HIGHLIGHTS

AEDV

en la 6ª edición del SPIN

Skin Inflammation & Psoriasis International Network Congress

PARIS 25-27 abril

Psoriasis

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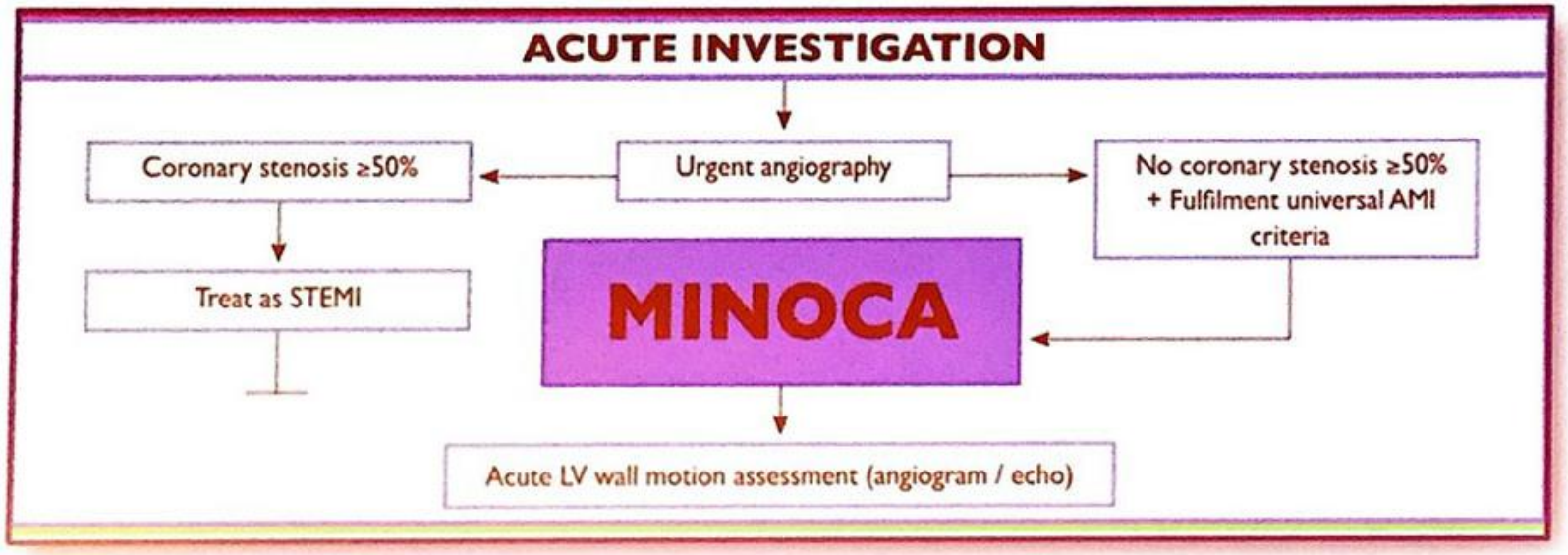
Iniciativa científica de:

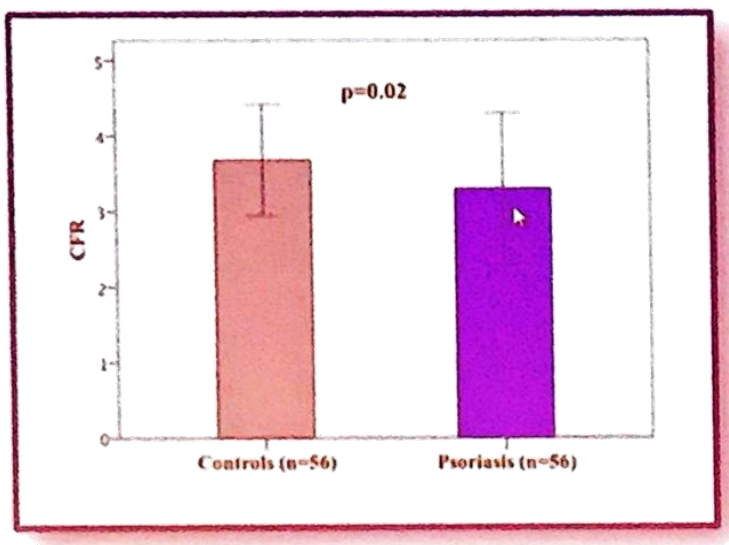
CARDIOVASCULAR DISEASE AND Ps
- Pianserico *et al*

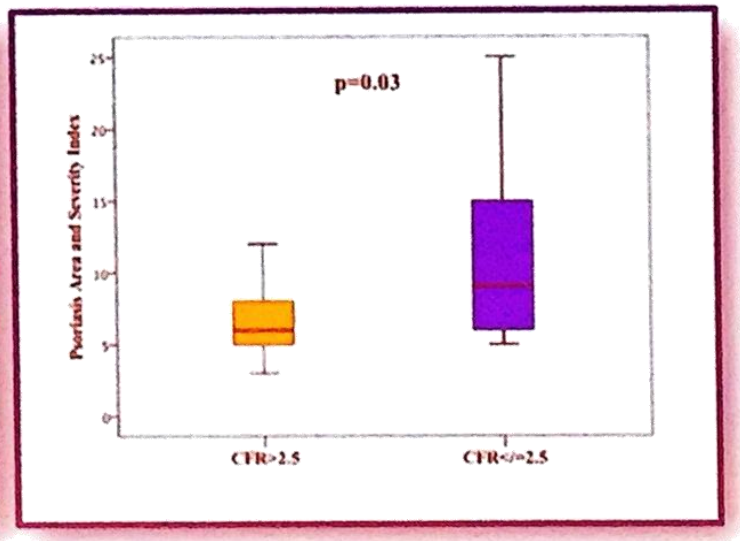
MINOCA
(Myocardial infarction with non-obstructive coronary arteries)



