Julia Riganti, MD,[i] Konstantinos Lallas, MD,[j] Kerry Peris, MD,[j,k] Dimitra Soudoert, MD,[l] Aimilios Lallas, MD,[j] Gabriella Fabbrocini, MD,[m] Elisabetti Lazaridou, MD,[n] Cristina Carrera, MD,[o] Maria Carmela Ammendola, MD,[p] Ernesto Rossi, MD,[q] Angela Patel, MD,[r] Dimitrios Rigopoulos, MD,[s] Alexander J. Stratigos, MD,[t] and Zoe Apalla, MD[u]

Malignancy

Malignancy Expert Opinion

(1) Discussion with Oncology needed

(2) Individual patient/tumor profile must be taken into account

(3) Treatment course (i.e. dual-ICI, anti-PD-1 monotherapy, etc.) must be taken into consideration and timeline of introduction IL-17 class biologic. IL-23 blockade may be first-line biologic due to in vivo data showing uncoupling of efficacy & toxicity in ICI.

(4) Acitretin should always be of consideration due to non-immunomodulating effect that could interact with ICI or other oncologic therapies.

(5) nbUVB phototherapy is safe in all instances.

(6) May consider TNF-i and methotrexate (even in combination) given 2024 data reflecting similar rates of cancer recurrence compared to NO immunosuppression.

Malignancy

Malignancy Expert Opinion

(1) Discussion with Oncology needed

(2) Individual patient/tumor profile must be taken into account

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(5) nbUVB phototherapy is safe in all instances.

(6) May consider TNF-i and methotrexate (even in combination) given 2024 data reflecting similar rates of cancer recurrence compared to NO immunosuppression.

DR. ISSA'S RECOMMENDATION:

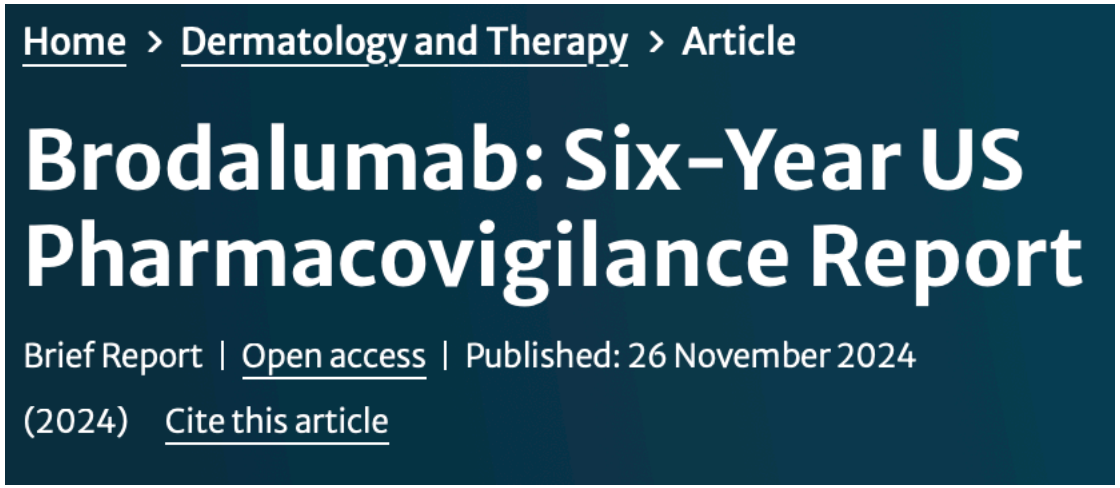
1) IL-23 INHIBITOR
2) ACITRETIN
3) NB-UVB

Suicidality

Suicidality

Do PsO Biologics Increase Risk of Depression/Suicidality?

- No completed suicides throughout the 6 years
- No new suicide attempts in year #6
- Depression rate over 6 years ~1.13 per 100 pts

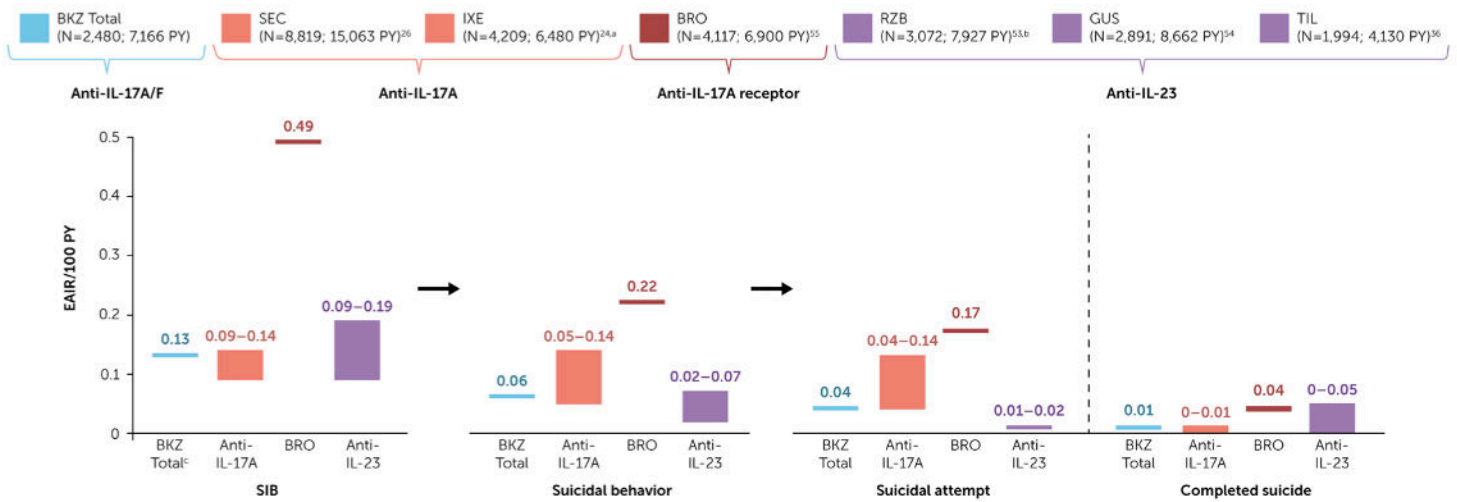


Suicidality

Does Bimekizmuab Increase Risk of Depression/Suicidality?

