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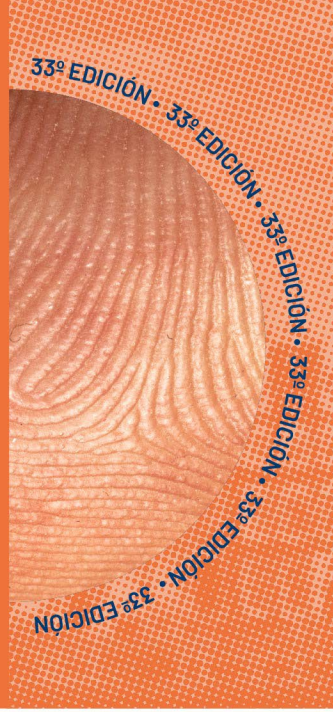

Psoriasis y otras enfermedades inflamatorias: novedades en patogenia

Sergio Alique García

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ser_alique

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NO TENGO CONFLICTOS DE INTERÉS

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Sumario

- Modificación de la enfermedad
- Diferencias poblacionales de la psoriasis
- Psoriasis pustulosa, ¿realmente es psoriasis?
- Monitorización farmacológica

Sumario

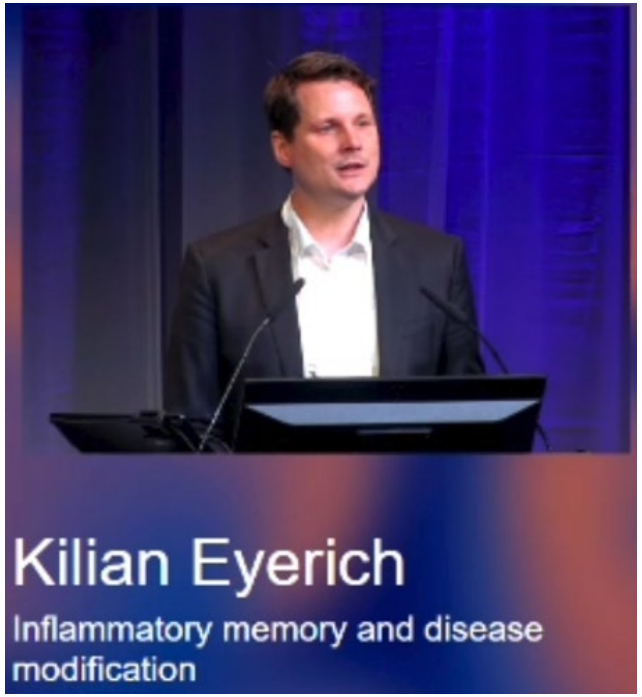
- **Modificación de la enfermedad**
- Diferencias poblacionales de la psoriasis
- Psoriasis pustulosa, ¿realmente es psoriasis?
- Monitorización farmacológica

Definición de modificación de la enfermedad

How could disease modification be defined in pso?

Topic A: Defining disease control, remission and modification

1	Disease control is defined by control of all symptoms of plaque-type psoriasis with treatment, appreciating that cessation of treatment will result in plaque-type psoriasis symptoms reappearing	97
2	Disease remission is defined by control of all symptoms of plaque-type psoriasis that is maintained beyond 3 months after cessation of treatment	78
3	Disease modification is defined by a change to the better in the characteristics or course, topography, or progression of the disease that is maintained beyond 3 months after cessation of treatment	71
4	Disease modification is caused by a fundamental change in the underlying immunopathology that allows disease remission	89
5	Disease modification is reflected by quantitative differences of the inflammatory activity of the skin and/or improvement/ prevention of comorbidities	95
6	Disease curation is the maximum result of disease modification	97
7	It is difficult to discriminate between disease control and disease modification of plaque-type psoriasis	79

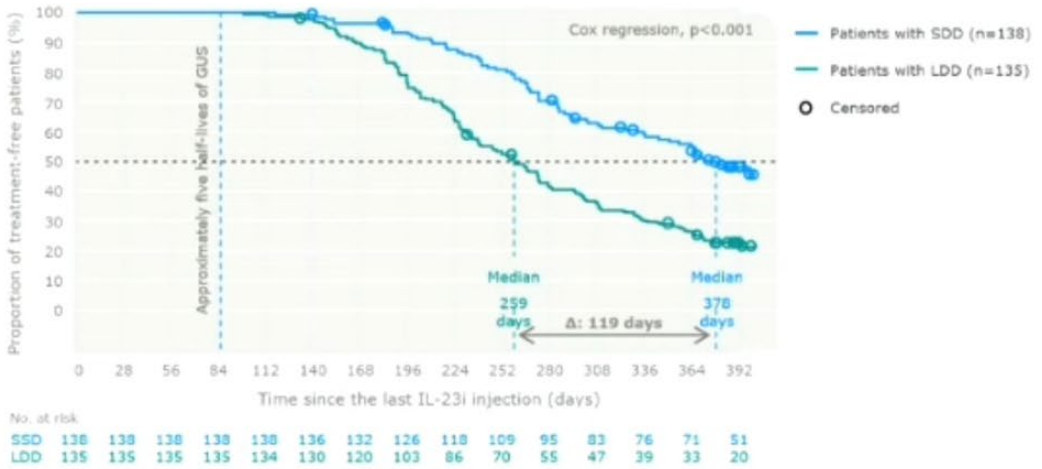


Eyerich K et al, JEADV 2023

Modificación de la enfermedad

GUIDE:
Disease modification (?) may happen in some patients

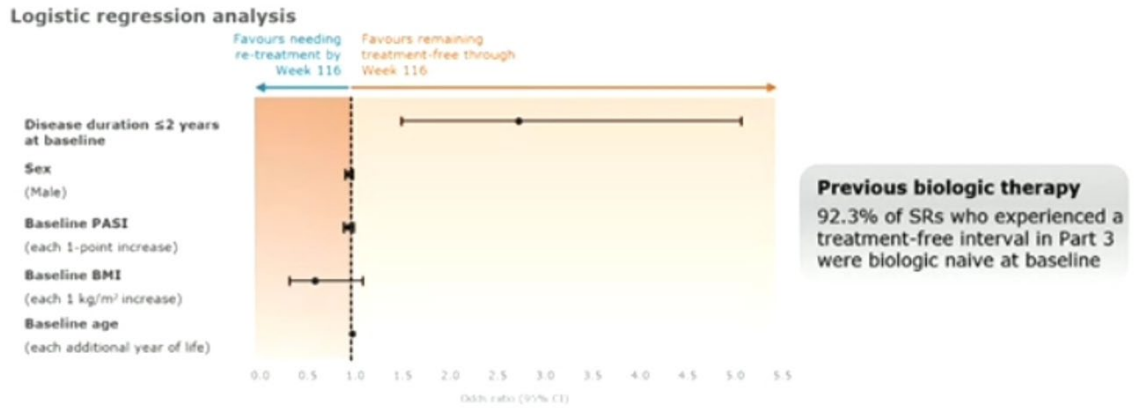
Time until loss of response: After discontinuation of IL-23i treatment, SRs (n=273) remained treatment-free for a median of 302 days



GUS, ustekinumab; LDD, long disease duration; SDD, short disease duration; SR, super responder; i, inhibitor.
Schakel K, et al. Presented at EADV, Berlin, Germany, 11–14th October 2021. P2042.