European Heart Journal (2018) 39, 119–17

Coronary Microvascular Dysfunction in Psoriasis





Atherosclerosis 2012;221:113-1

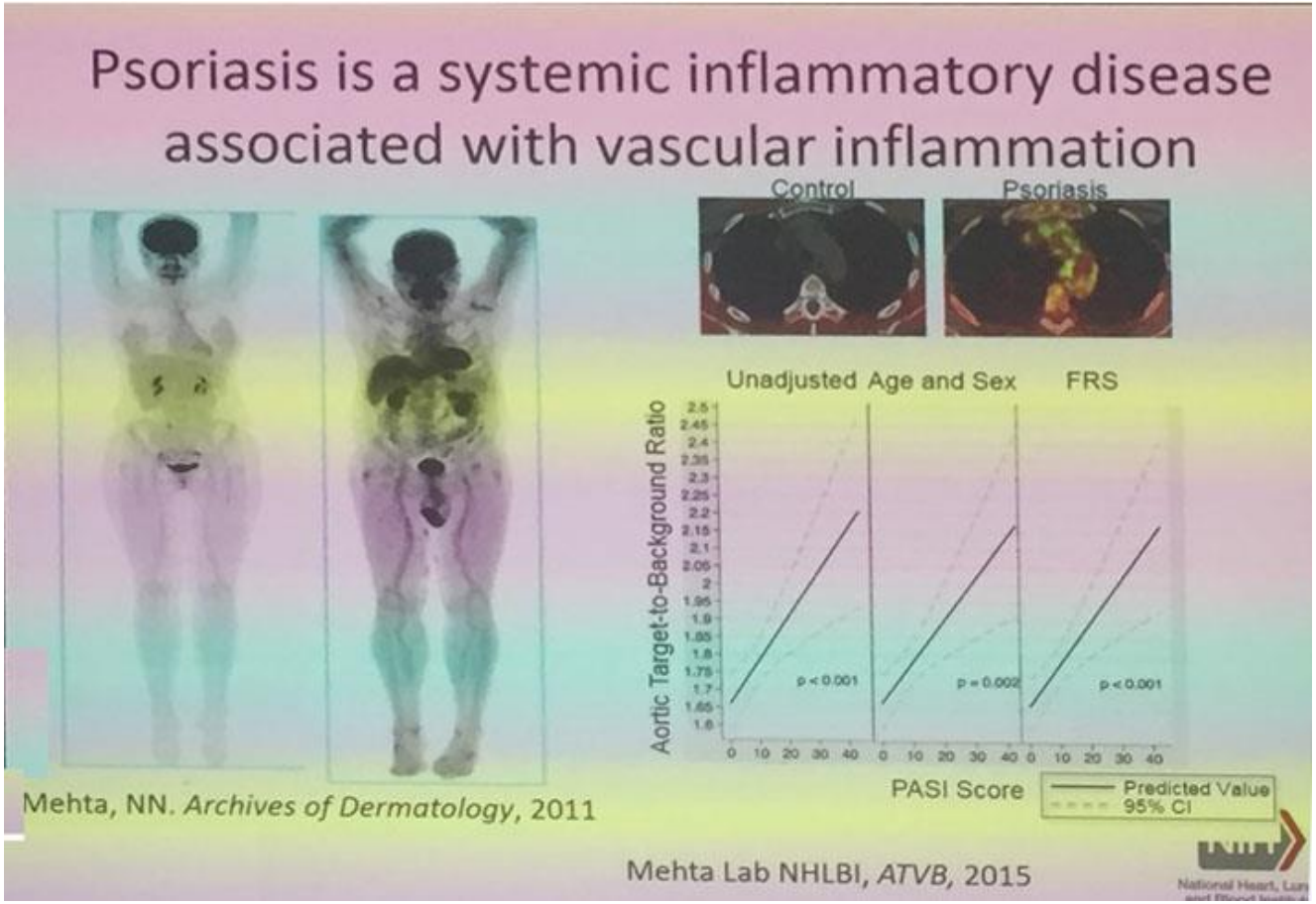
Characteristics of Patients Before and After TNF-α Inhibitor Treatment

	Before TNF-α inhibitor treatment	After TNF-α inhibitor treatment	p-value
PASI	17.5 ± 7.2	2.4 ± 3.2	<0.0001
hsCRP, mg/L	1.8 [0.3-3.3]	0.3 [0.12-2.6]	<0.0001
IL-6, pg/ml	0 [0-1.5]	0 [0-0]	0.3
VEGF, pg/ml	313 [107-531]	126 [79-411]	0.6
TNF-α, pg/ml	9.9 [7.8-10.5]	4.4 [3-5]	0.001
CFR	2.2 ± 0.7	3.04 ± 0.8	<0.0001

Mean ± SD or Median [range]

Piaserico S et al. *Atherosclerosis 2016*

CARDIOVASCULAR DISEASE AND Ps
- Mehta *et al*



If the cardioprotective effects of the biological therapy occur without being reflected in a significant way in the most used inflammation markers ..... → **At what level do they act?**

VIP-E → Anti-TNF reduces systemic inflammation, neutral imaging effects

- Anti-TNF therapy had anti-inflammatory effects in the skin and blood of patients with psoriasis *vs phototherapy*
- Both anti-TNF therapy and phototherapy had neutral impact on VI as assessed by ^{18}F-FDG PET/CT *compared with placebo*.
- Anti-TNF therapy had no impact on glucose metabolism with effects on *reducing inflammatory biomarkers including GlycA, TNF-alpha and hs-CRP*.

