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Are the concepts of induction of remission and treatment of subclinical inflammation in atopic dermatitis clinically useful?

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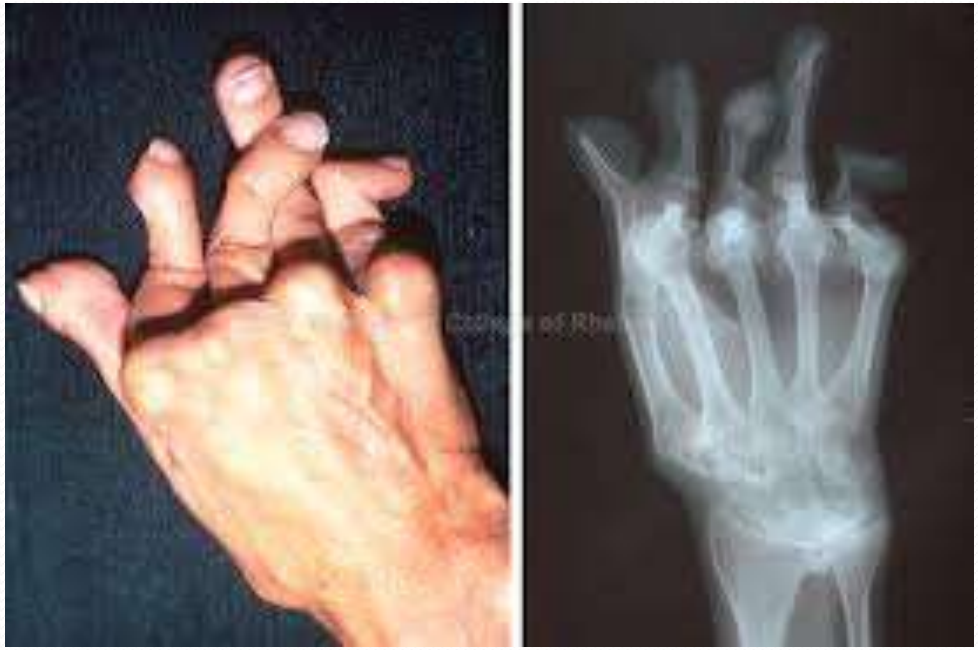
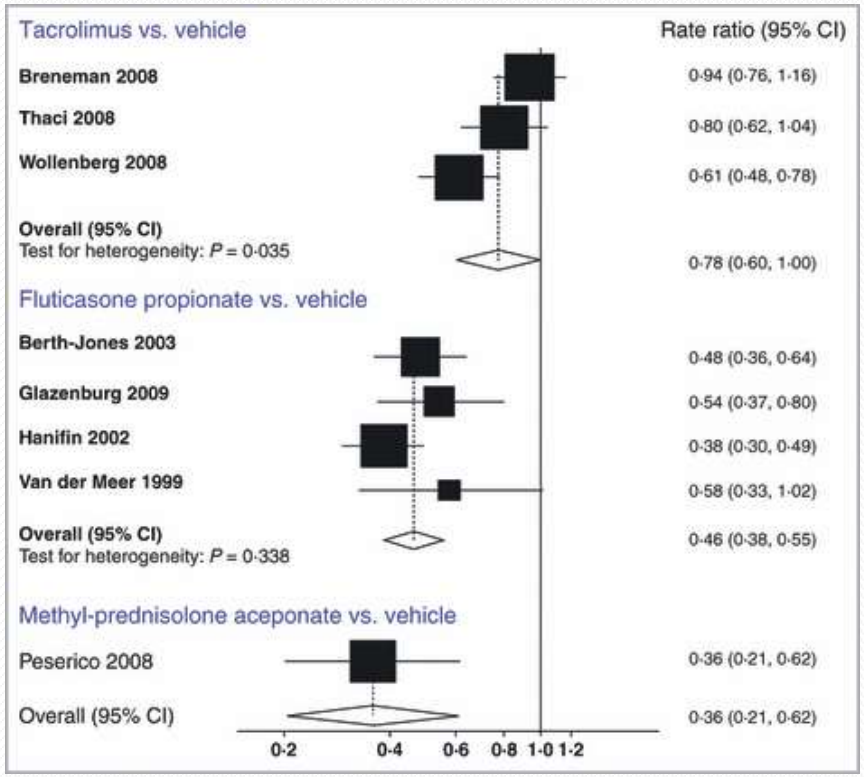
Background