Modificación de la enfermedad

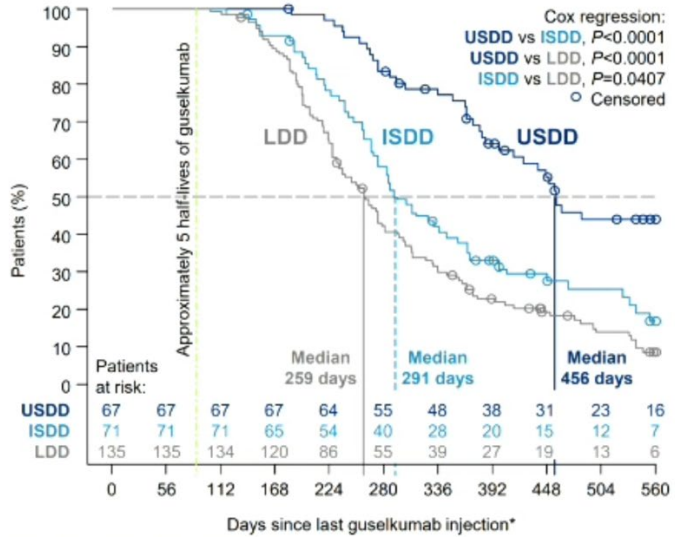
Super-response is associated to disease duration



Previous biologic therapy
92.3% of SRs who experienced a treatment-free interval in Part 3 were biologic naive at baseline

Results from an analysis of collinearity showed that the correlations among independent variables were statistically low enough to conclude no multicollinearity* (likelihood ratio: p<0.001)

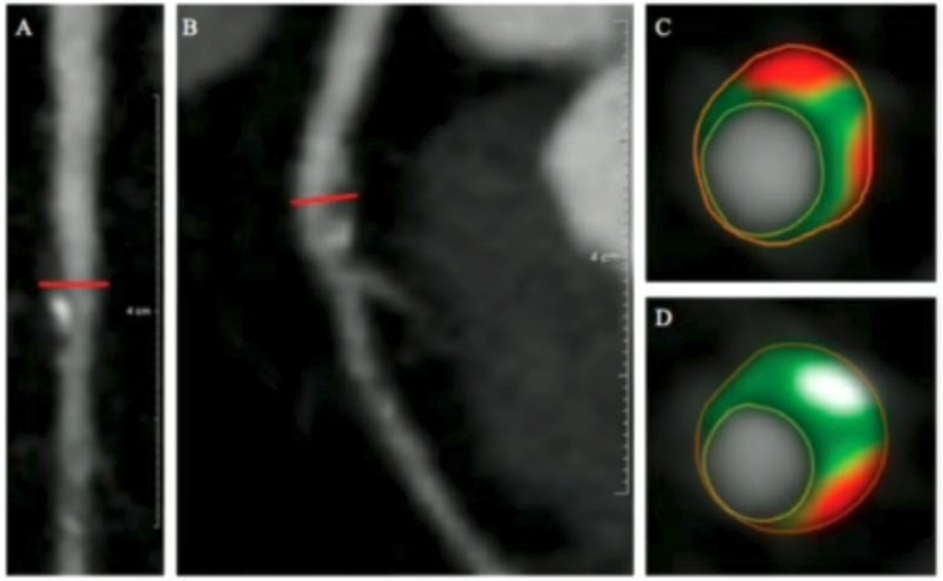
Ultra-short disease duration performs even better



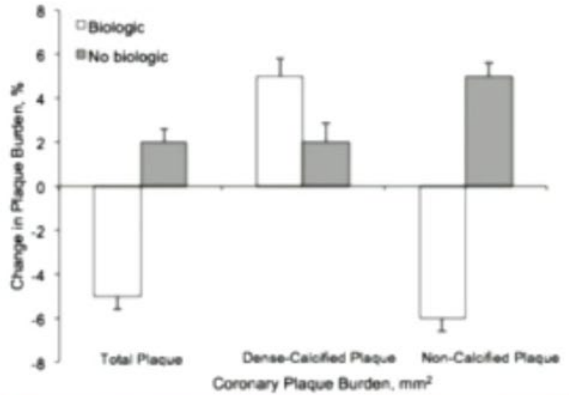
Schäkel K et al, AAD 2024

Comorbilidades cardiovasculares

Disease modification: development of comorbidities



Coronary CT angiography N=290, n=121 biologic naive, 1 year follow-up



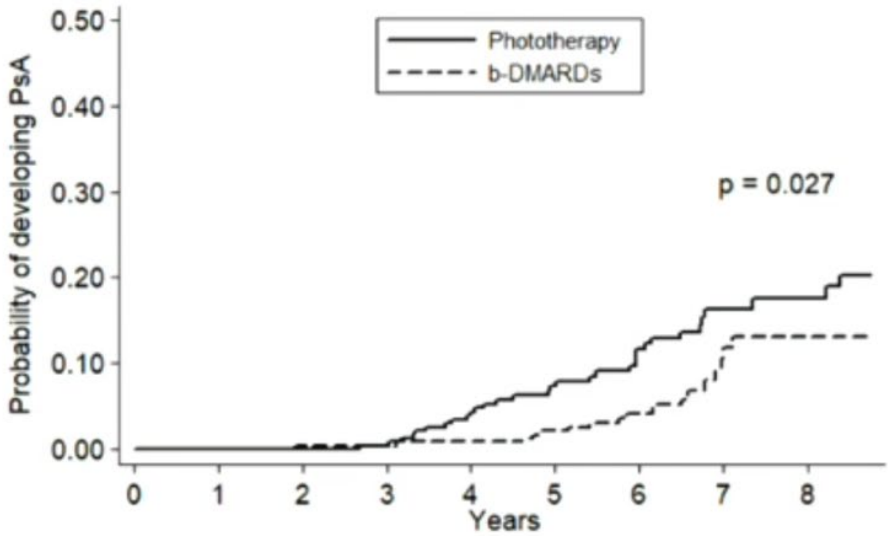
Treatments	Change over one-year (mm^3) (%)		P-value
Anti-TNF therapy (n = 48)	-0.06 (-5)	–	
vs. Anti-IL12/23	–	-0.02 (-2)	0.27
vs. Anti-IL17	–	-0.15 (-12)	0.08
vs. NBT	–	0.06 (5)	**0.009**
Anti-IL12/23 therapy (n = 19)	-0.02 (-2)	–	
vs. Anti-IL17	–	-0.15 (-12)	**0.01**
vs. NBT	–	0.06 (5)	0.09
Anti-IL17 therapy (n = 22)	-0.15 (-12)	–	
vs. NBT	–	0.06 (5)	**0.005**

Elnabawy YA, Cardiovasc Res 2019

Artritis psoriásica

Disease modification: development of comorbidities

	No PsA (n=413)	PsA (n=51)	P value*
Age, years	46.59±0.58	53.73±1.51	<0.001
Sex, male, n (%)	210 (45)	28 (55)	0.143
BMI, kg/m^2	26.83±0.13	26.45±0.52	0.357
Current smoker, n (%)	125 (27)	14 (27)	0.930
Psoriasis duration, years	22.38±0.40	25.33±0.82	0.013
Baseline PASI	12.48±0.27	11.14±0.69	0.098
Family history of PsA, n (%)	32 (7)	7 (14)	0.046
Body areas affected by psoriasis			
Scalp, n (%)	306 (66)	40 (78)	0.051
Folds, n (%)	193 (42)	16 (31)	0.116
Nails, n (%)	190 (41)	28 (55)	0.032
Comorbidities			
Type 2 diabetes, n (%)	79 (17)	7 (14)	0.506
Dyslipidaemia, n (%)	207 (45)	26 (51)	0.332
Hypertension, n (%)	195 (42)	25 (5)	0.283
Obesity, n (%)	53 (11)	9 (18)	0.340