Mehta Lab NHLBI; *Circulation CV Imaging, 2018.*

NIH
National Heart, Lung, and Blood Institute

Psoriasis → increased coronary plaque burden, which is *non-calcified*

Coronary Plaque (mm^2)	Psoriasis (n=105)	Healthy Volunteers (n=25)	P-value
Total Plaque Burden (X100)	1.22±0.31	1.04±0.22	0.001
Non-calcified Plaque Burden (X100)	1.18±0.32	1.03±0.21	0.004

Parameter	Unadjusted	Adjusted
Total Burden	0.15 (<0.001)	0.12 (0.01)
Non-calcified Burden	0.13 (0.003)	0.12 (0.01)

Adjusted for age, sex, SBP, LDL, HDL, Glucose, Current Smoking, Lipid Treatment

rman et al., *Circulation*, 2017

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High risk coronary plaque occurs over one decade earlier in psoriasis

Coronary Plaque Type (mm^2)	Psoriasis: age~46 (n=105)	Hyperlipidemia: age ~60 (n=100)	P-value
Total Plaque Burden (X100)	1.22±0.31	1.18±0.34	0.16
Non-calcified Plaque Burden (X100)	1.18±0.32	1.11±0.33	0.02
Presence of High-risk Plaque	36 (34%)	38 (38%)	0.58

Lerman et al., *Circulation*, 2017

NIH National Heart, Lung, and Blood Institute

If the cardioprotective effects of the biological therapy occur without being reflected in a significant way in the most used inflammation markers ..... → **At what level do they act?**

Biological therapy is associated with a reduction in systemic inflammation

	Non-Biologic Therapy (n=32)	Biologic Therapy* (n=89)
Cardiovascular Risk Factor	Change at 1-year	Change at 1-year
Blood Pressure	none	none
Glucose	none	none
Lipids	none	none
Inflammation	**none**	↓33%^

* Biologic therapy: anti-TNF, anti-IL12/23, anti-IL17

^Reduction in hs-CRP, p<0.001

Elnabawi et al., *CVR*, 2019

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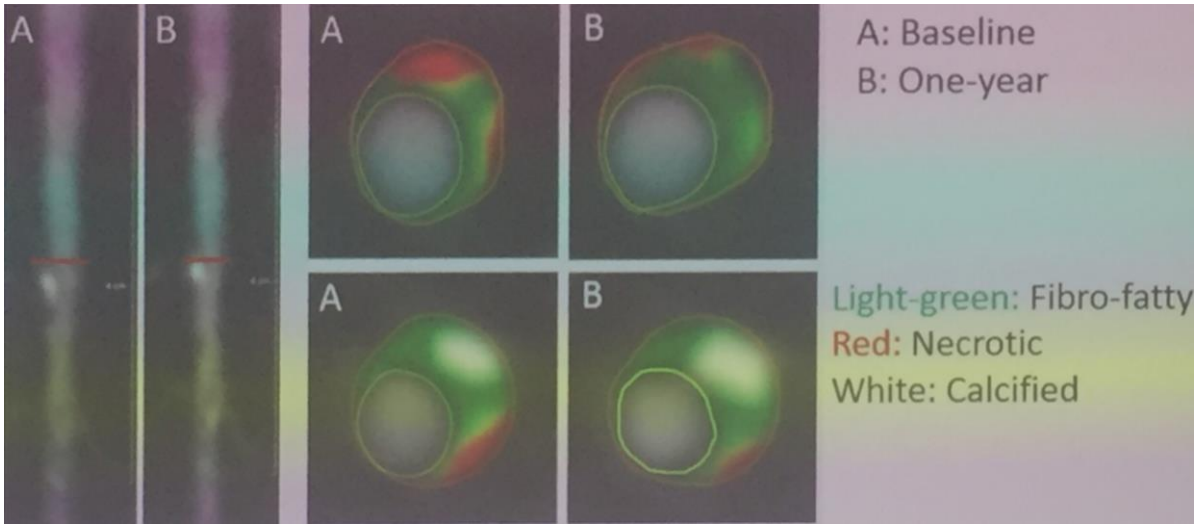


Biologic Therapy (n=267 arteries)

Coronary Plaque Type (mm^2)	Baseline	One-Year	% change (P-value)
Total Plaque Burden (X100)	1.30±0.60	1.24±0.60	-5% (0.009)
Non-calcified Plaque Burden (X100)	1.22±0.60	1.15±0.59	-7% (0.005)

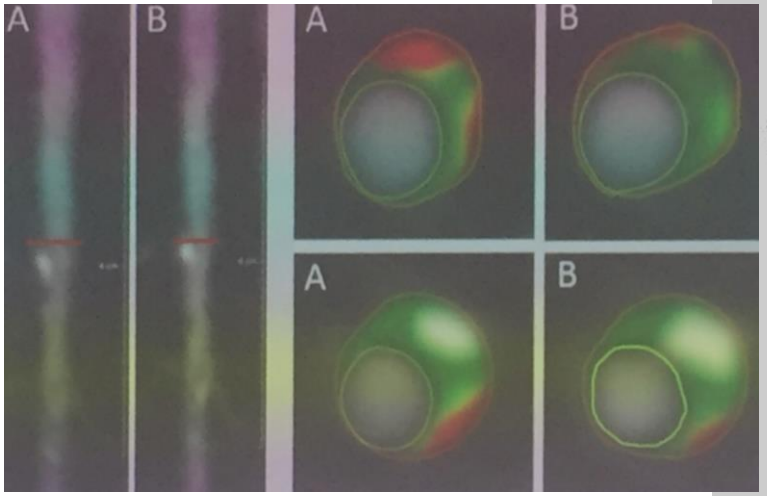
Non-biologic Therapy (n=96 arteries)