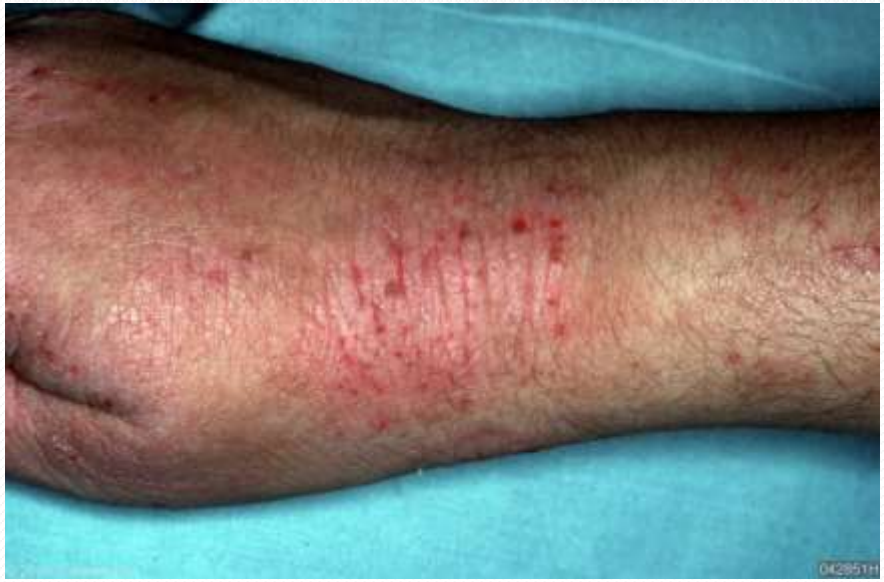
Schmitt et al. Br J Dermatol. 2011 Feb;164(2):415-28. doi: 10.1111/j.1365-2133.2010.10030.x. Epub 2010 Nov 23

Aim

(i) Is the notion of “subclinical inflammation” scientifically sound?

(ii) Does treatment corrects this subclinical inflammation?

(iii) Do different strategies for initial clearance of atopic dermatitis impact on long-term disease control



Question 1

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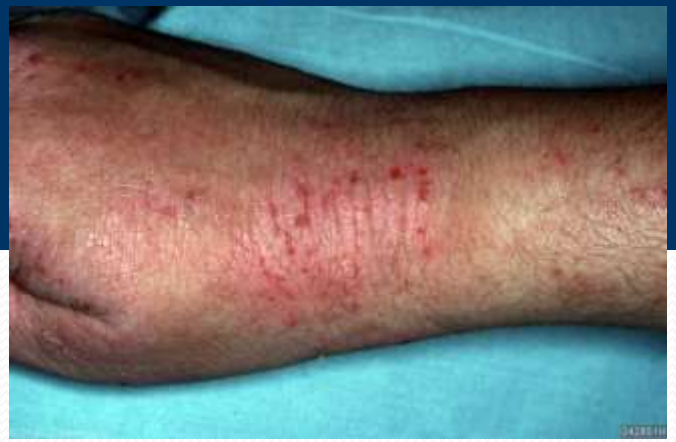
‘Is the notion of
“**subclinical inflammation**”
scientifically sound?’

Definition



	Signs	Symptoms	Science (biological markers)
Objective active lesion	✓	✓	✓
“eczema under the skin”		✓	✓
Non-lesional/ subclinical inflammation			✓