- Over 7166 PY of bimekizumab exposure, the EAIRs of adjudicated SIB, suicidal ideation, and suicidal behavior were 0.13/100 PY, 0.08/100 PY, and 0.06/100 PY, respectively, and the EAIR of depressive disorders TEAEs was 0.5/100 PY
- **Adjudicated SIB rate was in the same range as the general psoriasis population and patients receiving anti-IL-17A antibody and anti-IL-23 therapies.**

Figure S1. Rates of SIB TEAEs across anti-IL-17 and anti-IL-23 clinical development programs in psoriasis



Mental health outcomes in patients with moderate to severe psoriasis treated with bimekizumab: Analysis of phase 2/3 randomized trials

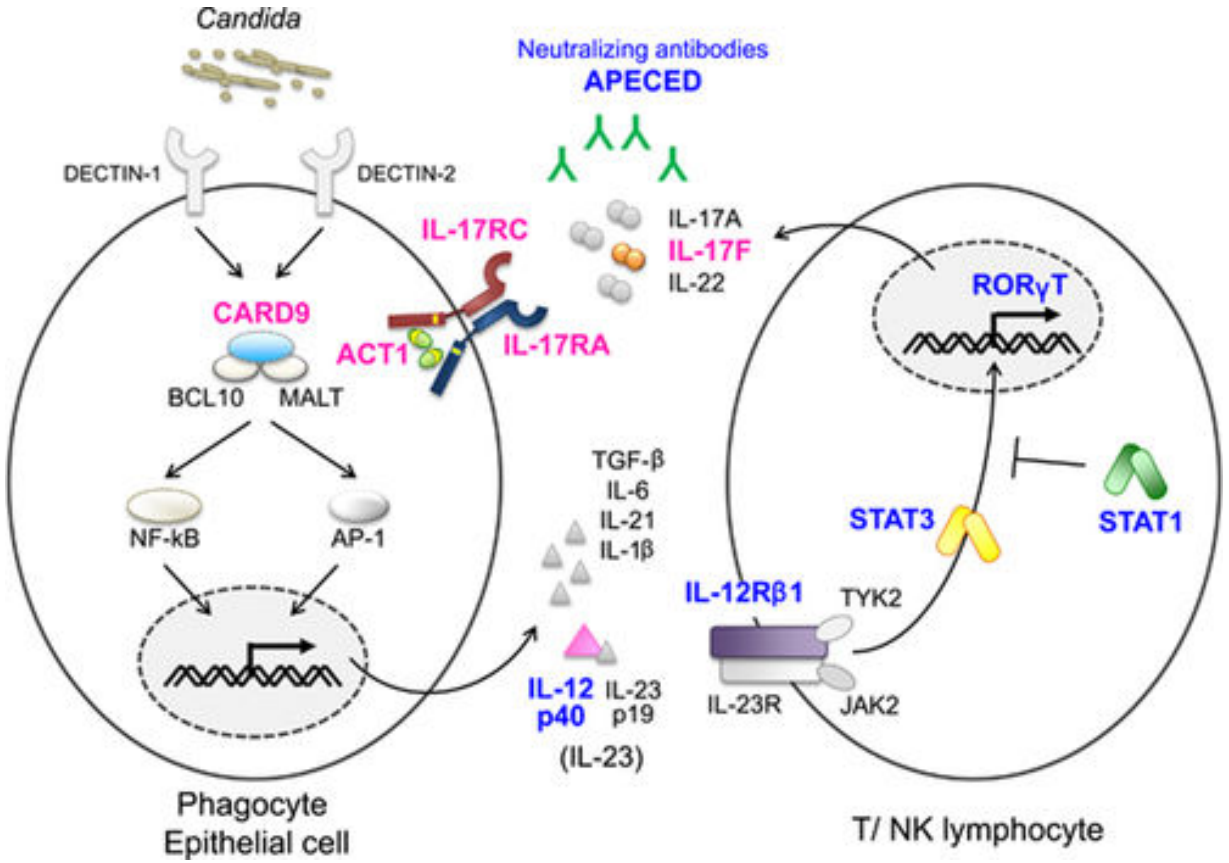
Andrew Blauvelt, MD, MBA,[a] April Armstrong, MD, MPH,[b] Joseph F. Merola, MD, MMSc,[c] Bruce Strober, MD, PhD,[d,e] Dirk de Cuyper, MD,[f] Luke Peterson, MS,[g] Owen Davies, MBA, PhD,[h] Jeffrey L. Stark, MD,[i] and Mark Lebwohl, MD[j]