Coronary Plaque Type (mm^2)	Baseline	One-Year	% change (P-value)
Total Plaque Burden (X100)	1.28±0.53	1.31±0.59	+2% (0.22)
Non-calcified Plaque Burden (X100)	1.19±0.41	1.25±0.41	+5% (0.17)

* Biologic therapy: anti-TNF, anti-IL12/23, anti-IL17

Elnabawi et al., *CVR*, 2019

NIH National Heart, Lung, and Blood Institute



High-risk plaque features decrease following biologic therapy

Biologic Therapy (n=267 arteries)

Coronary Plaque Type	Baseline	One-Year	% change (P-value)
Fibro-fatty Burden (mm2)	0.22±0.19	0.10±0.14	-55% (0.004)
Necrotic Core Burden (mm2)	0.07±0.19	0.03±0.19	-57% (0.03)

Non-biologic Therapy (n=96 arteries)

Coronary Plaque Type	Baseline	One-Year	% change (P-value)
Fibro-fatty Burden (mm2)	0.16±0.19	0.22±0.14	+38% (0.004)
Necrotic Core Burden (mm2)	0.06±0.19	0.08±0.19	+33% (0. 27)

* Biologic therapy: anti-TNF, anti-IL12/23, anti-IL17

Elnabawi et al., *CVR*, 2019

NIH
National Heart and Blood In

Subgroup analysis by biologic therapy

Anti-TNF Therapy (n=48)

Coronary Plaque Type (mm^2)	Baseline	One-Year	% change (P-value)
Total Plaque Burden (X100)	1.37±0.60	1.31±0.59	-4% (0.09)
Non-calcified Plaque Burden (X100)	1.28±0.60	1.22±0.59	-5% (0.06)

Anti-IL17 Therapy (n=22)

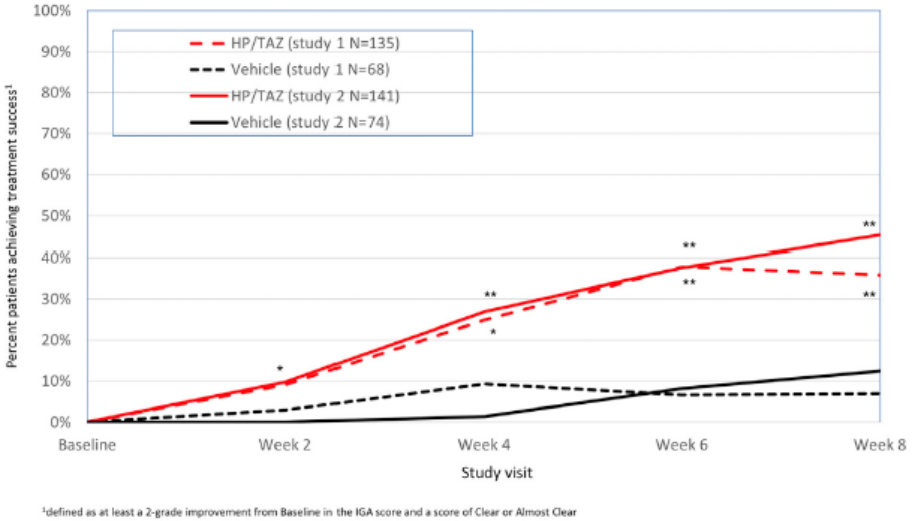
Coronary Plaque Type (mm^2)	Baseline	One-Year	% change (P-value)
Total Plaque Burden (X100)	1.31±0.60	1.15±0.59	-16% (0.0001)
Non-calcified Plaque Burden (X100)	1.23±0.58	1.08±0.57	-12% (0.001)

Elnabawi et al., *CVR,* 2019

DRUGS - TOPICAL THERAPY

New Combinations in psoriasis: halobetasol and tazarotene

- Two multicenter, randomized, double-blind, vehicle-controlled phase 3 studies (N =418)
- At least a 2-grade improvement from baseline in Investigator's Global Assessment score and a score of clear or almost clear).
- 35.8% (study 1) and 45.3% (study 2) of subjects were treatment successes compared with 7.0% and 12.5% of those treated with vehicle (P\.001).



[1]defined as at least a 2-grade improvement from Baseline in the IGA score and a score of Clear or Almost Clear

*P≤0.008 versus vehicle (study 1 at Week 4 and study 2 at Week 2
**P<0.001 versus vehicle

Safety and efficacy of a fixed combination of halobetasol and tazarotene in the treatment of moderate-to-severe plaque psoriasis: Results of 2 phase 3 randomized controlled trials

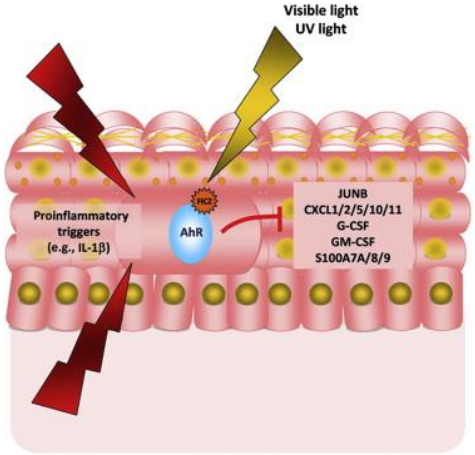
Linda Stein Gold, MD,[a] Mark G. Lebwohl, MD,[b] Jeffrey L. Sugarman, MD, PhD,[c] David M. Pariser, MD,[d] Tina Lin, PharmD,[e] Gina Martin, MOT,[f] Radhakrishnan Pillai, PhD,[f] Robert Israel, MD,[g] and Tage Ramakrishna, MD[g]
Detroit, Michigan; New York, New York; San Francisco and Petaluma, California; Norfolk, Virginia; and Bridgewater, New Jersey