Artritis psoriásica

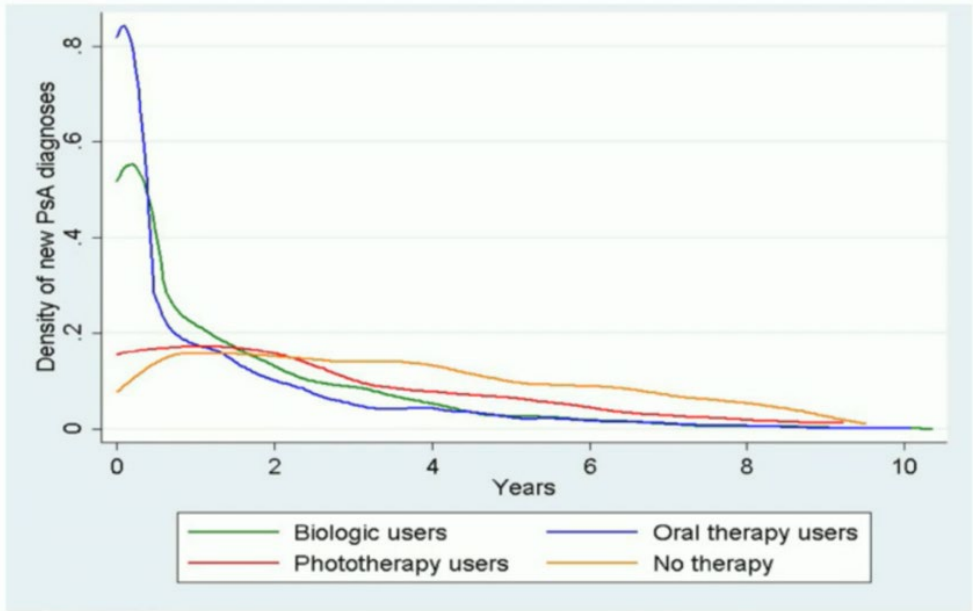
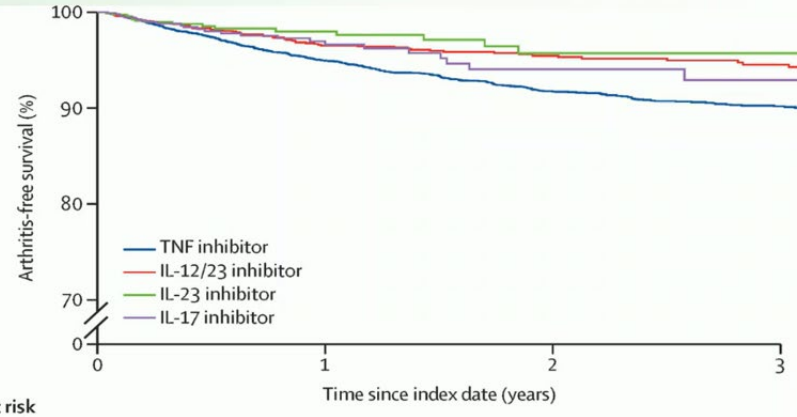


Figure 2 Timing of PsA diagnosis by therapy start. Among patients who receive a new diagnosis of PsA, we examined the time to new PsA diagnosis. Time represents the time from start in the study: initiation of the specified therapy or 1 year after psoriasis diagnosis for those who do not receive therapy. PsA, psoriatic arthritis.

s 2022;81:80–86.

Time to inflammatory arthritis by biologic class



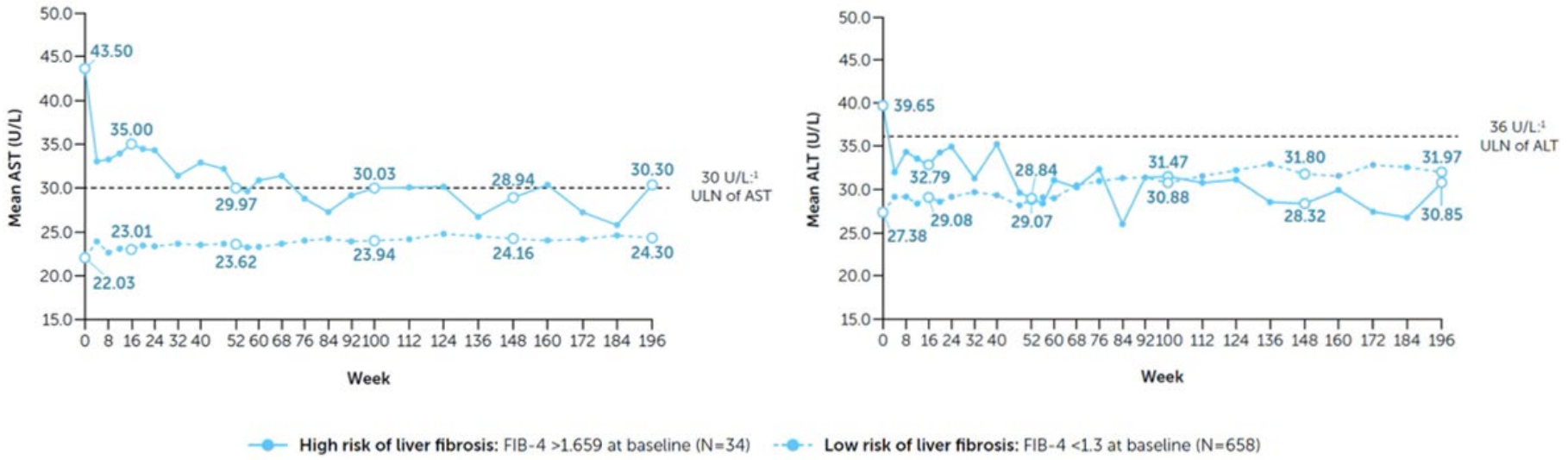
Protopathic Bias?

Number at risk (number censored)							
TNF inhibitor	9874 (522)	5342 (4518)	3904 (5829)	2919 (6760)	2244 (7389)	1716 (7889)	1330 (8268)
IL-12/23 inhibitor	2873 (132)	1415 (1466)	1088 (1768)	843 (2008)	658 (2190)	515 (2329)	397 (2445)
IL-23 inhibitor	1114 (130)	409 (729)	287 (849)	181 (954)	119 (1013)	76 (1056)	42 (1092)
IL-17 inhibitor	1355 (194)	468 (917)	284 (1098)	180 (1199)	130 (1246)	91 (1284)	57 (1317)

Singla S, Putman M, Liew J, Gordon K. Association between biological immunotherapy for psoriasis and time to incident inflammatory arthritis: a retrospective cohort study. *Lancet Rheumatol*. 2023;5(4):e200-e207. doi:10.1016/S2665-9913(23)00034-6

Comorbilidad hepática

Bimekizumab: change in mean clinical markers of liver fibrosis and key liver parameters over 4 years by risk of liver fibrosis

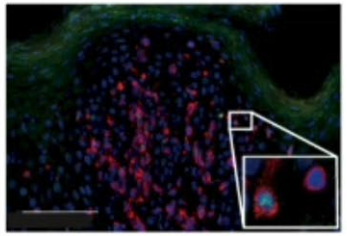


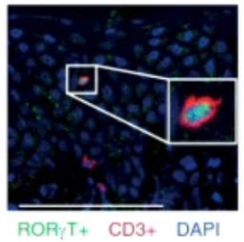
Risk of liver fibrosis defined by FIB-4 at baseline. BE VIVID lasted 52 weeks and BE SURE and BE READY lasted 56 weeks; to pool data across studies, Week 52 data presented here are from the Week 52 assessment in BE VIVD and the Week 56 assessment in BE SURE and BE READY, respectively. Data presented after Week 52 are from the BE BRIGHT OLE. Normal reference ranges for liver function tests (represented by the dotted lines) and platelets may vary depending on laboratory and patient characteristics (such as sex and BMI).[1,2] **1.** Lala V et al. Liver Function Tests (Updated July 2023). StatPearls. Available at: https://www.ncbi.nlm.nih.gov/books/NBK482489 [Accessed September 2024]; **2.** Amernia B et al. BMC Gastroenterol 2021;21:453.
All content on this slide is from Gisondi P et al. EADV 2024. Poster 3146.