Search Results

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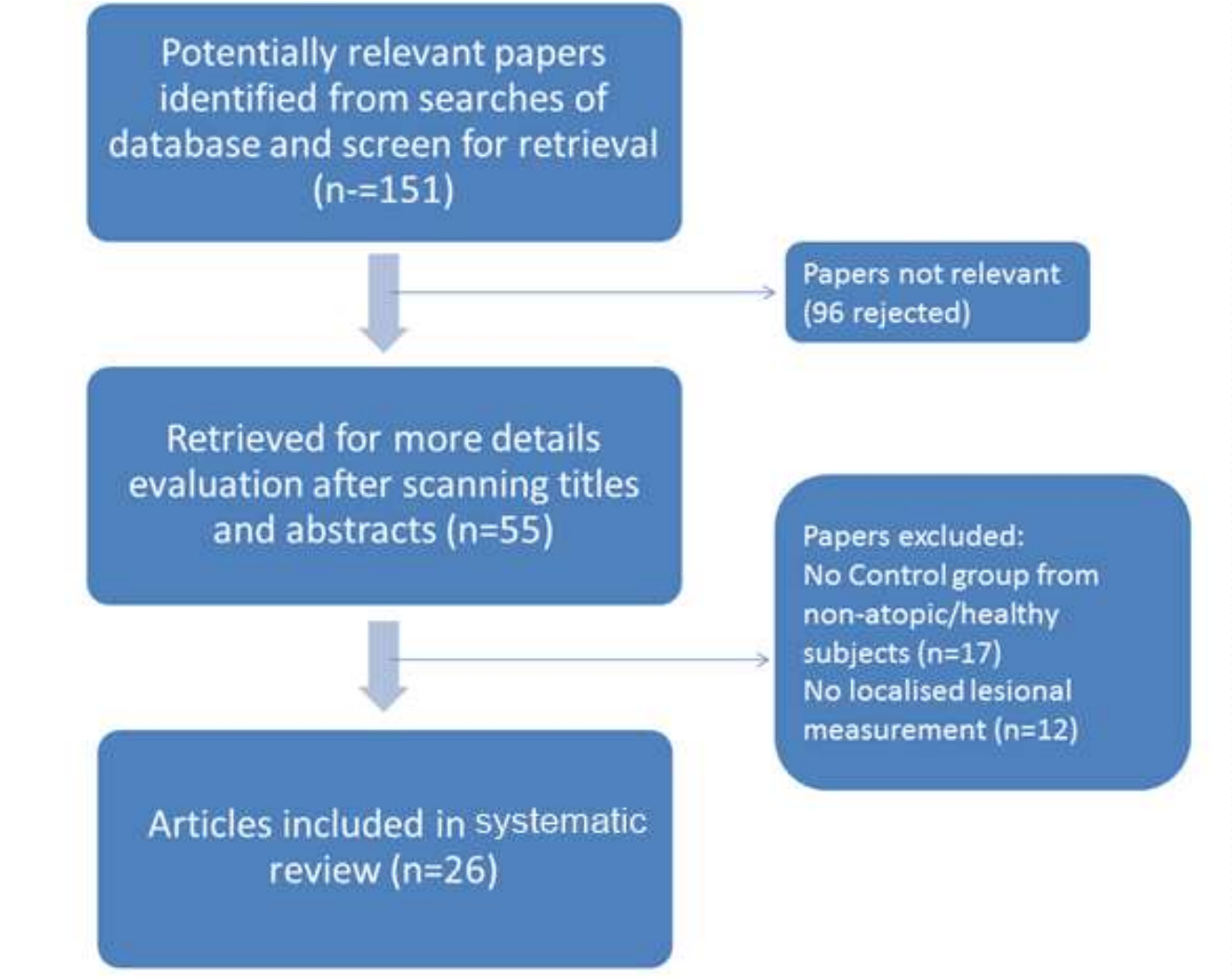

Results

	Non-lesional skin from patients with atopic dermatitis	Treated skin (previous active dermatitis)
Barrier dysfunction	4/5	0
Subclinical inflammation	6/10	4/4
Bacterial colonisation/ antibacterial peptides	3/3	0
Imaging	1/1	0
Others	3/3	0

Results

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normal skin **atopic non-lesional** **atopic lesional**