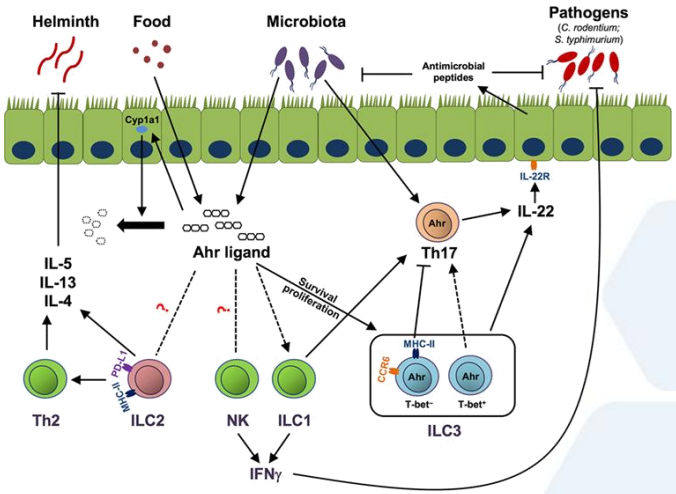
Slides provided by Dr. JM Carrascosa

J Am Acad Dermatol 2018;79:287-93.)

TAPINAROF (GSK2894512 CREAM) FOR THE TREATMENT OF PLAQUE PSORIASIS

- Nonsteroidal topical agent known as therapeutic aryl hydrocarbon receptor (AhR) modulating agents.
- Binding the AhR and activating the AhR pathway in multiple cells and tissue-based systems
- Controls the expression of IL-21 and IL-22 and plays an important role in the differentiation of T-helper 17 cells in vivo and in vitro
- Antioxidant by inhibiting reactive oxygen species





Slides provided by Dr. JM Carrascosa

Phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of plaque psoriasis

Kevin Robbins, BS, LLM,[a] Robert Bissonnette, MD,[b] Tomoko Maeda-Chubachi, MD, PhD,[c] Li Ye, MS,[a] Johnny Peppers, PhD,[d] Kelly Gallagher, MS,[a] and John E. Kraus, MD, PhD[c]
Collegeville, Pennsylvania; Montreal, Canada; and Morrisville, Raleigh, and Research Triangle Park, North Carolina

Am Acad Dermatol 2019;80:714-21.

TAPINAROF (GSK2894512 CREAM) FOR THE TREATMENT OF PLAQUE PSORIASIS

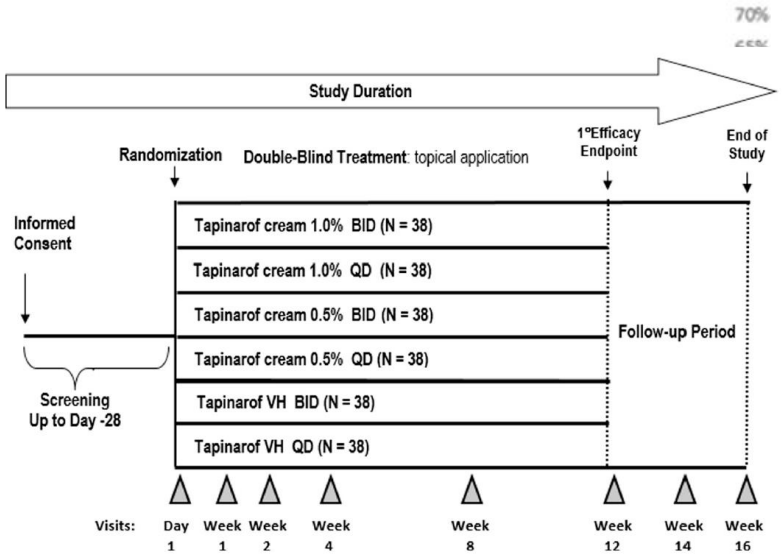
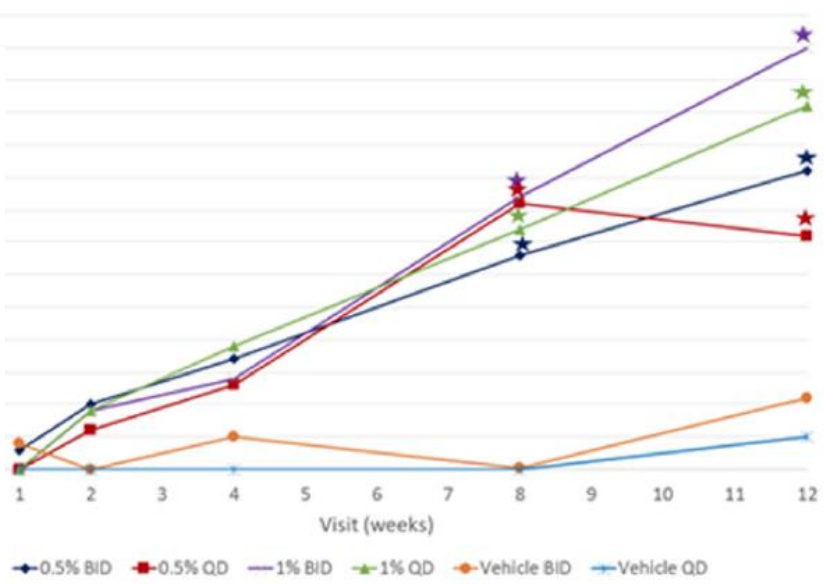


Fig 1. Study schematic. *BID*, Twice daily application; *QD*, once daily application; *VH*, vehicle.