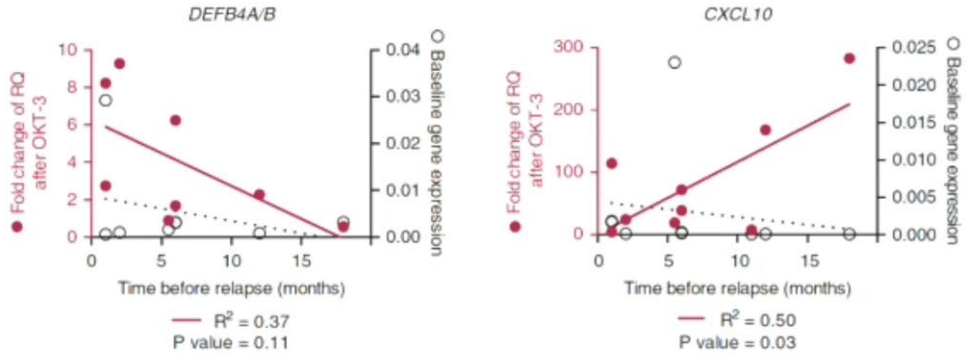
Células residentes de memoria

Resident T Cells in Resolved Psoriasis Steer Tissue Responses that Stratify Clinical Outcome

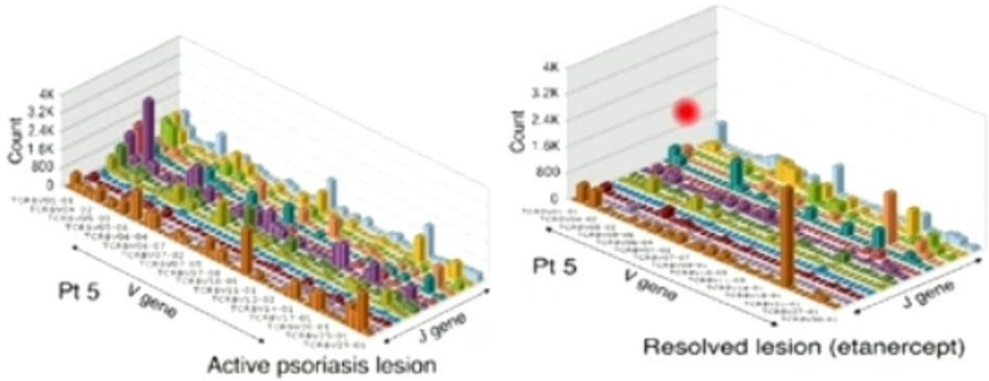
Irène Gallais Sérézal[1,2], Cajsa Classon[1], Stanley Cheuk[1], Mauricio Barrientos-Somarribas[4], Emma Wadman[1], Elisa Martini[1,2], David Chang[1], Ning Xu Landén[1,2], Marcus Ehrström[3], Susanne Nylén[1] and Liv Eidsmo[1,2]





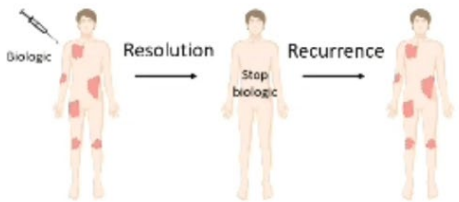


Sérézal IG et al, JID 2018

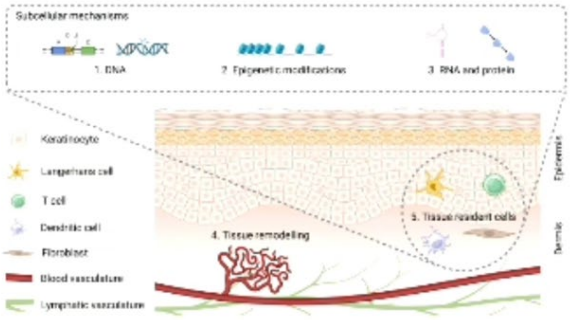


Células residentes de memoria

Improving outcomes through early intervention: Modulating inflammatory memory for drug-free remission

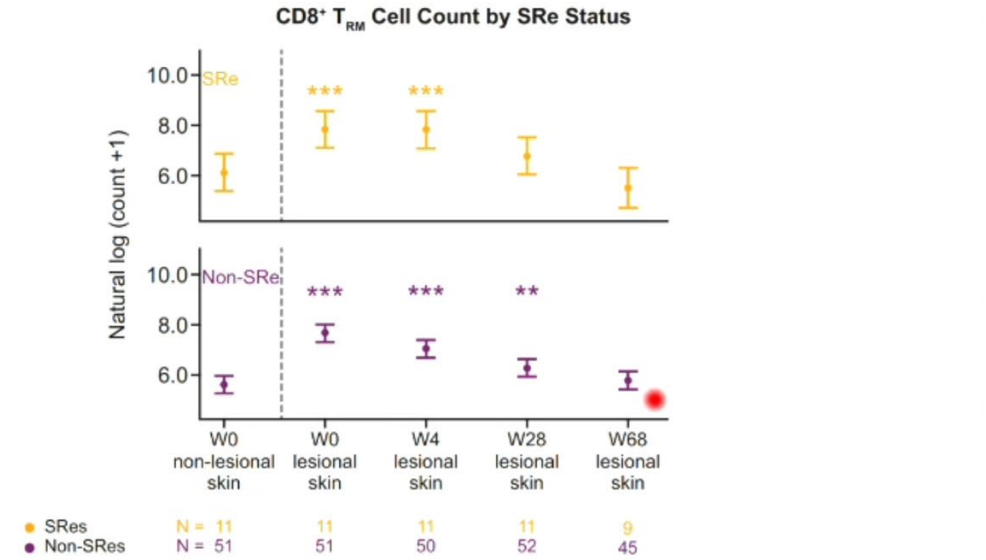


Mechanistic understanding of inflammatory memory in tissue



Francis et al, *J Allergy Clin Immunol* 2024
Francis et al, *Nat Commun* 2024

Guselkumab normalises TRM numbers in lesional skin



Julianty A et al, ISDS poster 2023

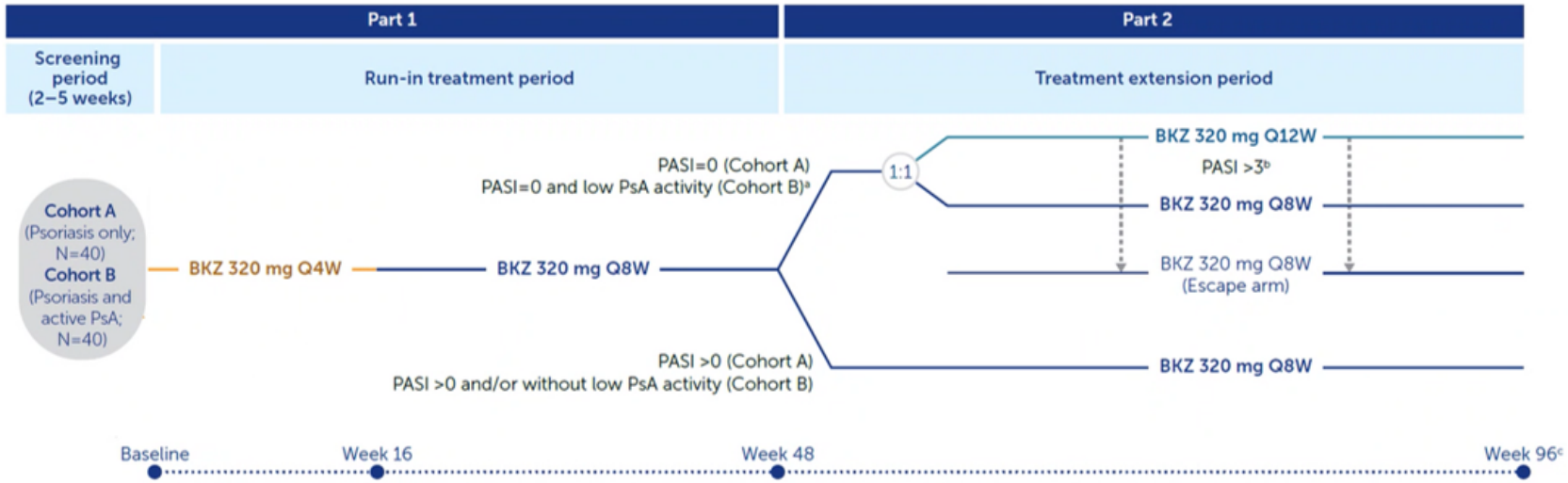
Modificación de la enfermedad

BIMEKIZUMAB disease modification study in PSO

BE UNIQUE Objectives

- Explore **very early (week 1) and long-term changes** in molecular transcriptome
- Provide a holistic view of participants during treatment: **skin and joint** assessments and biopsies
- Explore further **dosing interval extension** after 1 year of treatment in participants who achieve sufficient disease control