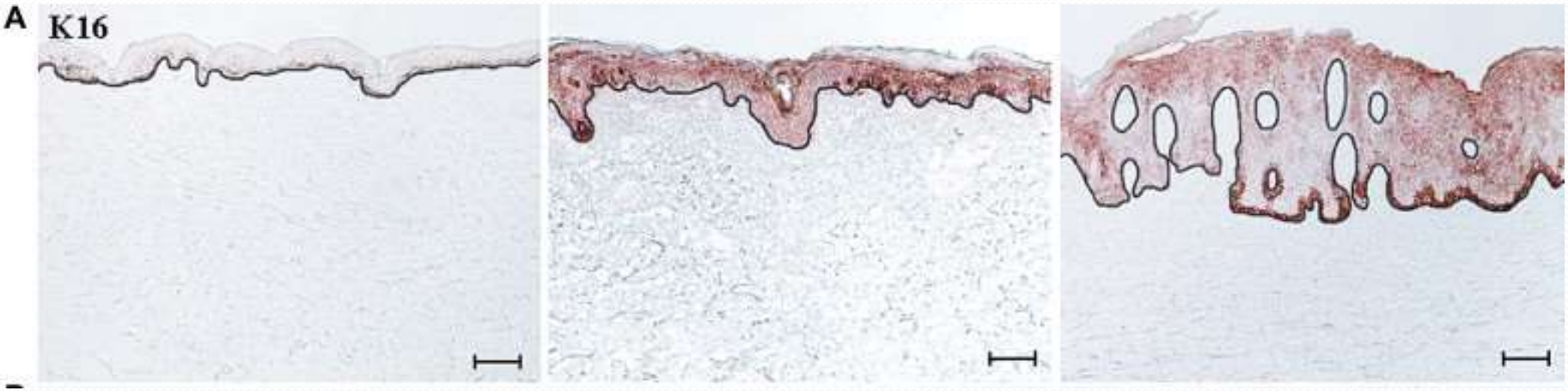

Fig 1 Characterization of ANL and AL skin compared with normal skin. A-D , Representative IHC staining of the proliferation markers
. K16 (Fig 1, A) and Ki67 (Fig 1, B) and of T cells (CD3 + cells; Fig 1, C) and myeloid dendritic cells (CD11c + cell...

Suárez-Fariñas et al, **Nonlesional atopic dermatitis skin is characterized by broad terminal differentiation defects and variable immune abnormalities.** Journal of Allergy and Clinical Immunology, Volume 127, Issue 4, 2011, 954 - 964.e4

Answer 1

"Nonlesional skin in atopic individuals is not normal."

Question 2

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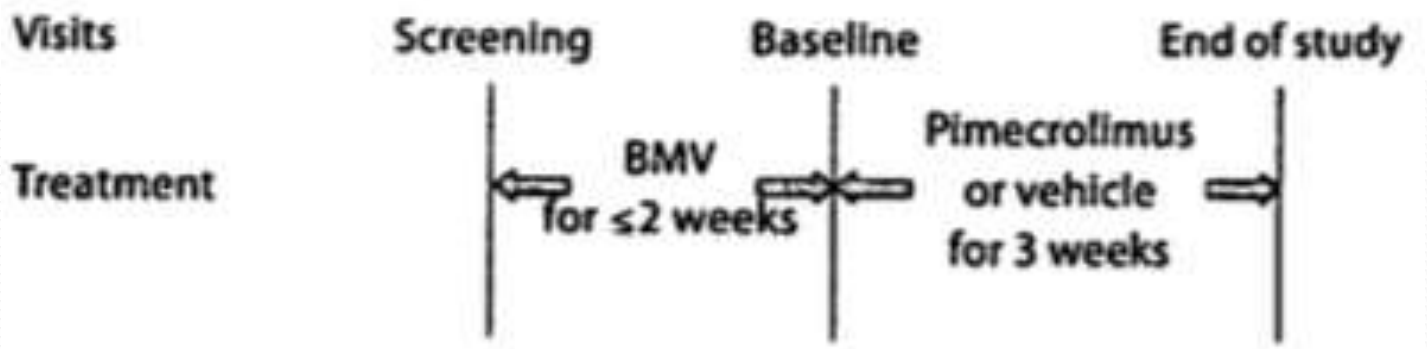
‘Does treatment corrects subclinical inflammation?’

Results

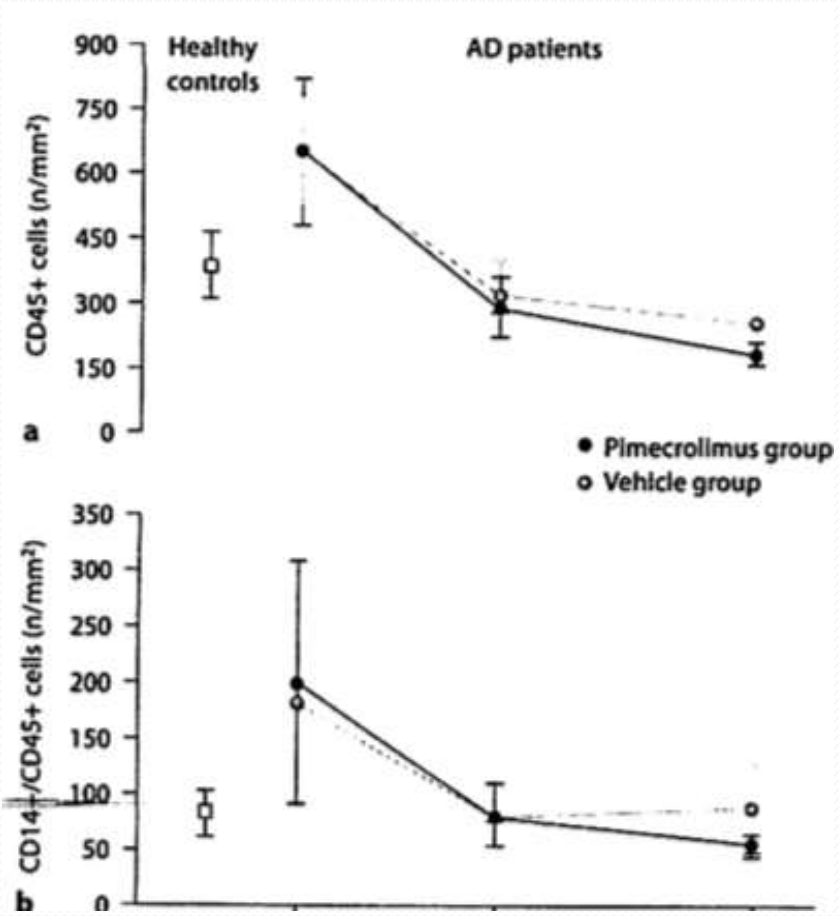
- One double-blind RCT was found
  - n=67
  - Patient: mild to moderate eczema
  - Intervention:
    - Open label, run-in period for all participants with topical betamethasone 0.1% ointment until clear (EASI≤1) for up to 2 weeks
    - Double-blind phase: 3 weeks of topical Pimecrolimus 1% cream or vehicle cream twice-daily
  - Outcome: IGA, EASI, skin biopsy