PGA 0 or 1 and a 2-grade improvement at week 12 was statistically significantly higher (at a .05 significance level) in the tapinarof groups (65% [1% twice daily], 56% [1% once daily], 46% [0.5% twice daily], and 36% [0.5% once daily]) than in the vehicle groups (11% [twice daily] and 5% [once daily]

Slides provided by Dr. JM Carrascosa

DRUGS - ANTI TNF AND SMALL MOLECULES

Adalimumab/Certolizumab – new data

- **pregnancy**
- Analysis of about **2100 prospectively documented pregnancies exposed to adalimumab** and with live births with known outcome showed no evidence for an increased rate of malformations in newborns. (1500 /1.trimester)
- **Data from > 500 prospectively collected pregnancies** (400/ 1.trimester), give evidence, that **Certolizumab** has no harmful effect on malformations
- **lactation**
- Data from literature show that **adalimumab** can be excreted into breast milk resulting in low concentrations (0,1 – 1 % of maternal serum level). After oral ingestion follows intestinal proteolysis → low bioavailability → no negative effect on breast-fed infant expected
- **Certolizumab** can be used during lactation

https://www.gelbe-liste.de/produkte/Cimzia-200-mg-Injektionsloesung-in-einem-Fertigpen_972925/fachinformatio
https://www.gelbe-liste.de/produkte/Humira-40-mg-0-4-ml-Injektionsloesung-im-Fertigpen_952401/fachinformation

Anti-TNF in elderly patients ?

https://www.colourbox.de/vektor/oma-frau-vektor-vektor-12111925

- n=145, ≥65 years, biologic naiv, PsA
- ETA n=68, ADA n=60, Go n=11, IFX n=6
- MDA T6 22.6%, T12 51.8%
- Drug discontinuation rate 5.5%, mean 6.8 months due to lack of efficacy, AE or lost to FU
- N=9 (6.2%) mild infections treated with antimicrobials without therapy interruption
- → age should not be considered a limitation to their use

MDA = minimal disease activity

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Biologics (anti-TNF) and elderly patients

- IMIDs - inflammatory bowel disease, rheumatoid arthritis, psoriasis; > 60 years
- meta-analysis 14 studies with n= 4719 older users of biologics, n=13,305 young users of biologics, and n= 3961 older patients who did not use biologics.
- pooled prevalence of **infections**: 13% in older and 6% in younger users of biologics → OR 2.28 (95% CI, 1.57-3.31)
- Older users of biologics had a 3-fold increase in risk of infection compared to patients who did not use biologics (OR, 3.60; 95% CI, 1.62-8.01)
- older age: significant increase in risk of **malignancy** (OR, 3.07; 95% CI, 1.98-4.62) compared to younger age
- no significant differences in odds of malignancy (0.54, 95% CI, 0.28-1.05) or death (OR, 1.52; 95% CI, 0.44-5.28) compared to older patients who did not u biologics.

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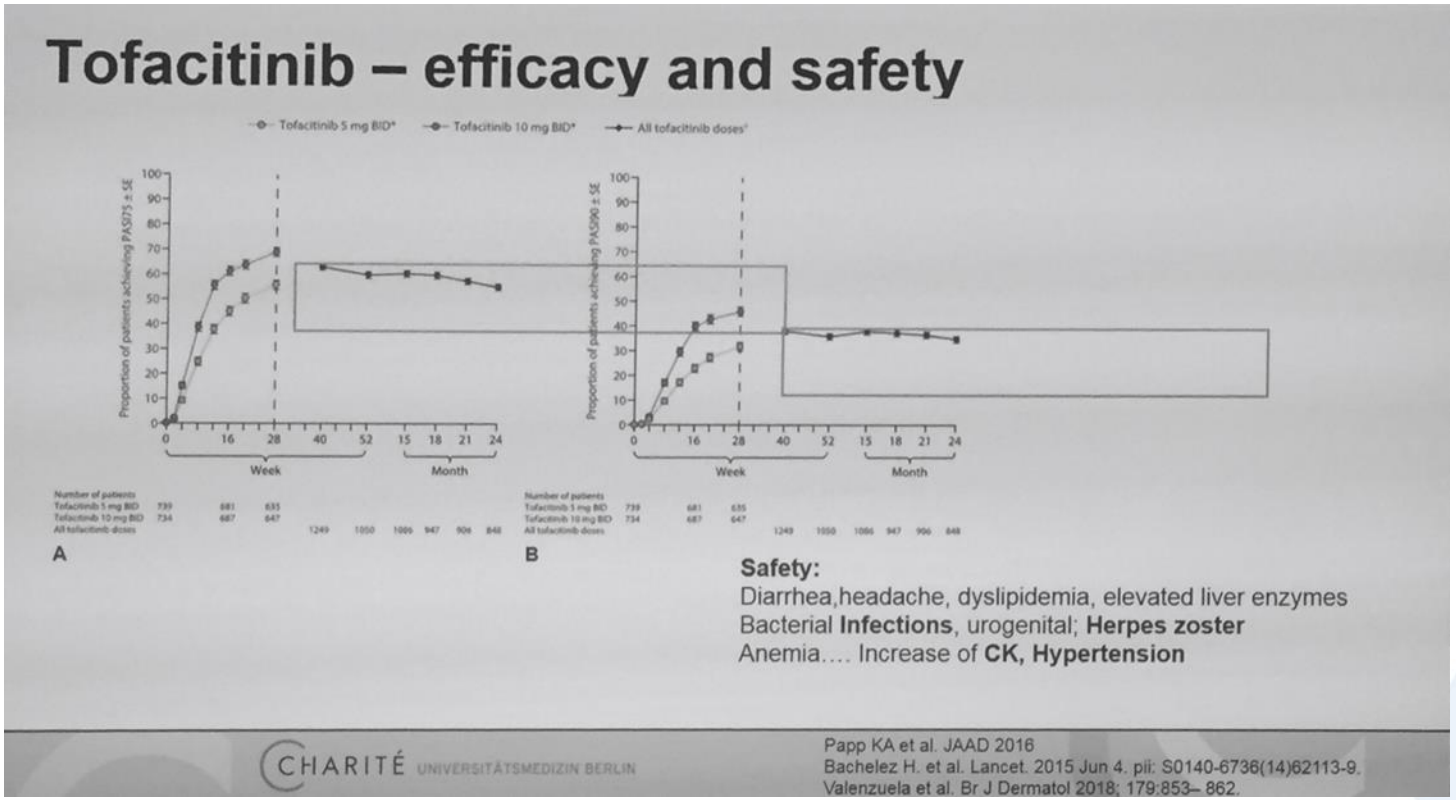
Borren NZ et al. Clin Gastroenterol Hepat