BE UNIQUE Study Design



[a] In addition to PASI=0, Cohort B patients must have low PsA disease activity at Week 48 (SJC ≤1 and no increase in concomitant medications for the treatment of PsA symptoms [such as non-steroidal anti-inflammatory drugs (NSAIDs), weak opioids, intra-articular injections] compared with baseline) to be randomised in the treatment extension period; [b] Patients in Cohort A and Cohort B who are randomised at Week 48 and who have a PASI score >3 during the treatment extension period will enter an escape arm and receive BKZ Q8W to study end, undergoing additional assessments; a lesional skin biopsy will be taken at the visit the patient has a PASI score >3, instead of at Week 96; [c] The safety follow-up visit will occur at least 12 weeks after the final dose and not before 4 weeks after the last skin biopsy. All content on this slide is from Gudjonsson JE et al. EADV 2024. Poster 3282.

Sumario

- Modificación de la enfermedad
- **Diferencias poblacionales de la psoriasis**
- Psoriasis pustulosa, ¿realmente es psoriasis?
- Monitorización farmacológica

Epidemiología

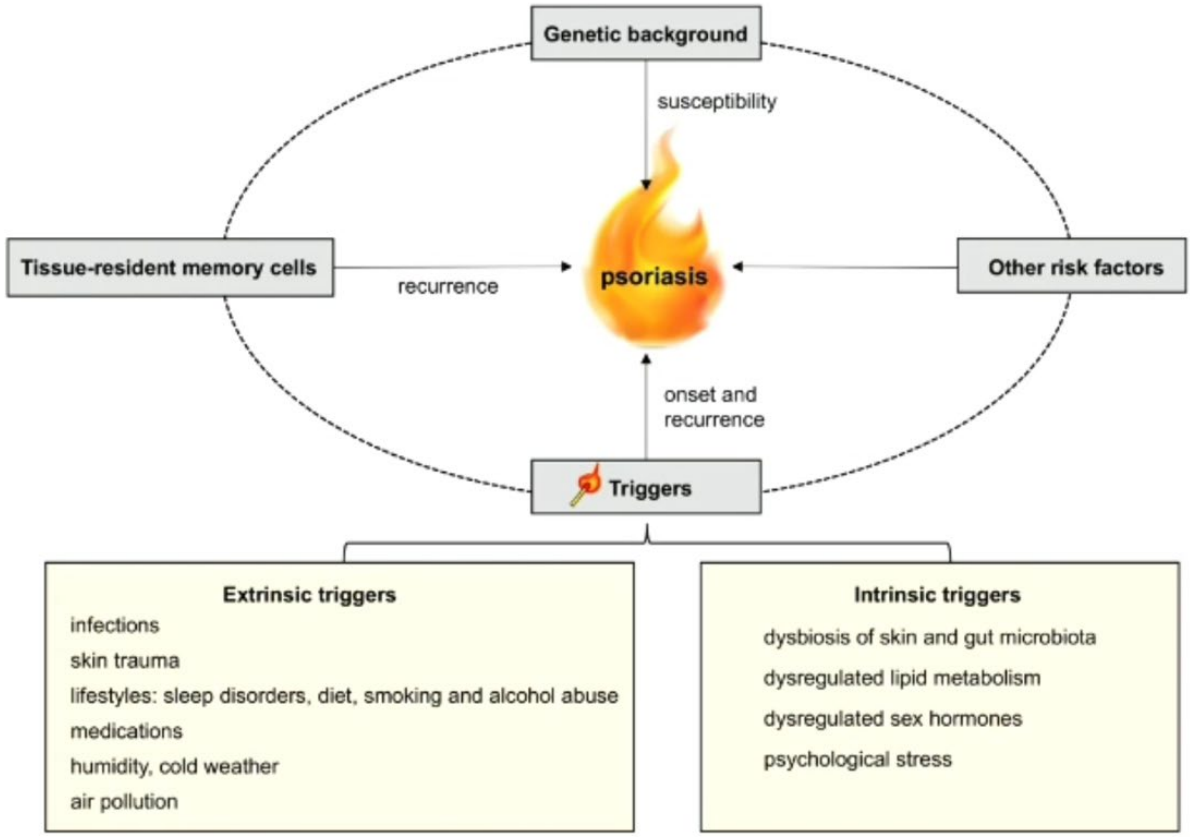
Regionally, the occurrence of the disease for the overall population varied from 0.11% (95% uncertainty interval 0.04% to 0.30%) in east Asia to 1.58% (0.50% to 5.73%) in Australasia, and 1.52% (0.87% to 2.74%) in western Europe.

Considering the estimate for the overall population, **Australia (1.88%, 0.59% to 6.10%), Norway (1.86%, 0.94% to 3.97%), Israel (1.81%, 0.83% to 4.44%), and Denmark (1.79%, 0.91% to 3.61%) had the highest estimates of the prevalence of psoriasis.**

The estimated prevalence of psoriasis in countries from **east Asia was much lower, Taiwan being the country with the lowest prevalence worldwide (0.05%; 0.02% to 0.16%).**

Parisi R, Iskandar IYK, Kontopantelis E, Augustin M, Griffiths CEM, Ashcroft DM; Global Psoriasis Atlas. National, regional, and worldwide epidemiology of psoriasis: systematic analysis and modelling study. BMJ. 2020 May 28;369:m1590. doi: 10.1136/bmj.m1590. PMID: 32467098; PMCID: PMC7254147.

Desencadentes



Triggers for the onset and recurrence of psoriasis

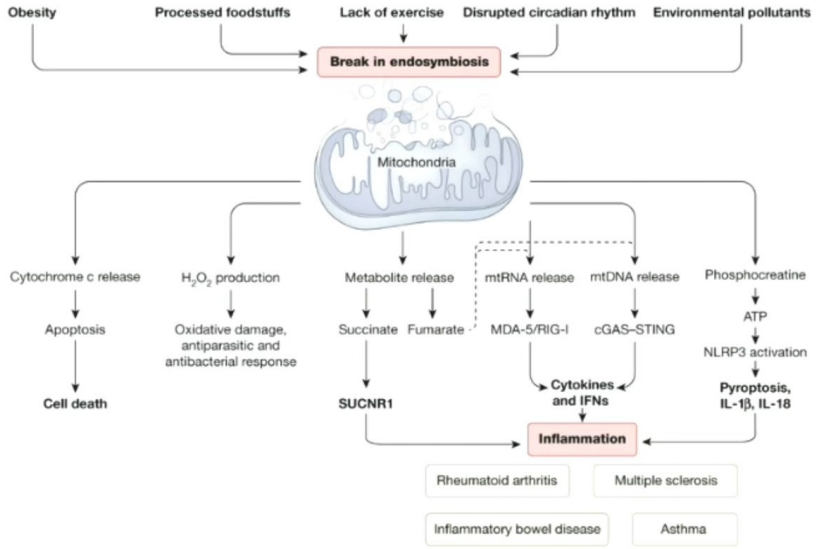
Liu, S., He, M., Jiang, J. et al. Triggers for the onset and recurrence of psoriasis: a review and update. Cell Commun Signal 22, 108 (2024). https://doi.org/10.1186/s12964-023-01381-0