Bangert et al.Dermatology. 2011 Feb;222(1):36-48

Results

- Less drop out rate in pimecrolimus group (11.8% vs. 42.4%. P<0.05)
- In pimecrolimus group, 53% remained in remission at end of 3 weeks follow up, compared to 27% in the vehicle group (p=0.03).



Bangert et al. Clinical and cytological effects of pimecrolimus cream 1% after resolution of active atopic dermatitis lesions by topical corticosteroids: a randomized controlled trial. Dermatology 2011; 222:36-48.

Answer 2

"More longer term studies needed for treatment of subclinical inflammation."

Question 3

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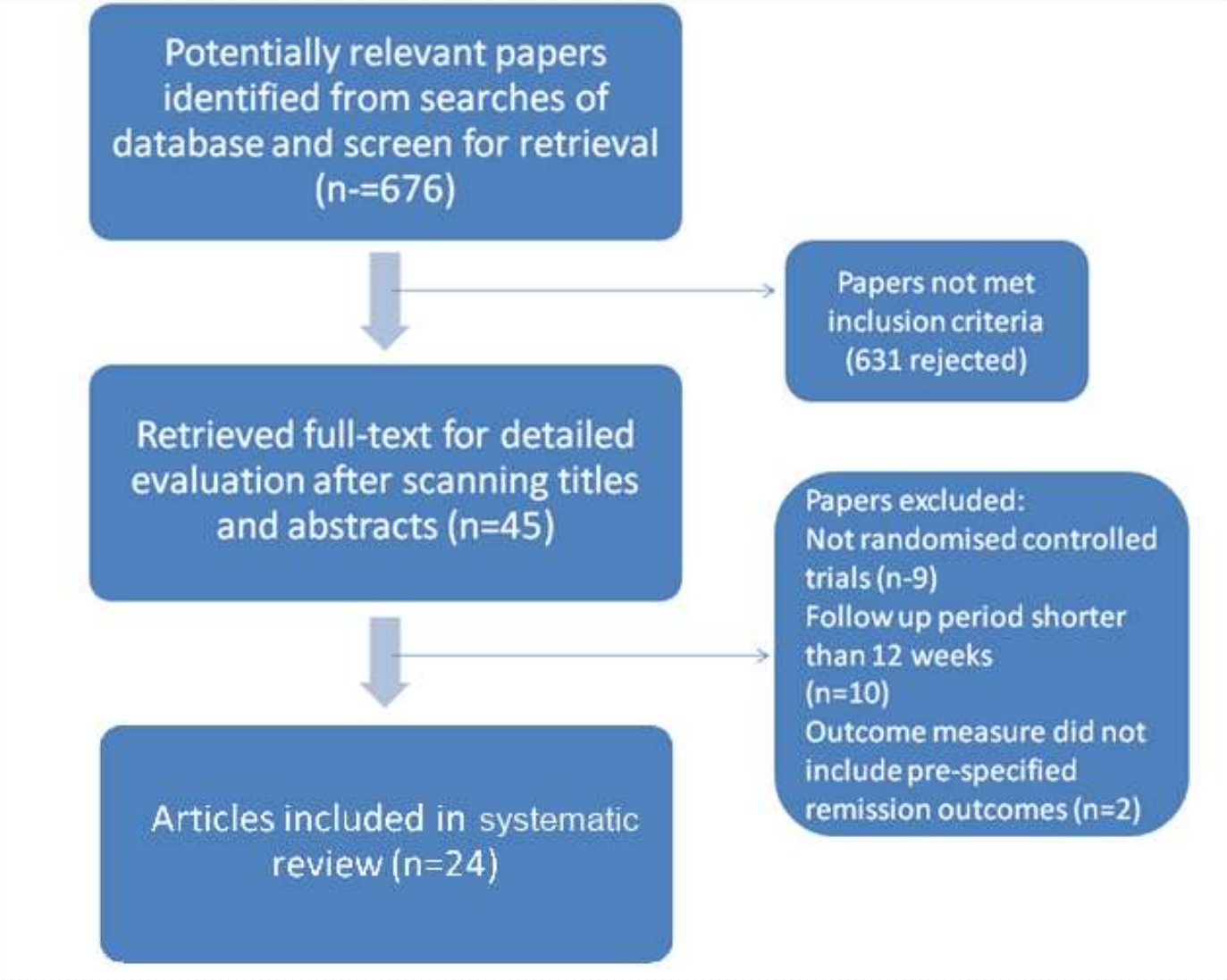
‘Do different **strategies** for initial clearance of atopic dermatitis impact on **long-term disease control?**’

Search Results



Results – Topical treatments

- Induction of remission/stabilisation duration ranging from 2 to 16 weeks
- Only 9 out of 14 studies reported predefined definition of remission
- Failure to get control of atopic dermatitis with initial therapy was associated with a higher risk of relapsing.
  - Fluticasone studies (RR = 1.31, 95% CI = 1.02-1.68)
  - Tacrolimus studies (RR= 1.36, 95% CI = 1.12- 1.66)

Results - fluticasone

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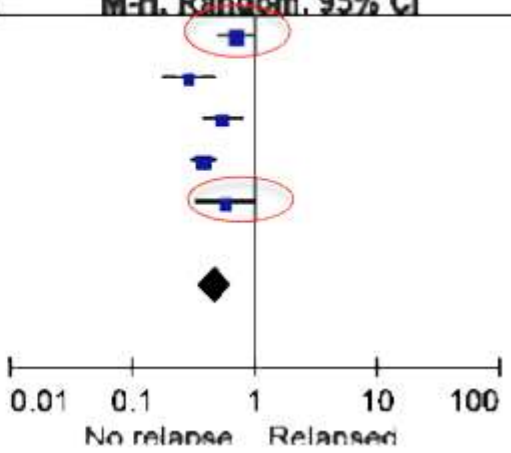
Study or Subgroup	Percentage achieved remission	Experimental Events	Experimental Total	Control Events	Control Total	Weight	Risk Ratio M-H, Random, 95% CI
Berth-Jones 2003	74%	27	68	41	73	21.9%	0.71 [0.50, 1.01]
Berth-Jones 2003	82%	13	70	54	84	16.6%	0.29 [0.17, 0.48]
Glazenburg 2009	84%	17	39	29	36	20.7%	0.54 [0.37, 0.80]
Hanifin 2002	94%	58	229	79	119	25.5%	0.38 [0.30, 0.49]
Van Der Meer 1999	55%	9	23	21	31	15.2%	0.58 [0.33, 1.02]
Total (95% CI)			**429**		**343**	**100.0%**	**0.48 [0.35, 0.65]**
Total events		124		224			

Heterogeneity: Tau² = 0.08; Chi² = 12.19, df = 4 (P = 0.02); I² = 67%
Test for overall effect: Z = 4.69 (P < 0.00001)



Results - Systemic treatments

- Ciclosporin
  - After a single 12-week course of ciclosporin
    - Mean duration of remission was 66 days
    - Three patients (16%, 95% CI = 4.2% -37%) remained in remission for nine months after one course of 12-week therapy.
- PUVA vs. UVA
  - The median length of remission after 15 treatments each:

    12 weeks after PUVA vs. 4 weeks after UVA therapy (P = 0.012).
  - Two of 15 PUVA-treated patients (13%, 95%CI =2.3-37.5%) remained free of relapse for longer than 12 months, but none of the UVA-treated patients did.

Answer?

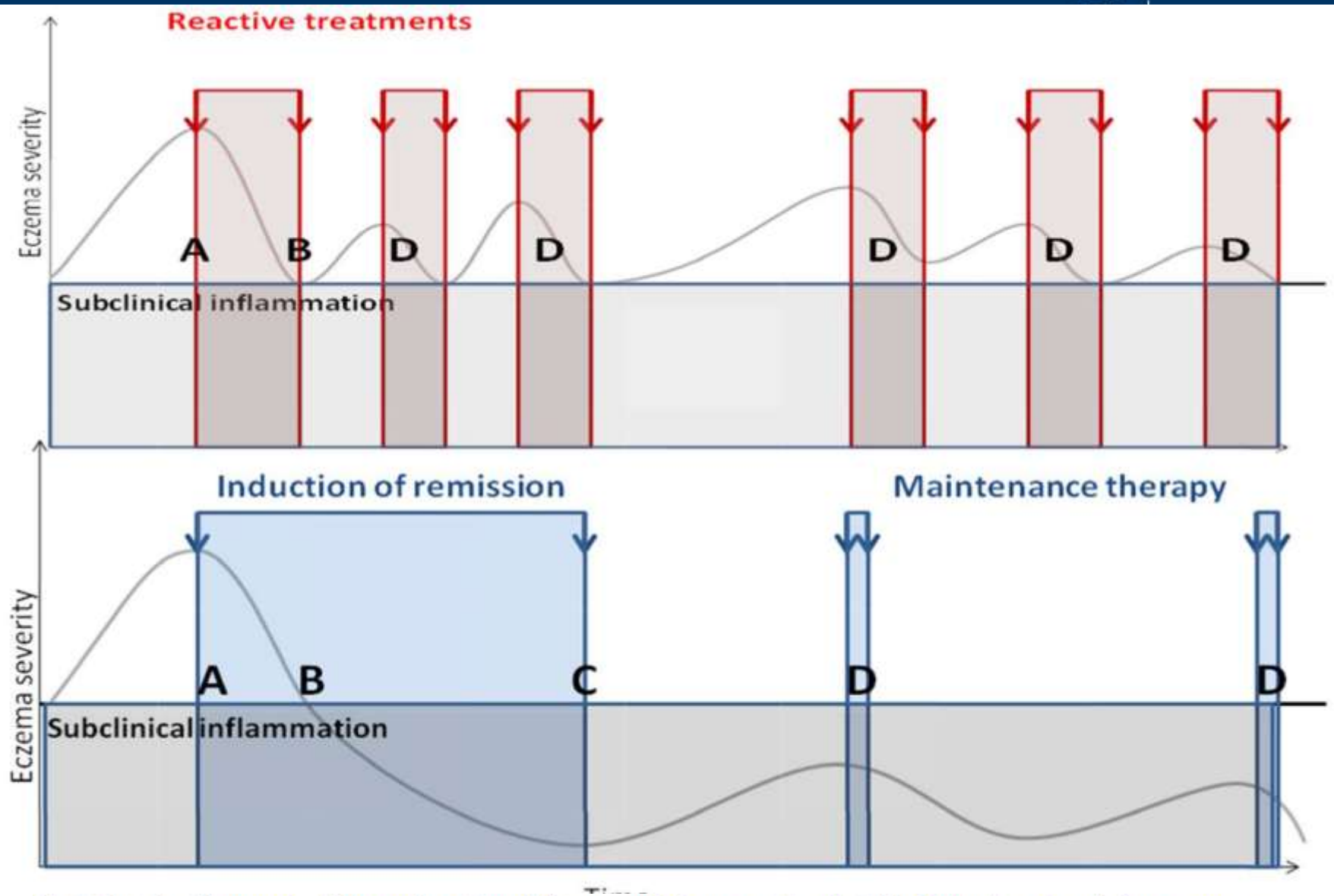
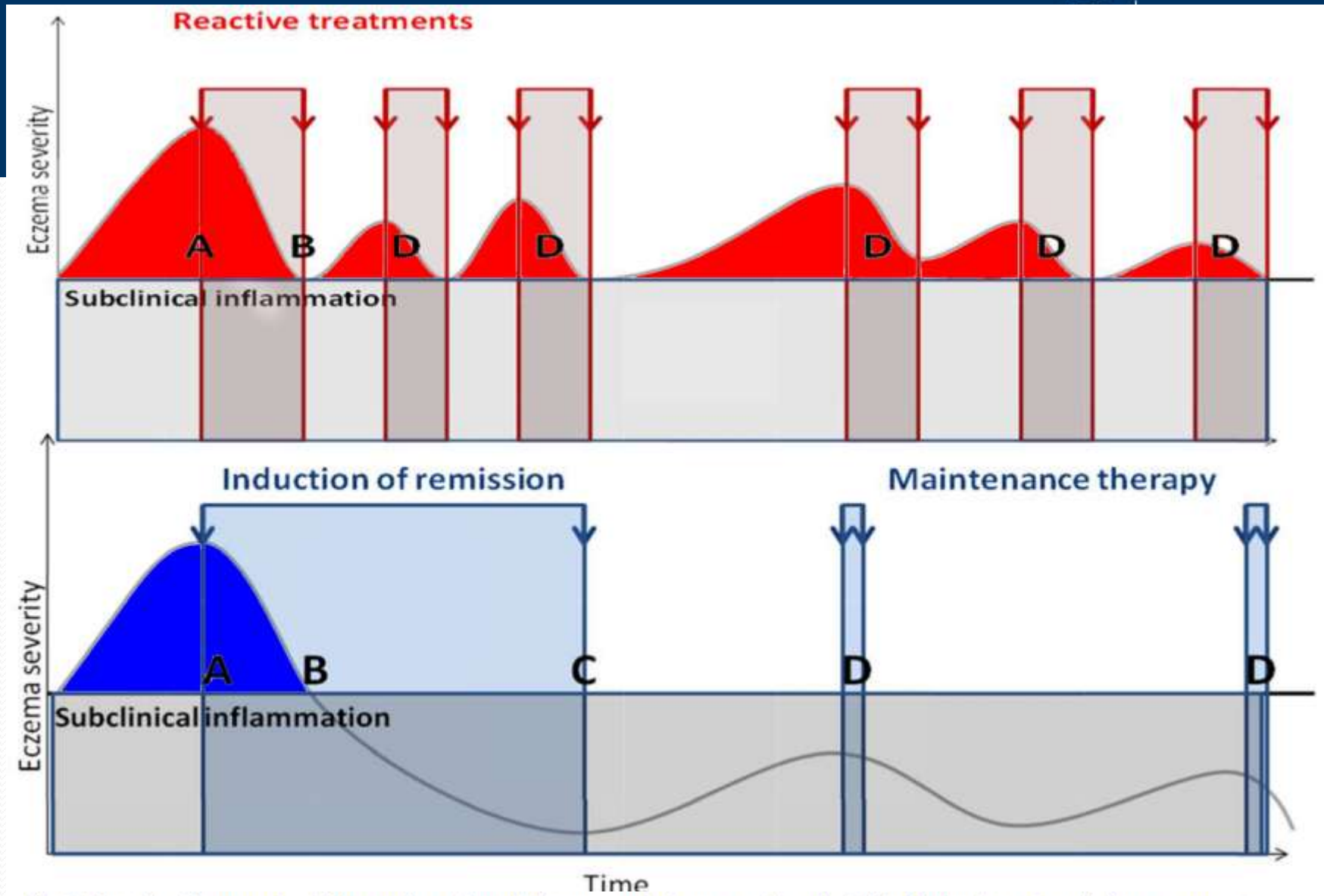


Fig 2. Putative diagram (top) illustrating what might currently happen when the initial induction of remission treatment period (started at point A) ceases once signs and symptoms have reduced (clinical remission or point B) as opposed to what might happen (bottom) if initial induction of remission extended to clear subclinical disease (subclinical remission or point C). Each induction of remission period is followed by maintenance or proactive treatment, requiring 2 consecutive days treatment per week to previously active sites (points D).



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"Research, the answer lies within, and we must based on evidence."

Conclusion

- We found consistent evidence of subclinical inflammation in non-lesional normal appearance and treated skins in patients with atopic dermatitis.
- We also found some evidence that treatment may improve these subclinical changes, although longer term studies are needed.
- Lower success rate of inducing remission were associated with higher risk of relapse during long-term follow up.

Reference

- Tang, T.S., T. Bieber, and H.C. Williams, *J Allergy Clin Immunol*. 2014 Mar 18.

- Nankervis H, Samuels, HJ, Delamere F, Thomas, K, Williams HC. *The Global Resource of Eczema Trials*. Centre of Evidence Based Dermatology.

Acknowledgement

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Prof. Thomas Bieber

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Rheinische
Friedrich-Wilhelms-
Universität Bonn

Centre of Evidence-based Dermatology, Nottingham

Centre of Evidence Based dermatology

"Treat eczema under the skin."

"Get control, before keep control."

Prof. Hywel Williams