DRUGS - ANTI TNF AND SMALL MOLECULES

- Small molecules →
  - Tofacitinib →



DRUGS - ANTI TNF AND SMALL MOLECULES

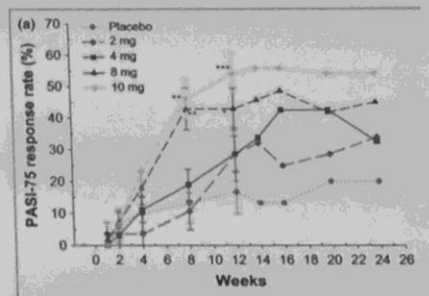
- Small molecules →
  - Baricitinib →

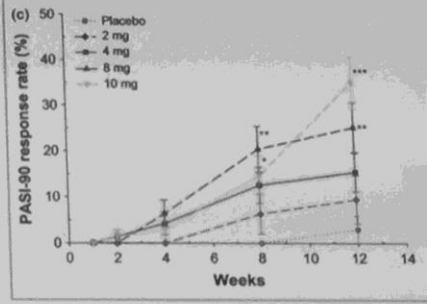
A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate-to-severe psoriasis.
Papp KA, Menter MA, Raman M, Disch D, Schlichting DE, Gaich C, Macias W, Zhang X, Janes JM.
Br J Dermatol.2016;174(6):1266-76.

Safety
Infections 26.5 (Plc) vs 21.1% (baricitinib)
Most frequent nasopharyngitis
No opportunistic infections

More laboratory AEs (9.3% vs 0%):
Most frequent: increased CK

Higher rate of AEs
in 8-and 10mg-groups





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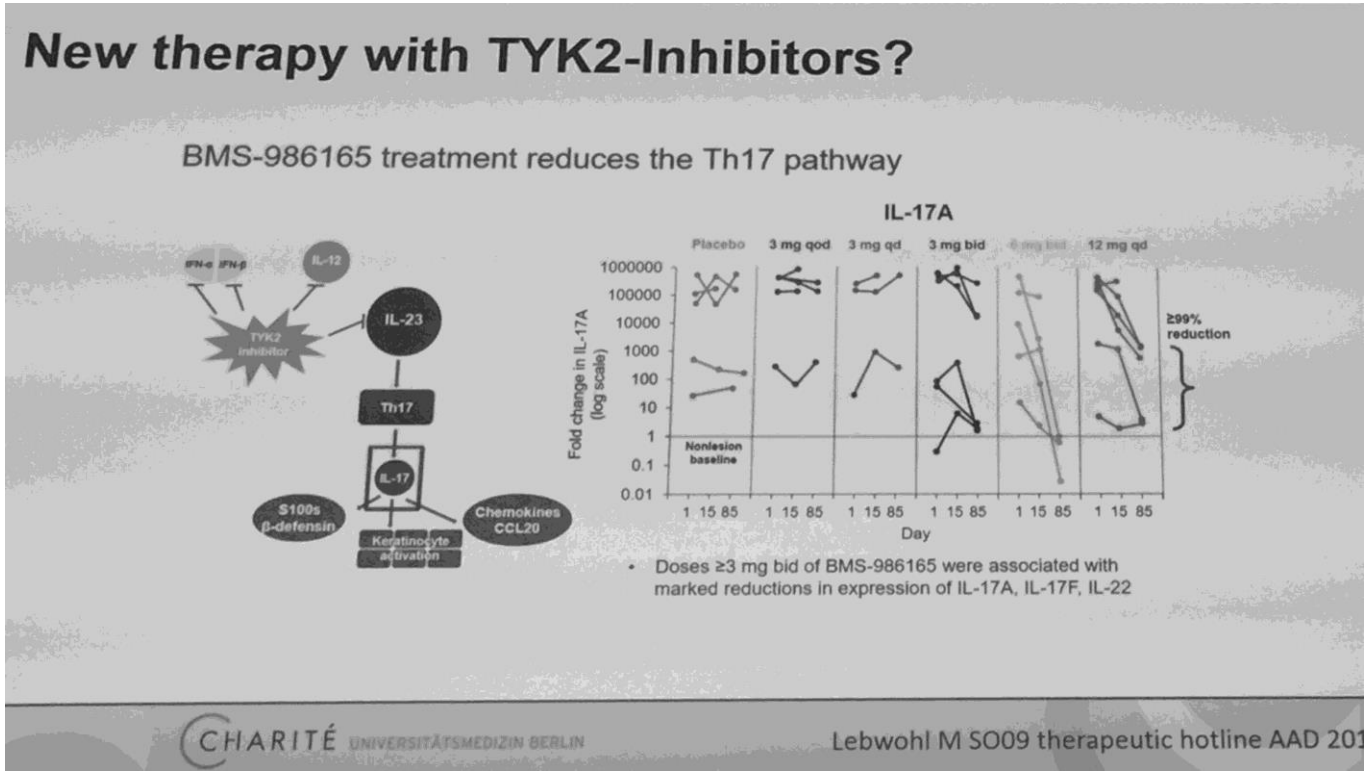
Lebwohl M SO09 - therapeutic hotline AAD 2019