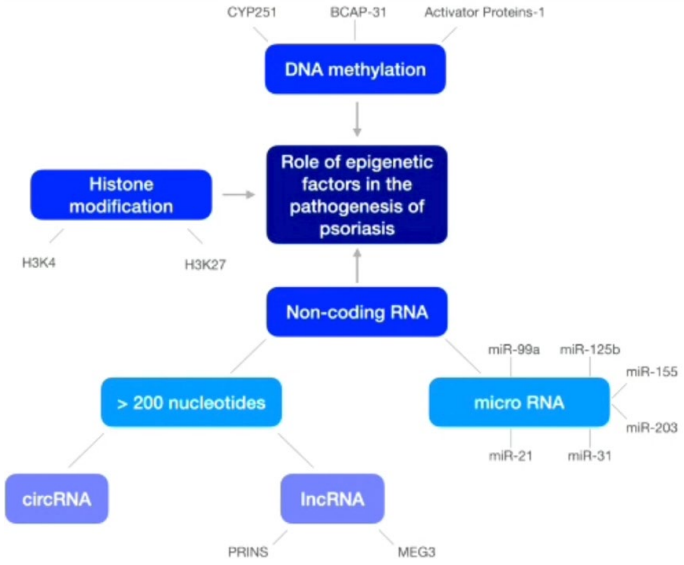
Desencadenantes

Human leukocyte antigen (HLA) alleles associated with psoriasis pathogenesis.

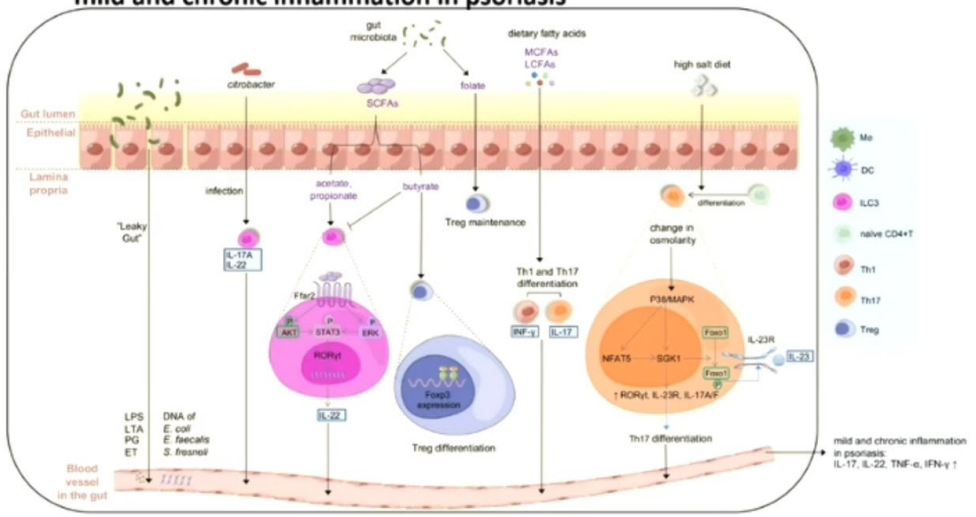
HLA Alleles	Type of Psoriasis	Ethnic Group Association	Drug Response
HLA Cw6	Droplet psoriasis Type I psoriasis [27]	In the general population varies from 14.1% to 59.1% [27]; more frequently in Caucasian patients than in the Asian population [27,39]	Responds better to treatment with methotrexate, biologic drugs directed against (IL)-12/23, IL-17, and IL-23 [12]
HLA Cw1	Erythroderma, pustular psoriasis, and psoriatic arthritis [12]	Most common in the Asian population [12]	Worse response to biologic therapy resistance to alefacept [31,32]
HLA Cw12	Severe psoriasis [13]	Most common in the Turkish population [13]	No research
HLA B-27	Psoriatic arthritis [35,36]	Diverse in ethnic group [35,36]	Predictor of good response to biological disease-modifying antirheumatic drugs (bDMARDs) [40]

Also associated with psoriasis pathogenesis: HLA-C*18, HLA-B57, HLA-DR*07, HLA-DQA1*:02:01 and DQB*:02:02





The dysbiosis of gut microbiota and diet may induce mild and chronic inflammation in psoriasis



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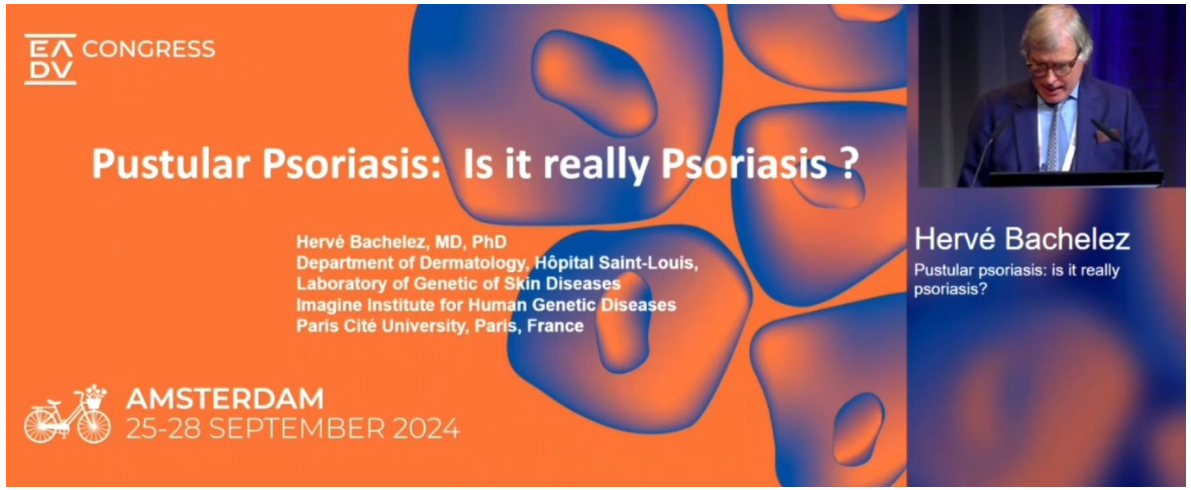

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PUSTULAR PSORIASIS: CLINICAL CONTINUUM OR SEPARATE ENTITY

Why so much attention now?

There remains a substantial unmet medical need

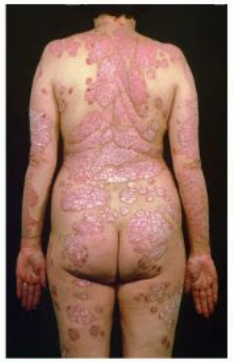
Dramatic progress in science and practice of psoriasis vulgaris (PsV) with treatments that are highly effective in the great majority of patients

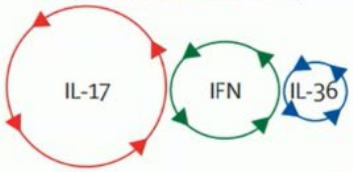
Extension clinical trials (biologics and small molecules) investigating subtypes of psoriasis including pustular forms

Significant scientific and therapeutic advances in generalised pustular psoriasis (GPP) and separation from PsV

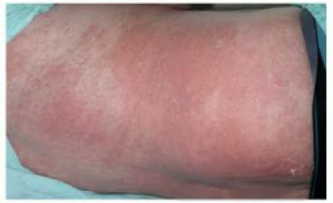
CLINICAL CONTINUUM OR SEPARATE ENTITY?

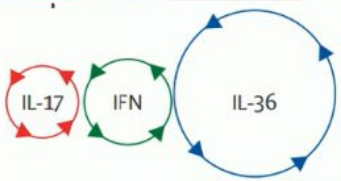
Psoriasis Vulgaris



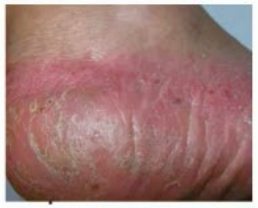


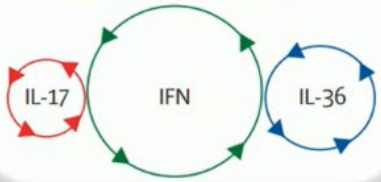
GPP



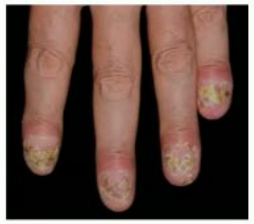


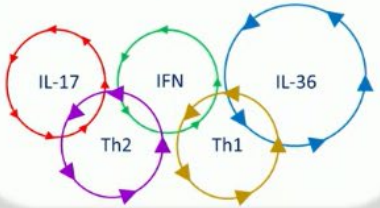
Paradoxical psoriasis



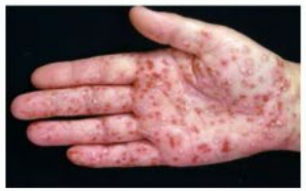


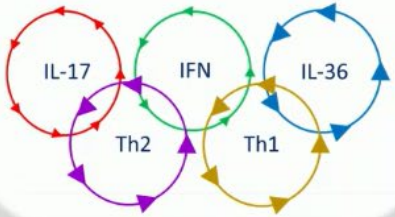
ACH





PPP

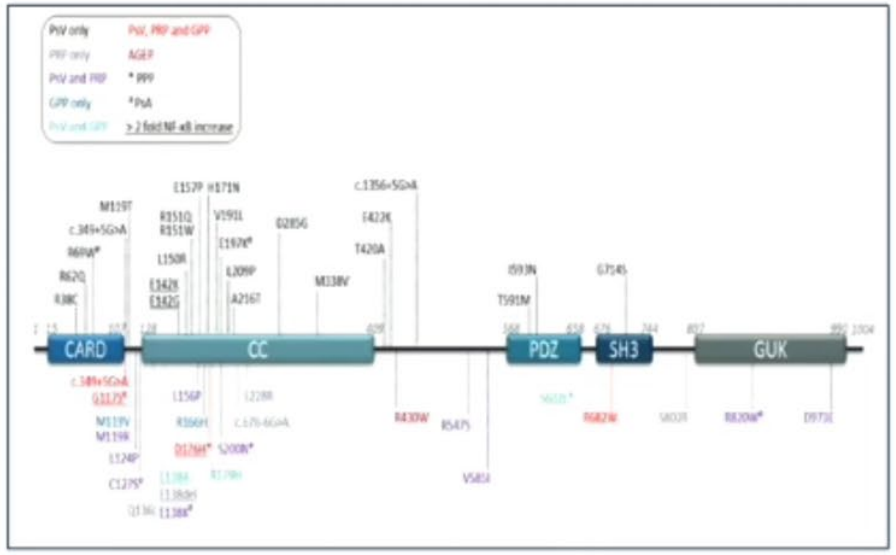


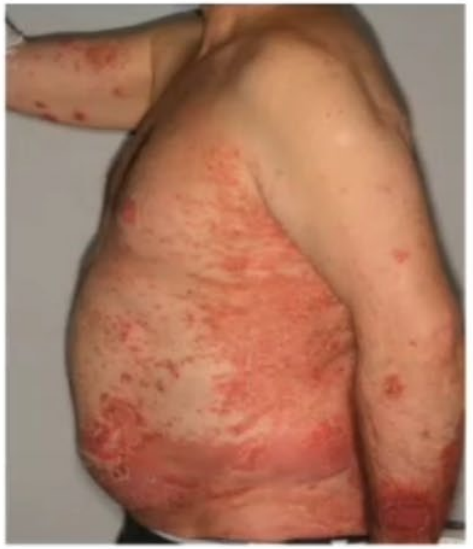


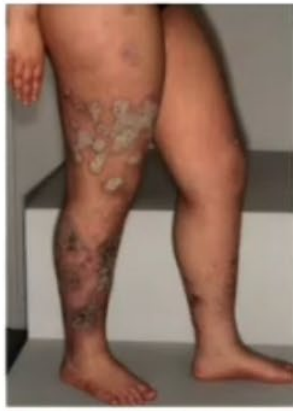
After: *Griffiths, Armstrong, Gudjonsson, Barker LANCET 2021*

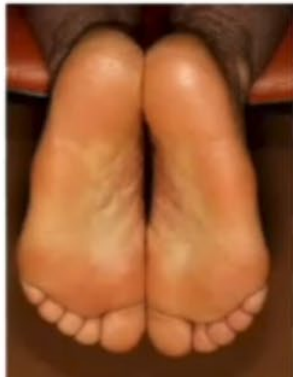
Psoriasis pustulosa

CARD14 Gain-of-Function (GOF) Mutations identified in Psoriasis Vulgaris, Pityriasis Rubra Pilaris and Pustular Psoriasis (GPP, Palmoplantar pustulosis)









Israel L, Mellett M. Frontiers Immunol 2018

- Heterozygous, homozygous and compound heterozygous mutations
- CARD and Coiled-Coil domains are hot spots (>60% of published variants)

Fuchs-Telem D, et al. Am J Hum Genet 2012; Berki D, et al. J Invest Dermatol 2015; Mossner R et al. J Invest Dermatol 2015; Niaouris A, et al. J Invest Dermatol 2023

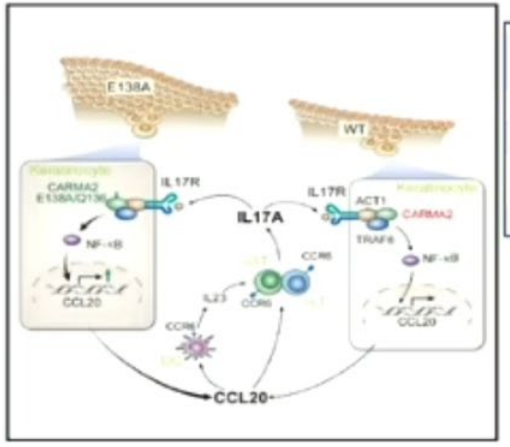
Psoriasis pustulosa

Animal and Human Studies support the central pathogenic role of IL23/IL17-driven inflammation in *CARD14* mutated genotypes

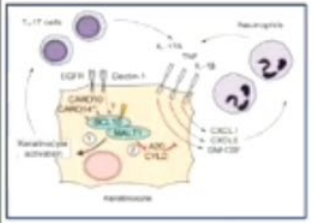
Article

Immunity

Gain-of-Function Mutation of *Card14* Leads to Spontaneous Psoriasis-like Skin Inflammation through Enhanced Keratinocyte Response to IL-17A



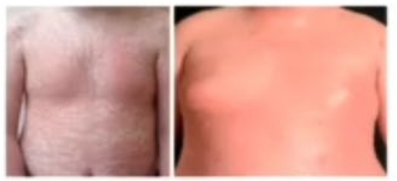
Wang M, et al. Immunity 2018



Kurgyis Z, et al. Sci Immunol 2021

***CARD14*-associated papulosquamous eruption: A spectrum including features of psoriasis and pityriasis rubra pilaris**

Brittany G. Craiglow, MD,[a] Lynn M. Boyden, PhD,[b] Rongbuu Hu, MD,[a] Marie Virtaneu, MD,[a] John Su, MD,[a,c] Gabriela Rodriguez, MD,[a] Catherine McCarthy, MD, PhD,[a] Paula Luna, MD,[b] Margarita Larralde, MD, PhD,[b] Stephen Humphrey, MD,[a] Kristen E. Holland, MD,[a] Marcia Hogeling, MD,[a] Benjamin Hidalgo-Matlock, MD,[a] Bruno Ferrari, MD,[a] Esteban Fernandez-Faith, MD,[b,c] Beth Drolet, MD,[a] Kelly M. Cordoves, MD,[a,c,d] Anne M. Bowcock, PhD,[a,c,e,f] Richard J. Amaya, MD,[a,c] Kurt Asbach, MD,[a] Richard J. Asbach, MD,[a] Richard P. Lifton, MD, PhD,[b] Leonard M. Milstone, MD,[a] Amy S. Paller, MD,[a,c] and Keith A. Choate, MD, PhD[a,c,e,f]



J Am Acad Dermatol 2018

CAPSULE SUMMARY

- Caspase recruitment domain family member 14 gene (*CARD14*) mutations have been associated with psoriasis and familial pityriasis rubra pilaris.
- Characteristic features of subjects with *CARD14* mutations include early onset, prominent facial involvement, and favorable response to ustekinumab therapy.
- Subjects with suggestive clinical findings should undergo genetic testing, given the high probability of response to ustekinumab if *CARD14* mutations are found.

Sumario

- Modificación de la enfermedad
- Diferencias poblacionales de la psoriasis
- Psoriasis pustulosa, ¿realmente es psoriasis?
- **Monitorización farmacológica**

Definición

THERAPEUTIC DRUG MONITORING: WHAT?

Solution ⟹ therapeutic drug monitoring (TDM)

Definition

TDM is a multi-disciplinary clinical specialty aimed at improving patient care by **individually adjusting the dose of drugs** for which clinical experience or clinical trials have shown it improved outcome in the general or special populations. It can be based on a *a priori* pharmacogenetic, demographic and clinical information, and/or on the ***a posteriori* measurement of blood concentrations of drugs** (pharmacokinetic monitoring) and/or biomarkers (pharmacodynamic monitoring).

⟹ **Proactive vs. reactive TDM**

Reference: https://iatdmct.org/about-us/

THERAPEUTIC DRUG MONITORING: WHY?

Why should you use therapeutic drug monitoring?

- Clinical case we discussed (safety) ⟹ possibly overdosed?
- Insufficient response (efficacy) ⟹ possibly underdosed?
- Very expensive medication (cost) ⟹ lowering burden on healthcare expenditure
- Personalised dosing ⟹ evolution to personalised medicine

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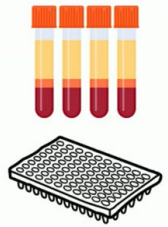
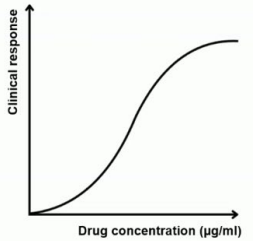
THERAPEUTIC DRUG MONITORING: HOW?

How do you use therapeutic drug monitoring?

Collection of blood sample
Important prerequisite:
Convenient
Patient-friendly



Detection of serum drug levels
Important prerequisite:
Consistent, sensitive and specific tests



Interpretation of drug level in relation to target concentration
Important prerequisite:
Reliable exposure - clinical response relationship

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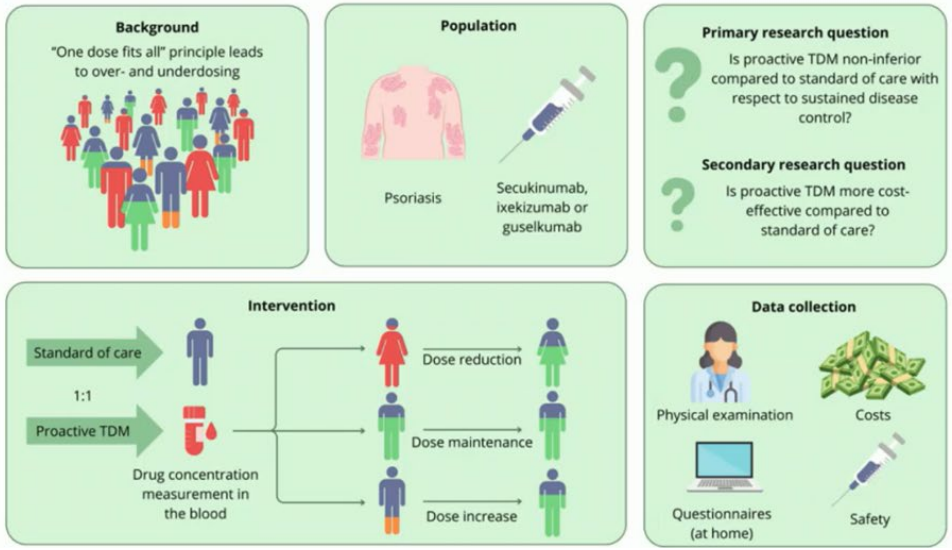
Objetivo

HELIOS

Proactive therapeutic drug monitoring



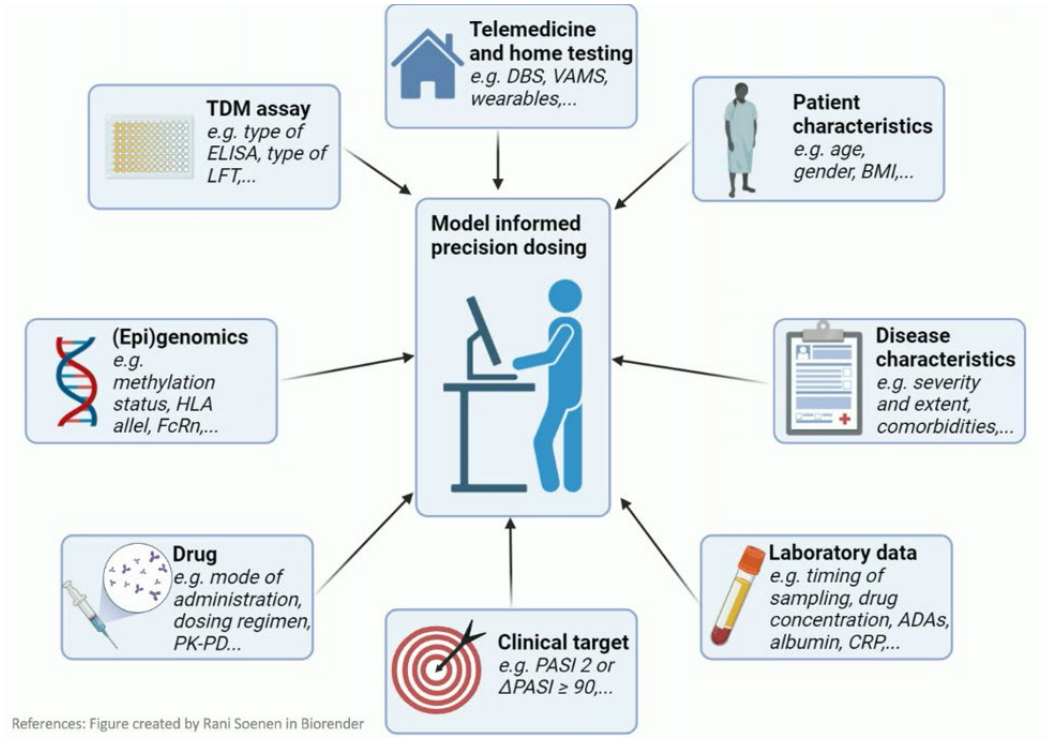
HELIOS
Track, believe, achieve

ClinicalTrials.gov: NCT06398106

Expected total savings for the Belgian health care system: €4.379.086,69 (9%)

Expected to start in October 2024

24



References: Figure created by Rani Soenen in Biorender

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La Academia Española de Dermatología y Venereología expresa su agradecimiento al patrocinador UCB, por su especial apoyo y contribución con la actividad formativa Highlights 2024.

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