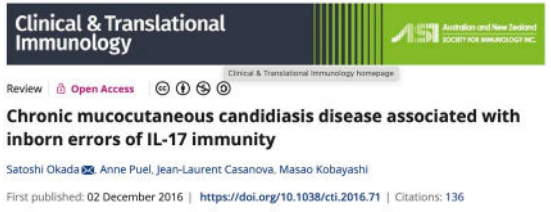
Candidiasis

Candidiasis

Candidiasis Pathophysiology

- IL-17A & IL-17F are essential for mucocutaneous immunity against *Candida spp. (C. albicans* most commonly)
- IL-23-deficient mice with impaired IL-17A and IL-17F expression also vulnerable
- Chronic mucocutaneous candidiasis (CMC) = recurrent or persistent infection in skin, nails, and oral & genital mucosa
  - CMC Disease (CMCD) = absence of any other clinical signs
  - Syndromic = infectious phenotype in patients with inherited or acquired T-cell deficiency (i.e. APECED)
  - **All a/w impaired IL-17 immunity***
- IL-17 produced by Th17 cells, RORγT+ γT-cells, group 3 innate lymphoid cells → all have essential roles in host defense against mucocutaneous candidiasis
- Neutrophilic deficiency disorders implicated in **INVASIVE FUNGAL INFXN***



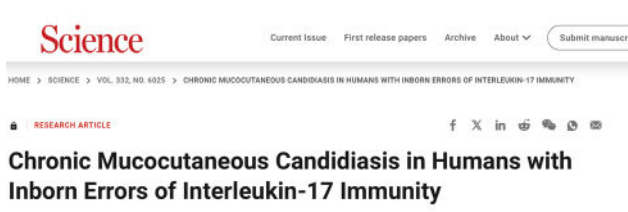

Clinical & Translational Immunology

Review | Open Access

Chronic mucocutaneous candidiasis disease associated with inborn errors of IL-17 immunity

Satoshi Okada, Anne Puel, Jean-Laurent Casanova, Masao Kobayashi

First published: 02 December 2016 | https://doi.org/10.1038/cti.2016.71 | Citations: 136


Science

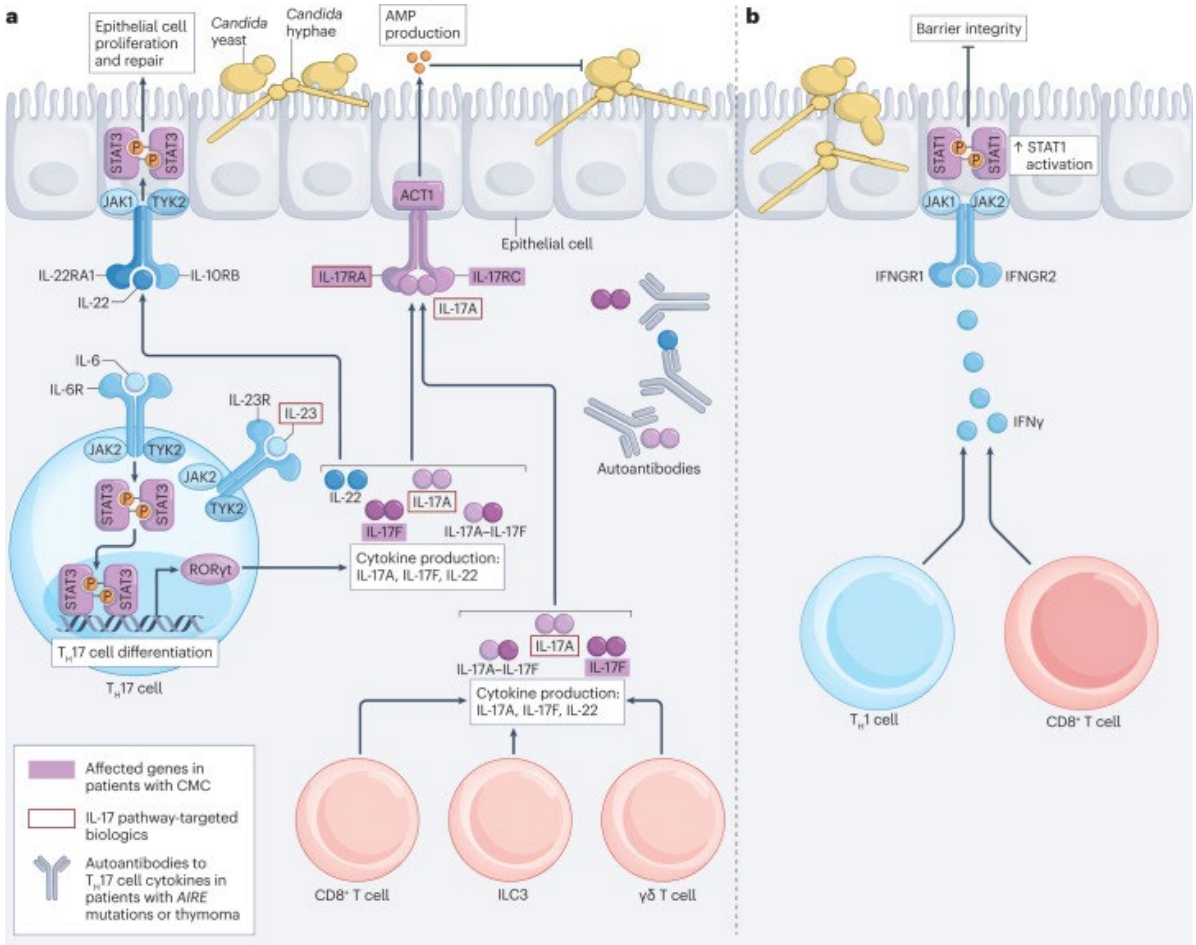
RESEARCH ARTICLE

Chronic Mucocutaneous Candidiasis in Humans with Inborn Errors of Interleukin-17 Immunity

Candidiasis

- Oral, pharyngeal, esophageal, vulvovaginal
- IL-17A/F produced by Th17, CD8+ T cells, ILC3, and yd-T cells. IL-17R (RA/RC) found on epithelial cells.
  - IL-17A/F bind to epithelial cell IL-17R → **antimicrobial peptide (APM production** → restrict Candida growth
- IL-22 also produced by Th17 cells → binds epithelial cells → STAT3 signaling to cause **proliferation and repair**
- Mucosal CD4+ TH1 cells and CD8+ T cells locally produce increased levels of **interferon-γ (IFNγ),** which also maintains **barrier integrity**

Mucosal Immunity



Candidiasis

IL-17C & IL-17RE are Dispensable for Immunity

- IL-17C and IL-17RE are expressed in the skin and have been shown to be pathogenic in mouse models of dermal inflammation
  - IL-17C produced by epithelial cells (i.e. keratinocytes), NOT lymphocytes
  - IL-17C mRNA is induced in mucosal epithelia by Candida
- IL-17C -/- and IL-17RE -/- mice are resistant to candidiasis:
  - Cutaneous
  - Oropharyngeal
  - Disseminated
- IL-17RC (co-receptor for IL-17RA) is required, and IL-17RC -/- mice exhibit delayed healing

Fig 1. IL-17C$^{-/-}$ and IL-17RE$^{-/-}$ mice are resistant to oropharyngeal candidiasis.

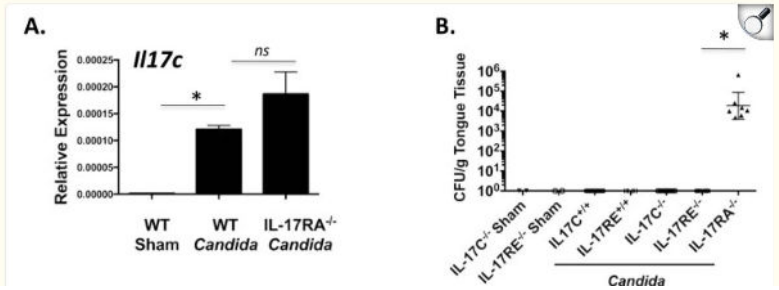


Fig 2. IL-17C$^{-/-}$ and IL-17RE$^{-/-}$ mice are resistant to systemic candidiasis.

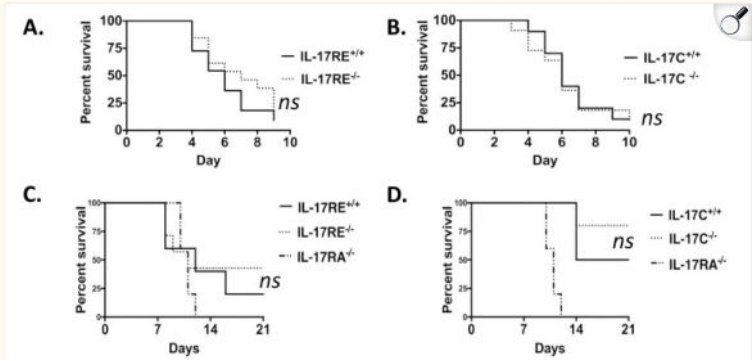
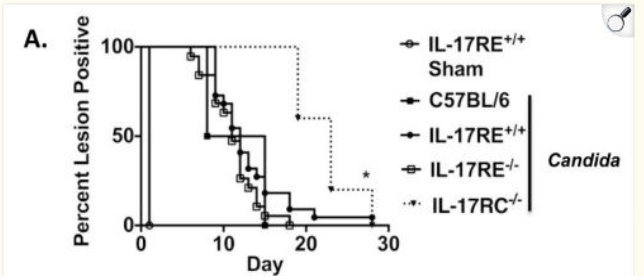
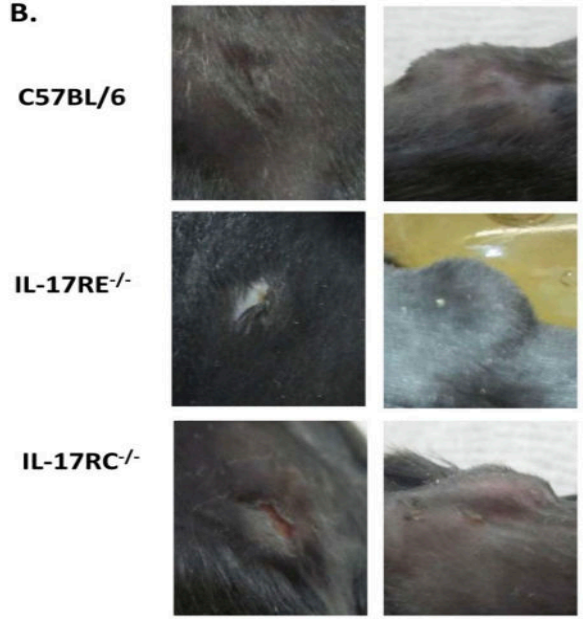


Fig 3. IL-17RE$^{-/-}$ mice are resistant to cutaneous candidiasis.





PLOS ONE

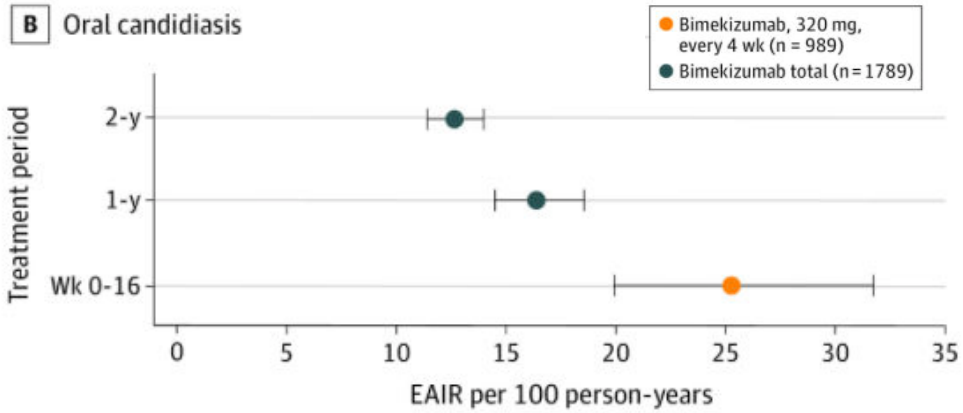
PLoS One. 2015 Apr 7;10(4):e0122807. doi: 10.1371/journal.pone.0122807

Signaling through IL-17C/IL-17RE Is Dispensable for Immunity to Systemic, Oral and Cutaneous Candidiasis

Candidiasis

IL-17 Inhibition and Risk of Candidiasis

- Phase 2/3 trials and pooled safety analyses
  - Brodalumab: 4.0-6.5%
  - Secukinumab: 1.7-4.7%
    - **300mg: 3.55 per 100 PYs**
    - **150mg: 1.85 per 100 PYs**
  - Ixekizumab: 3.3-3.6%
- Bimekizumab
  - Incidence decreased with longer duration of exposure



THE LANCET *Regional Health* Europe

ARTICLES · Volume 13, 100266, February 2022 · *Open Access* Download Full Issue

Risk of candidiasis associated with interleukin-17 inhibitors: A real-world observational study of multiple independent sources

Research

JAMA Dermatology | Original Investigation

Bimekizumab Safety in Patients With Moderate to Severe Plaque Psoriasis
Pooled Results From Phase 2 and Phase 3 Randomized Clinical Trials

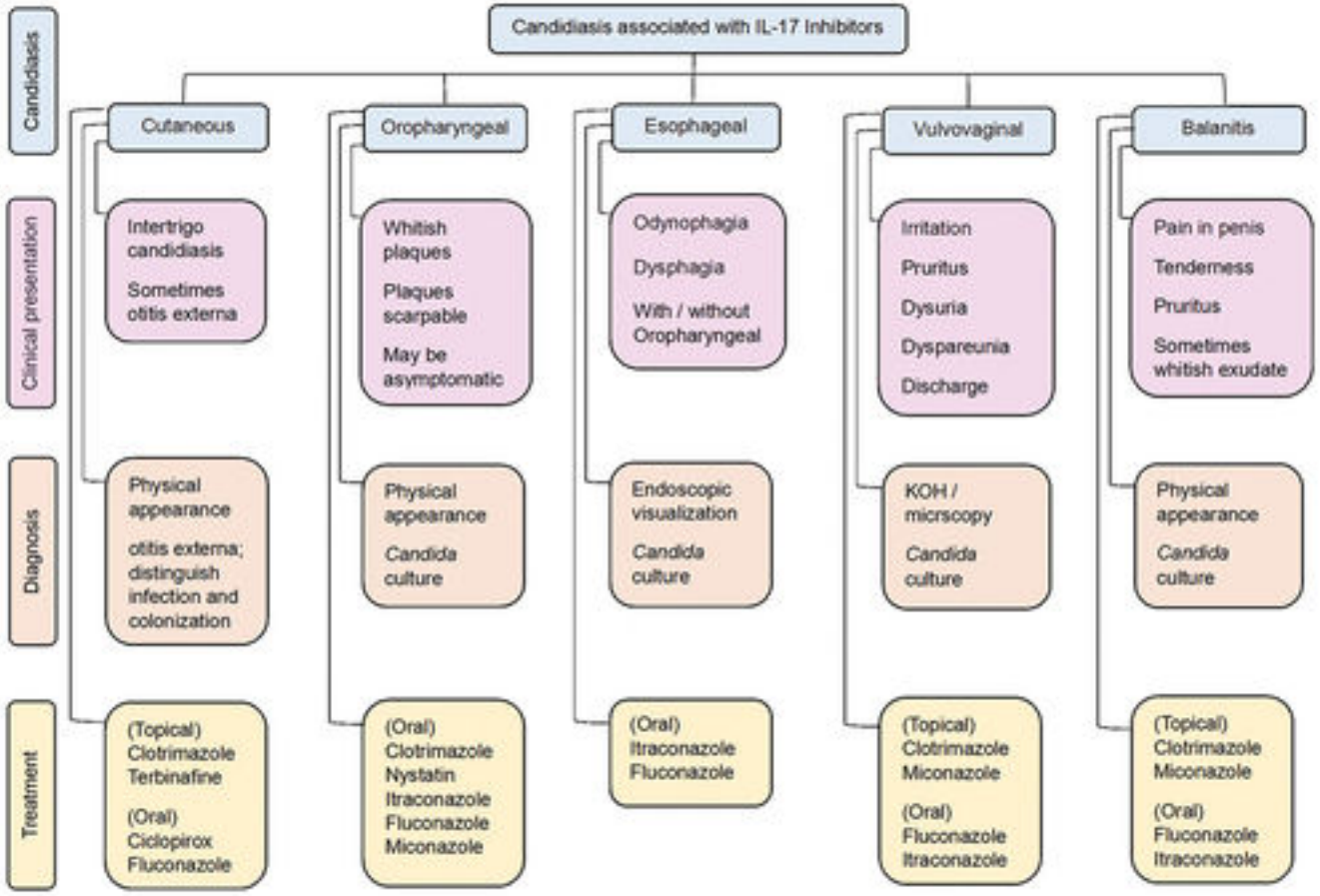
Kenneth B. Gordon, MD; Richard G. Langley, MD; Richard B. Warren, MD, PhD; Yukari Okubo, MD, PhD; Linda Stein Gold, MD; Joseph F. Merola, MD; Luke Peterson, MS; Krista Wixted, BS; Nancy Cross, MD; Delphine Deherder, MSc; Diamant Thaçi, MD, PhD

Candidiasis

Managing Candidiasis

- **Clotrimazole, nystatin and miconazole** were the most studied topical drugs and demonstrated similar efficacy with complete cure rates of 73%-100%.
- Single-drug therapy was as effective as combinations of antifungal, antibacterial and topical corticosteroid.
- Four studies investigated systemic therapy, and **oral fluconazole demonstrated similar efficacy to oral ketoconazole and topical clotrimazole**.

Keep it simple!



JEADV JOURNAL OF THE EUROPEAN ACADEMY OF DERMATOLOGY & VENEREOLOGY

Review Article

Cutaneous candidiasis – an evidence-based review of topical and systemic treatments to inform clinical practice

E.H. Taudorf, G.B.E. Jemec, R.J. Hay, D.M.L. Saunte

First published: 09 July 2019 | https://doi.org/10.1111/jdv.15782 | Citations: 61

Review

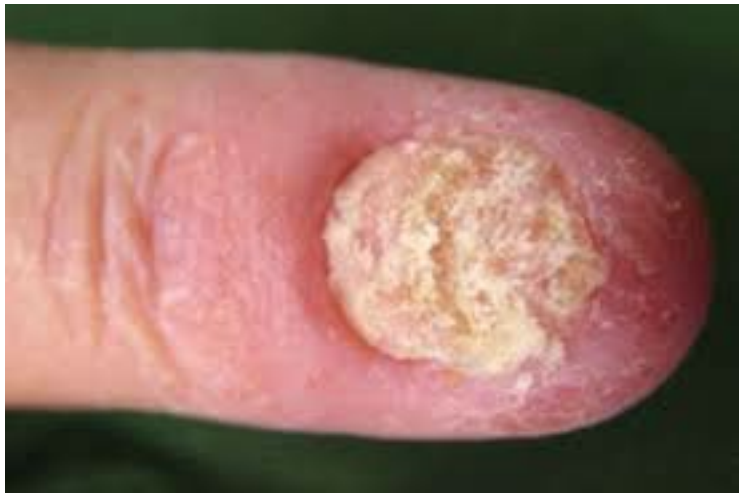
Risk of candidiasis associated with interleukin-17 inhibitors: Implications and management

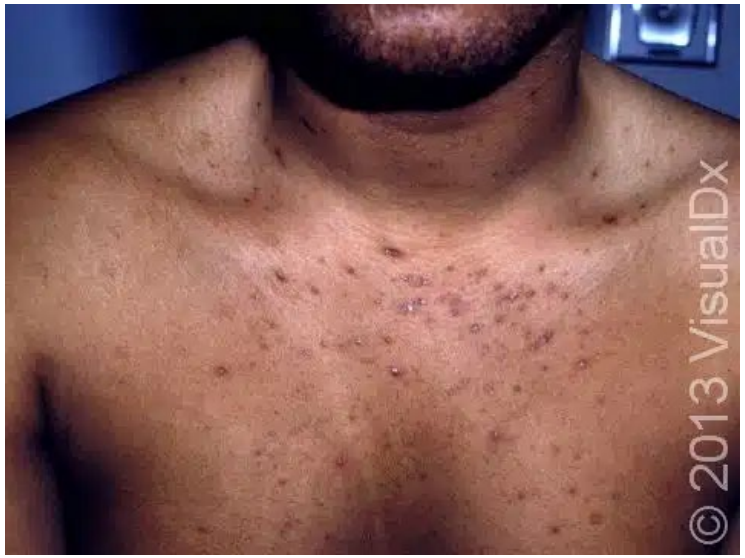
Hazrat Bilal, Muhammad Nadeem Khan, Sabir Khan, Wenjie Fang, Wenqiang Chang, Bin Yin, ...show all

Pages 30-44 | Received 07 Jun 2023, Accepted 27 Sep 2023, Published online: 20 Oct 2023

Candidiasis

Cutaneous Candidiasis





- Generalized cutaneous
- Intertrigo
- Erosio interdigitalis blastomycetica
- Candidal folliculitis
- Angular cheiltis
- Candidal balanitis
- **DDx: impetigo, HSV, exanthematous drug eruption, lichen sclerosis**

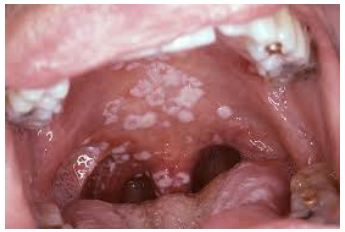
Candidiasis

Cutaneous Candidiasis

- Rx Topical
  - Nystatin 100,000 U/gram cream, ointment, or powder q8-12 hrs until healed
  - Azoles
    - Miconazole 2% cream and/or powder BID until healed
    - Ketoconazole 2% cream/shampoo QD for at least 2 weeks
    - Econazole
    - Efinaconazole (nails)
- Oral PO
  - **Fluconazole 150mg once weekly for 2-4 weeks**
  - Terbinafine
  - Griseofulvin

Candidiasis

Oropharyngeal Candidiasis



- Rx Topical
  - Miconazole 2% oral gel – 4x/d
    - Be aware of drug-drug interactions as may get systemically absorbed!
- Rx Oral Lozenge/Troche
  - Clotrimazole 10mg 5x/d for 10 days
- Oral Swish/Spit
  - **<u>Nystatin 100,000 U/mL 5mL 3-4x/day</u>**
    - Has sucrose so may develop dental caries in patients with dry mouths (i.e. head & neck radiation, Sjogren)*
  - Amphotericin B 50-100mg/ml (compounded*) 3-4x/d for weeks
- Oral Swish/Ingested
  - Nystatin 100,000 U/mL
  - Itraconazole solution – 200mg QD for 1-4 weeks, held in mouth prior to swallowing
- Oral PO
  - **<u>Fluconazole – 200mg on day 1, then 100 mg QD for 6 days</u>**
  - Posaconzaole, voriconazole, or amphotericin B for resistant cases

TABLE 1.

Non-Triazole Treatment Recommendation Summary for Oropharyngeal Thrush[20,22–27]

Agent (First/ Second Line)	Route	Dose/Duration	Side Effects	Contraindications	Relative Cost	Appropriate Patient Characteristics	Kidney/ Liver Adjustments	Next Drug in Line after Failure (First/ Second Line)
Clotrimazole (First)	Troche	10 mg 5x daily; 7-14 days	Hepatic enzyme elevation	--	$	Mild disease Pregnancy	--	Fluconazole
Miconazole (First)	Buccal Tablet	50 mg 1x daily; 7-14 days	Local site reactions (burning, pain, bad taste)	--	$$$$ (no generic)	Mild disease Pregnancy	--	Fluconazole
Nystatin (Second)	(1) Suspension (2) Pastilles	(1) 400,000-600,000 units 4-6x daily; 7-14 days (2) 1-2 pastilles (200,000 units each) 4x daily; 7-14 days	Dental caries	--	$	Mild disease Pregnancy	--	Fluconazole

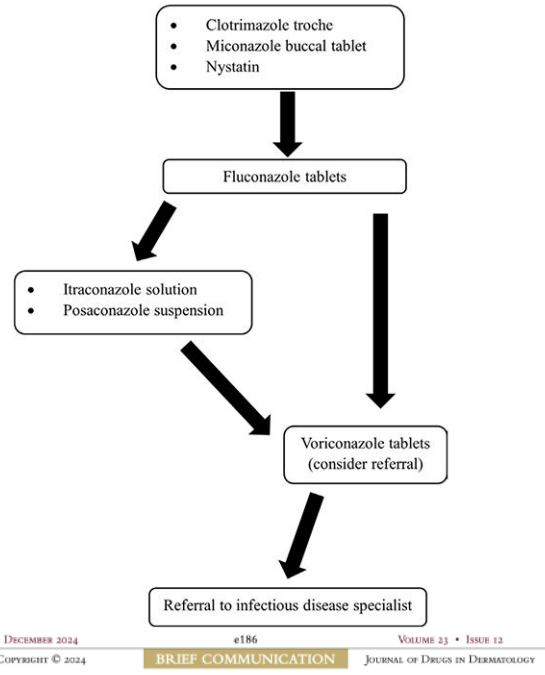
TABLE 2.

Triazole Treatment Recommendation Summary for Oropharyngeal Thrush[20,22–27]

Agent (First/ Second Line)	Route	Dose/ Duration	Side Effects	Contraindications	Relative Cost	Appropriate Patient Characteristics	Kidney/ Liver Adjustments	Next Drug in Line after Failure (First/ Second Line)
Fluconazole	Oral (Tablets)	100-200 mg 1x daily; 7-14 days	Hepatotoxicity Dermatologic reactions: rash, SJS/TEN, DRESS, AGEP, Sweet's syndrome, alopecia Prolonged QT interval Torsades de Pointes	Pregnancy Drugs that prolong the QT interval (erythromycin, pimozide, quinidine)	$	Mild disease with HIV Moderate to severe disease	Kidney: For creatinine clearance ≤50 mL/minute, normal dosage for loading dose; reduce maintenance dose by 50%	Itraconazole (First) Posaconazole (First) Voriconazole (Second)
Fluconazole	Oral (Tablets)	100 mg 1x daily; 3x weekly	Hepatotoxicity Dermatologic reactions: rash, SJS/TEN, DRESS, AGEP, Sweet's syndrome, alopecia Prolonged QT interval Torsades de Pointes	Pregnancy Drugs that prolong the QT interval (erythromycin, pimozide, quinidine)	$	Recurrent infection	Kidney: For creatinine clearance ≤50 mL/minute, normal dosage for loading dose; reduce maintenance dose by 50%	--
Itraconazole	Oral Solution	200 mg 1x daily; 28 days	Nausea Headache Abdominal pain	Pregnancy Non life-threatening indications in patients with ventricular dysfunction Significant drug interactions; consult database	$$	Moderate to severe disease Fluconazole refractory	--	Voriconazole
Posaconazole	Oral Suspension	400 mg 2x daily; 3 days, THEN 400 mg 1x daily; 28 days	Gastrointestinal side effects (nausea, vomiting, diarrhea) Hypokalemia Fever Hepatic enzyme elevation	Pregnancy Statins, pimozide, astemizole, quinidine, terfenadine, efavirenz, fosamprenavir, ergot alkaloids, drugs the prolong the QTc interval Proarrhythmic conditions: cardiomyopathy and QTc prolongation Monitoring and dosage adjustment with some drugs	$$$	Moderate to severe disease Fluconazole refractory	--	Voriconazole
Voriconazole	Oral (Tablets)	200 mg 2x daily*	Visual abnormalities Hepatic enzyme elevation Skin reactions: Photosensitivity	Pregnancy Carbamazepine, rifampin, long-acting barbiturate, sirolimus, pimozide, astemizole, quinidine, terfenadine Severe hepatic impairment* Monitoring and dosage adjustment with some drugs	$$	Moderate to severe disease Fluconazole refractory	Liver: Standard loading dose for mild-moderate insufficiency* Reduce maintenance dose by half Do not give in severe insufficiency*	IV echino-candins (refer/admit)

Abbreviations: SJS: Stevens-Johnson Syndrome; TEN: Toxic epidermal necrolysis; DRESS: Drug reaction with eosinophilia and systemic symptoms; AGEP: Acute generalized exanthematous pustulosis
*Requires trough concentrations during therapy; consider referral for drug administration
†Child-Pugh A and B
‡Child-Pugh C

FIGURE 1. Next steps for Oropharyngeal Thrush Unresponsive to Treatment.[20]



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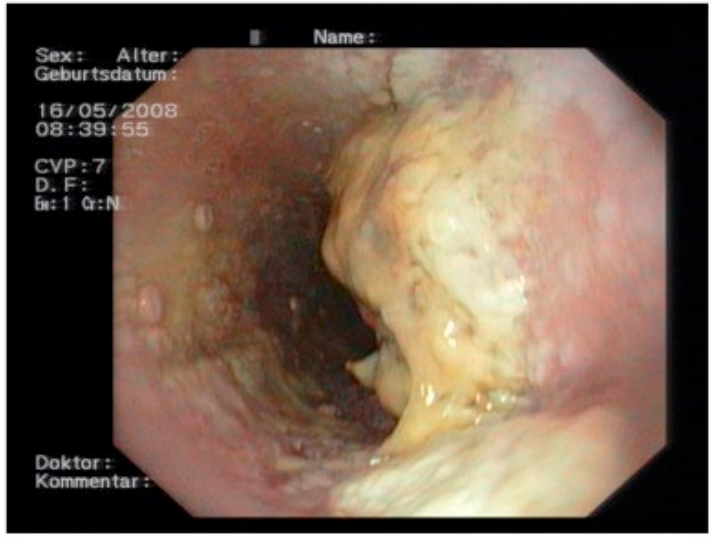
Practical Update on Treatment of Oral Candidiasis

Dina Zamil MD, Theodore Rosen MD

Candidiasis

Esophageal Candidiasis

- Oral
  - **1st-Line: PO Fluconazole 200-400mg QD for 14-21 days**
  - PO itraconazole 200mg QD for 14-21 days
  - PO voriconazole 200mg BID for 14-21 days
  - Refractory:
    - Amphotericin B deoxycholate 0.3 to 0.7 mg/kg per day
    - Posaconazole 400mg BID



Diagnose with help from ENT
(will need endoscopy + culture)

Candidiasis

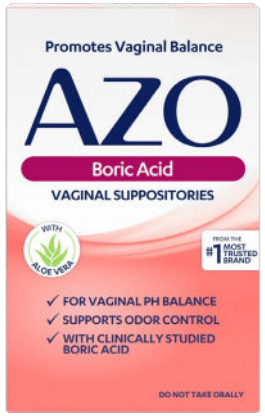
Managing Vulvovaginal Candidiasis

- OTC Intravaginal Agents
  - Boric Acid, Clotrimazole, Miconazole, Tioconazole
- Rx Intravaginal Agents
  - Butoconazole, Nystatin, Terconazole
- Oral
  - Fluconazole 150mg tablet single dose
  - Ibrexafungerp 150mg BID for 1 day
    - Triterpenoid class – similar MoA to echinocandins (targets same enzyme)
    - Inhibit glucan synthesis of fungal wall

Table 2: Topical antifungal treatment for vulvovaginal candidiasis

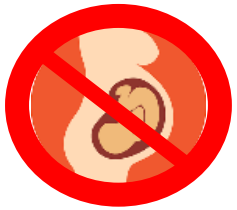
Antifungal	Mode of administration	Regimen
Clotrimazole 1–2%	Cream	Daily for 3–14 days
Miconazole 2–4%	Cream	Daily for 3–14 days
Miconazole 100, 200 and 1,200 mg	Vaginal suppository	One suppository daily for 7, 3 or 1 day(s), respectively
Tioconazole 6.5%	Ointment	Single application therapy
Butoconazole 2%*	Cream	Single application therapy
Terconazole 0.4–0.8%*	Cream	Daily for 3–7 days
Terconazole 80 mg*	Vaginal suppository	One suppository daily for 3 days
Nystatin	Vaginal cream, tablet or pessary	One or two 100,000 units for 14 days
Boric acid	Vaginal suppository	One 600 mg suppository daily for 3 weeks

** Medical prescription is required for marked medication.*



Candidiasis

Pregnancy



- **Oral Azoles (Fluconazole)**
  - Single 150mg dose of fluconazole has been a/w spontaneous abortion and congenital anomalies

Current guidelines state that <u>only topical azole</u> therapy should be used to treat VVC in pregnancy.****

<u>Oral fluconazole safe during breastfeeding.*</u>**

- **Topical Azoles**
  - Butoconazole
  - Clotrimazole
  - Miconazole
  - Teraconazole
  - Tioconazole
- **Nystatin**
- **Boric Acid**

JOURNAL ARTICLE

Vulvovaginal Candidiasis: A Review of the Evidence for the 2021 Centers for Disease Control and Prevention of Sexually Transmitted Infections Treatment Guidelines FREE

Paul Nyirjesy ✉, Carolyn Brookhart, Gweneth Lazenby, Jane Schwebke, Jack D Sobel

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Candidiasis

Dr. Issa's Pearls

- IL-17A/F signaling through IL-17RA is critical for mucocutaneous fungal immunity
- Relatively low frequency of OPC and the lack of CMC in these patients likely reflect that mucosal IL-17 responses are not completely inhibited by these biologics and are consistent with the notion that profound and sustained inhibition of the IL-17 pathway is required for the development of mucosal fungal disease
- There appears to be dose-dependent candidiasis AE event rate as observed with secukinumab and when considering bimekizumab reduction in AE rate after year 1 (after reduction in dose)
- Collaborate with PCP, ENT and/or Infectious Disease specialist for treatment of complicated cases (e.g. recurrent, immunosuppressed [e.g. HIV], treatment-resistant, non-C. Albicans)

Thank You!

Email:
drnaiemissa@gmail.com