DRUGS - ANTI TNF AND SMALL MOLECULES

- Small molecules →
  - TYK2-Inhibitors→



DRUGS - ANTI TNF AND SMALL MOLECULES

- Small molecules →
  - TYK2-Inhibitors→

New therapy with TYK2-Inhibitors?

	Placebo (n=45)	BMS-986165				
		3 mg qod (n=44)	3 mg qd (n=44)	3 mg bid (n=45)	6 mg bid (n=45)	12 mg qd (n=44)
Serious AEs	1 (2)	1 (2)	1 (2)	1 (2)	0	0
AEs	23 (51)	26 (59)	24 (55)	29 (64)	36 (80)	34 (77)
Drug-related AEs	7 (16)	6 (14)	7 (16)	13 (29)	12 (27)	10 (23)
Discontinuations due to AEs	2 (4)	1 (2)	2 (5)	1 (2)	3 (7)	1 (2)
Most frequently reported AEs						
Nasopharyngitis	2 (4)	1 (2)	4 (9)	5 (11)	7 (16)	2 (5)
Headache	2 (4)	4 (9)	4 (9)	3 (7)	3 (7)	2 (5)
Diarrhea	2 (4)	1 (2)	1 (2)	2 (4)	2 (4)	4 (9)
Nausea	2 (4)	4 (9)	0	1 (2)	1 (2)	2 (5)
URTI	0	1 (2)	3 (7)	1 (2)	4 (9)	1 (2)
Acne	0	1 (2)	0	1 (2)	2 (4)	4 (9)

Data are n (%)

- Preliminary but reassuring safety data suggest that TYK2 inhibition with BMS-986165 is selective and well tolerated
- Presence of acne is of note, and has been seen with other agents that block this pathway

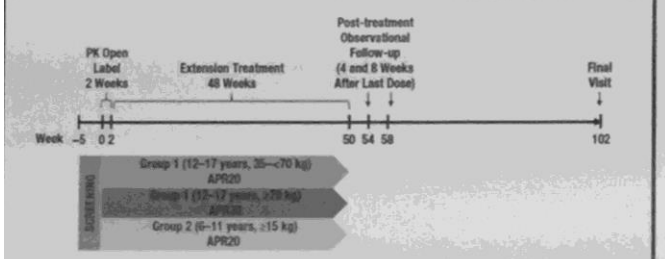
Papp K, et al. N Engl J Med 2018; Epub ahead of print; Papp KA, et al. EADV 2018, P1997 Sponsored by Bristol-Myers Squibb

DRUGS - ANTI TNF AND SMALL MOLECULES

- Small molecules →
  - Apremilast→

oster 9879 – Apremilast – pediatric psoriasis

Figure 1. Study Design



- n=42
- PASI score, mean (SD) 18.8 (11.7) 15.7 (3.4) 18.1 (6.1)
- group 1 (12-17y),
- BW. ≥35 to <70 kg received APR20;
- BW. ≥70 kg APR30
- group 2 (6 -11y), BW ≥15 kg received APR20.

Inclusion criteria
Pediatric patients from 6 to 17 years
moderate to sever plaque psoriasis: PASI score ≥12, BSA ≥10%, sPGA ≥3, for ≥6 months
No sufficient control by topical therapy, candidate for systemic therapy/phototherapy
Previous therapy: ≤1 systemic therapy for psoriasis
(NO titration of dosage!)

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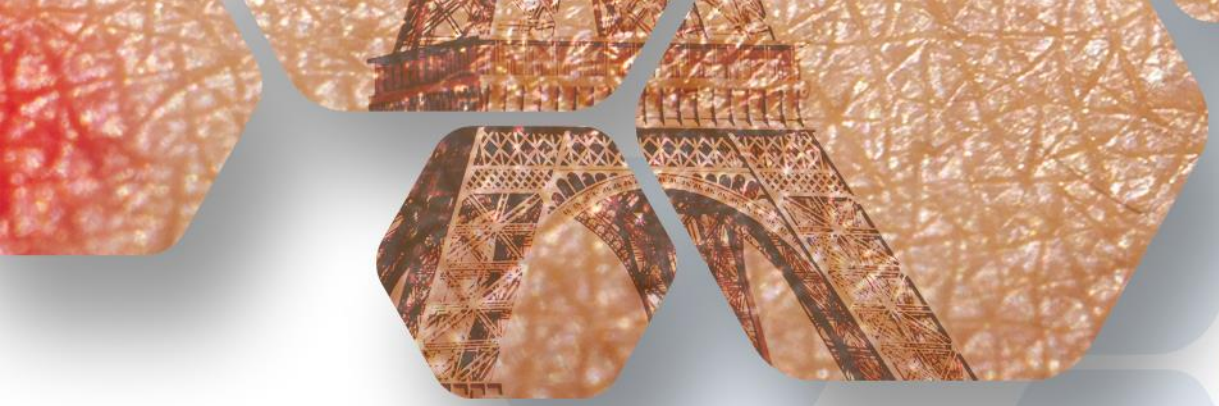
Paller A et al. Poster 9879 AAD 2019



GRACIAS

Iniciativa científica de: