UniversitätsCentrum Evidenzbasierte Gesundheitsversorgung

Universitätsklinikum Carl Gustav Carus
DIE DRESDNER.

8th Georg Rajka Symposium Nottingham, May 23, 2014

Systemic anti-inflammatory treatments for atopic dermatitis

Prof. Jochen Schmitt

Disclosure

J. Schmitt has received honoraria for CME certified educational talks that received direct or indirect sponsoring from Abbott (now AbbVie) and Novartis.

He received funding for investigator initiated research from Novartis, Pfizer, ALK and MSD.

He acted as an advisory board member for Novartis and La Roche

Burden of Atopic Eczema

- High prevalence: infants: 20%, pre-school children 11% [1,2]
- Significant impact on quality of life (patients and families)
- Direct and indirect cost comparable to those of asthma
- Frequent cause of sleeping problems in childhood [3]
- Comorbid rhinitis and/or asthma
- Comorbid mental health problems [4,5]

~10% of patients receive systemic immunomodulating treatment

[1] Williams, Clin Exp Dermatol 2000
[2] Schmitt, JDDG 2009
[3] Smaldone, Pediatrics 2007
[4] Schmitt, JACI 2010
[5] Schmitt, BJD 2009

Indication for systemic treatment

Objectively severe disease

(intensity / extent / high expression area)

Subjectly severe disease

(symptoms, quality of life)

Failure to respond to topical treatments

J ALLERGY CLIN IMMUNOL
FEBRUARY 2014

Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: A systematic review

Evelien Roekevisch, MD,[a] Phyllis Ira Spuls, MD, PhD,[a] Denise Kuester, BA,[b,c] Jacqueline Limpens, PhD,[a] and Jochen Schmitt, MD, MPH[b,c] *Amsterdam, The Netherlands, and Dresden, Germany*

Search criteria

P – Patients of all ages with moderate-to-severe AD

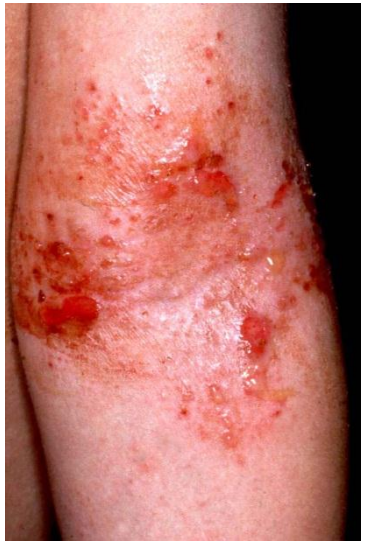
I – Systemic immunomodulating therapy

C – Placebo or active comparator

O – HOME core outcome domains

S – RCTs and open-label extensions of RCTs

What is moderate-to-severe atopic eczema?



No established definition

- patients described as having moderate-to-severe AE
- “patients with not adequately controlled AE despite the use of topical anti-inflammatory therapy”

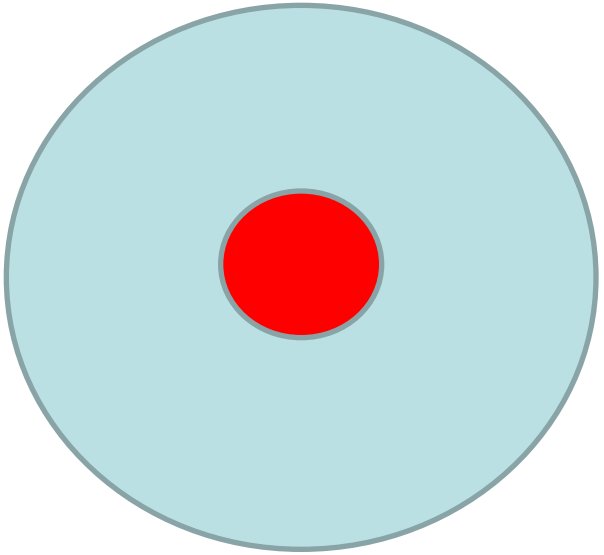
- Rajka and Langeland score >4.5
- objective SCORAD >20
- BSA >10%

HOME core outcome domains for AE trials

- Clinical signs
- Symptoms
- Quality of life
- Long term control of flares

home

Harmonizing Outcome Measures for Eczema



Safety and Tolerability outcomes

Incidence rates per patient week for

- Adverse events (AEs)
- Serious adverse events (SAEs)
- Withdrawals because of AEs or SAEs

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Literature search: Medline, Embase, Central until 06/2012

Identification, abstraction, quality assessment by ≥ 2 reviewers

Cochrane Risk of Bias tool

Grading the quality of evidence and formulating recommendations using the GRADE methodology
(only possible for clinical signs)

Meta-analysis of qualitatively homogeneous trials intended

Rules for rating the strength of evidence using GRADE

Grade	Definition
High	Further research is **very unlikely to change** our confidence in the estimate of effect.
Moderate	Further research is likely to have an important impact on our confidence in the estimate of effect and **may change** the estimate.
Low	Further research is very likely to have an important impact on our confidence in the estimate of effect and is **likely to change** the estimate.
Very low	Any estimate of effect is **very uncertain**.

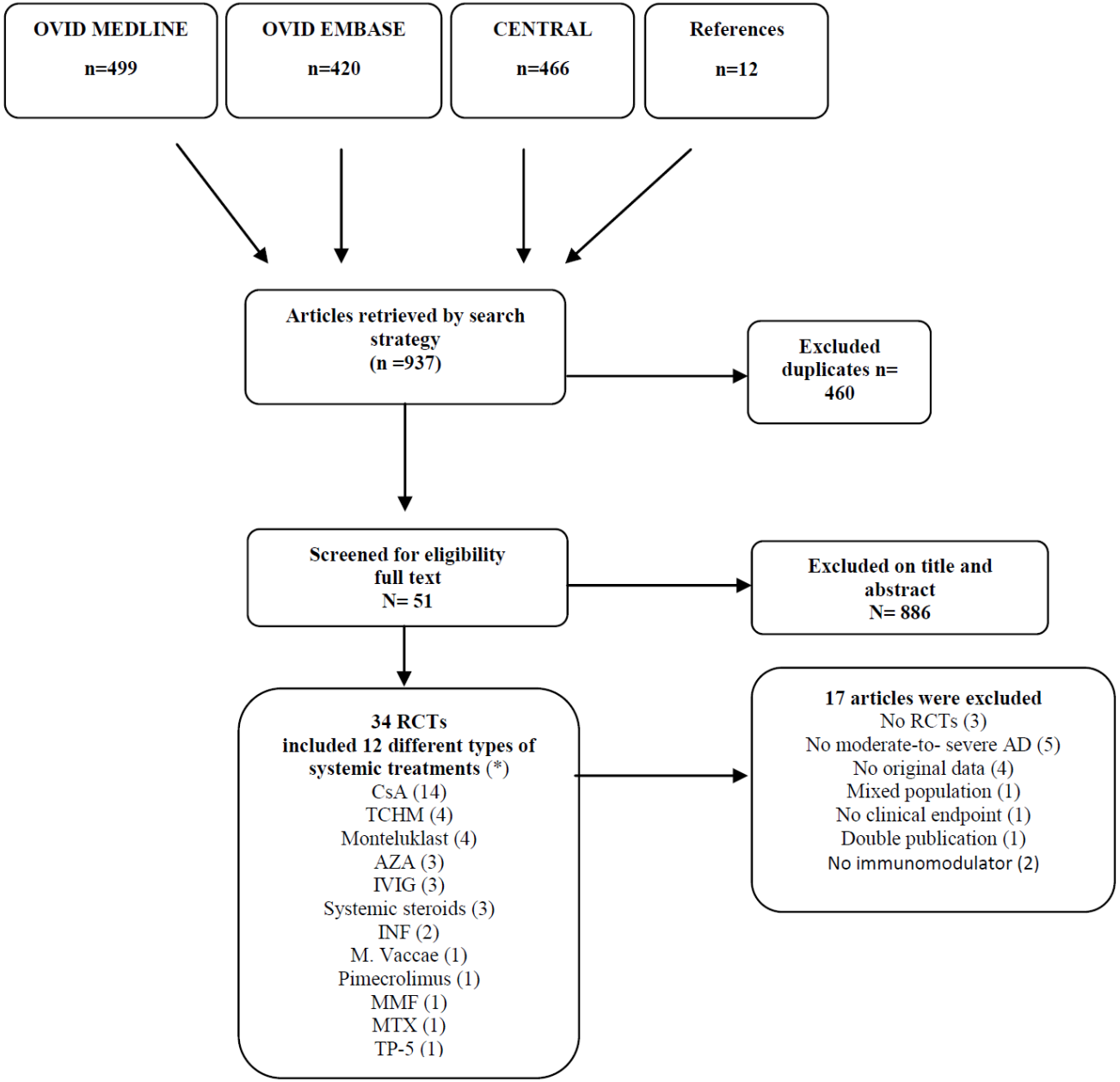
RCT starts with GRADE “high”

Rules for rating the strength of evidence using GRADE

RCT starts with GRADE “high”

DOWNgrading:
- Risk of Bias: 1 item “high” in majority of studies → -1; 2+ items “high” → -2
- Inconsistency of results: -1 if only quantitatively; -2 if qualitatively
- Indirectness of evidence: -1 if population highly selected (AE subgroup)
- Imprecision of results: total n for comparison < 100: → -1; < 20 → -2
- Publication bias: strong evidence (funnel plot): -2; ALL studies <100 AND funded by industry AND in favor of investigated drug: -1

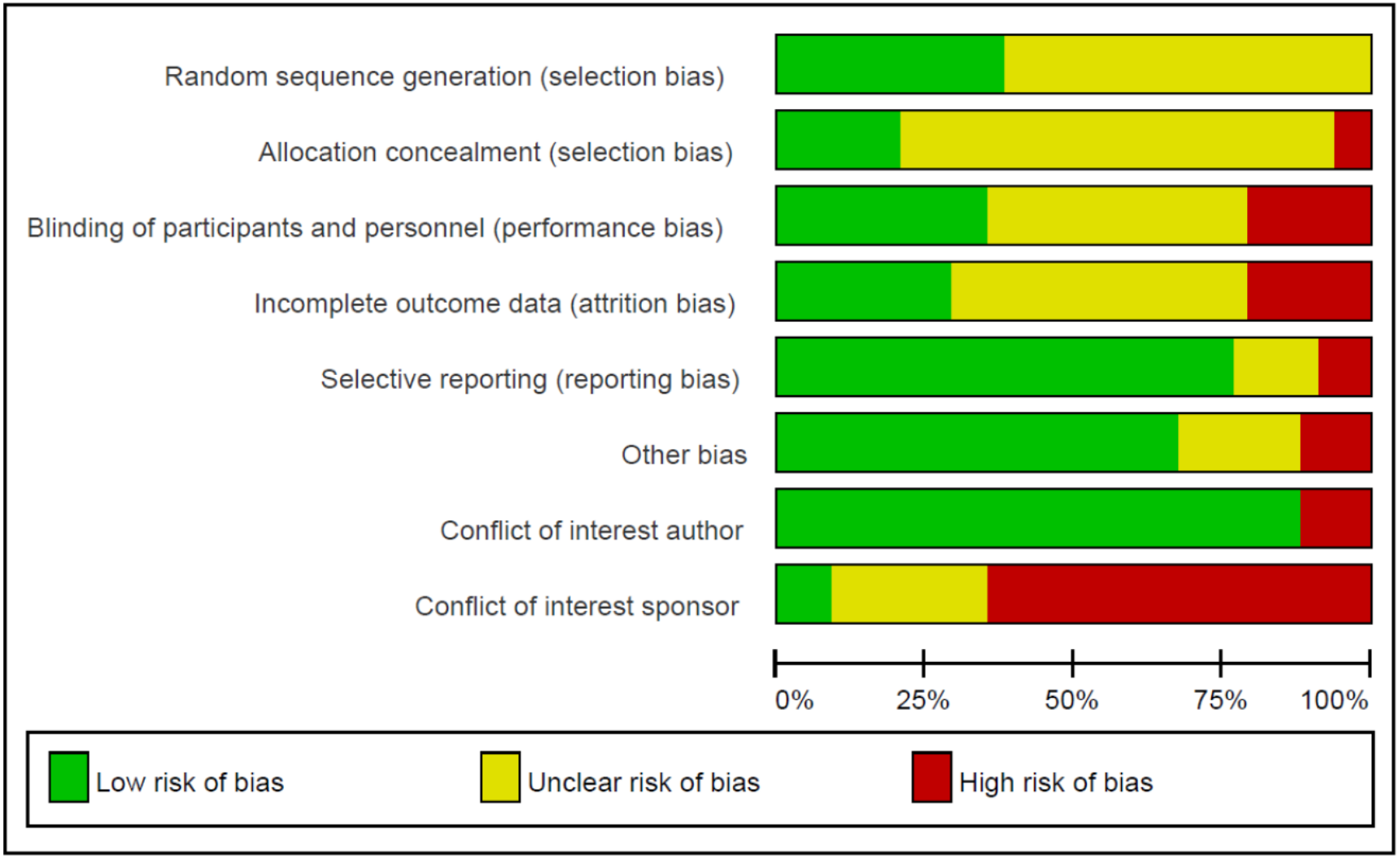
UPgrading:
- Dose-response relationship present: +1


OVID MEDLINE
n=499
OVID EMBASE
n=420
CENTRAL
n=466
References
n=12
Articles retrieved by search strategy
(n =937)
Excluded duplicates n= 460
Screened for eligibility full text
N= 51
Excluded on title and abstract
N= 886
34 RCTs
included 12 different types of systemic treatments (*)
CsA (14)
TCHM (4)
Monteluklast (4)
AZA (3)
IVIG (3)
Systemic steroids (3)
INF (2)
M. Vaccae (1)
Pimecrolimus (1)
MMF (1)
MTX (1)
TP-5 (1)
17 articles were excluded
No RCTs (3)
No moderate-to- severe AD (5)
No original data (4)
Mixed population (1)
No clinical endpoint (1)
Double publication (1)
No immunomodulator (2)

Results

- 32/34 trials (94%) recruited <100 patients
- 5 trials investigated long-term treatment ≥16 wk
- 24 trials (71%) allowed concomitant use of TCS
- 8/34 trials were head-to-head trials
- 44% of trials included children & adults, 15% only children, 41% only adults

Risk of Bias


Random sequence generation (selection bias)
Allocation concealment (selection bias)
Blinding of participants and personnel (performance bias)
Incomplete outcome data (attrition bias)
Selective reporting (reporting bias)
Other bias
Conflict of interest author
Conflict of interest sponsor
0%
25%
50%
75%
100%
Low risk of bias
Unclear risk of bias
High risk of bias

Results

Agent	Trials (n)	Benefits (mean improvement in signs score)	Harms (weekly rate of AE)
Cyclosporin A (CsA)	14	52-95%	1
Azathioprine (AZA)	3	26-43%	6-23%
Methotrexate (MTX)	1	48%	24%
IVIG	3	11-30%	1-3%
Systemic steroids	3	43%, 2x	0-20%, reb s
Mycophenolate	1	maint ce	5
IFN-γ	2	36-4 n.r.	1
Montelukast	4	24-51%	n.r.
TCHM	4	1 %	1
Mycobacterium vaccae	1	n.r.	n.r.
Pimecrolimus	1	35-47%	8%
Thymopentin (TP-5)	1	21%	n.r.

Outcomes

- 33/34 trials (97%) assessed clinical signs using a score
  - 12 different clinical signs scores were used as the primary outcome measures.
  - 50% of studies used an unvalidated score

→Cross-trial comparison impossible

→Meta-Analysis impossible

→Barrier to research communication

→Barrier to evidence-based clinical decision making

Recommendations

Nr of RCTs (Total participants)	Comparison	GRADE	Conclusion
2 (182)	CsA higher v lower dose	High quality	Higher dosages of CsA are more effective than lower dosages of CsA in patients with severe AD.
5(146)	CsA v Placebo	Moderate quality	CsA is effective in patients with moderate-to-severe AD.
1 (38)	CsA v prednisolone	Low quality	CsA is more effective than prednisolone to induce stable remission in patients with severe AD.
1 (30)	CsA v topical tacrolimus	Low quality	CsA and topical tacrolimus 0.1% may be equally effective in patients with moderate-to-severe AD.
1(50)	CsA v MMF	Very low quality	CsA and MMF may be equally effective as a maintenance treatment patients with severe AD
1(14)	CsA v IVIG	Very low quality	Current evidence on the comparative effectiveness of CsA vs. IVIG for AD is very weak and favours CsA.
1 (72)	CsA v UVAB	Very low quality	CsA may be more effective than UVAB in patients with severe AD.
2 (98)	AZA v Placebo	Very low quality	AZA is effective in many patients with moderate-to-severe AD.
1(42)	AZA v MTX	Moderate quality	MTX and AZA are both equally effective in patients with severe AD.
1(103)	Pimecrolimus v placebo	Moderate quality	Systemic pimecrolimus is effective in some patients with moderate-to-severe AD.
2 (134)	INF v placebo	Moderate quality	INF is effective in some patients with severe AD.
2 (67)	Sys. sterodis v placebo	Very low quality	Systemic glucocorticosterodis (beclomethasone diproprionate and flunosolide) may be effective to induce remission in patients with moderate-to-severe AD.
2 (74)	Montelukast v Placebo	Very low quality	We do not know whether or not montelukast is effective in a subgroup of patients with moderate-to-severe AD.
2 (63)	Montelukast v TCS, antihistamine, +- antibiotic	Very low quality	We do not know whether or not montelukast is more, equally, or less effective as combined treatment with antihistamine, topical steroid +- antibiotic in patients with moderate-to-severe AD.
1 (166)	M. Vaccae v placebo	Moderate quality	M. Vaccae is not effective for patients with severe AD and is not recommended based on current evidence.
1(39)	TP-5 v Placebo		Current evidence does not recommend the use of TP-5 for patients with severe AD.
4 (79)	TCHM v Placebo	Very low quality	Current evidence is insufficient to recommend the use of TCHM for patients with moderate-to-severe AD.
2 (49)	IVIG v placebo /waiting control	Very low quality	Current evidence is insufficient to recommend the use of IVIG for patients with severe AD.

Recommendations

CsA is currently recommended as the first-line short-term systemic treatment option

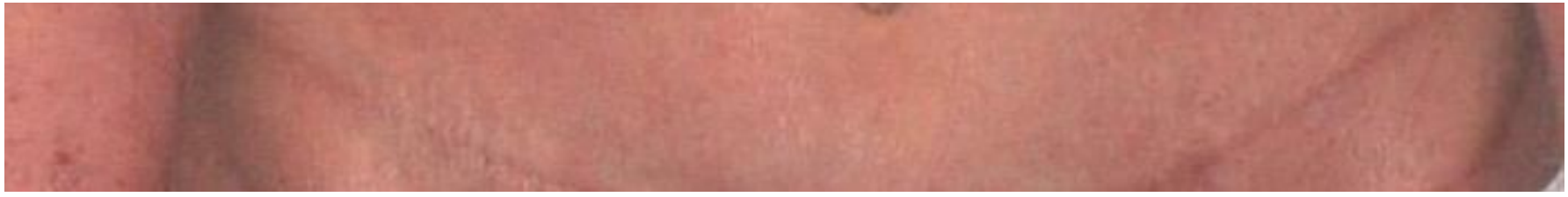
AZT is currently recommended as the second-line systemic treatment option

MTX is currently recommended as the third-line systemic treatment option for adults

MMF may be considered as maintenance treatment after induction of remission by CsA

IFN may be considered with closely monitoring of adverse effects.

Systemic steroids, IVIG, Montelukast, TCHM, TP-5, M.vaccae are currently not recommended as systemic treatments for AE based on trial evidence



Conclusions from SR

Despite 34 trials on 12 interventions we cannot provide strong recommendations

- Most trials were small
- Outcomes are often inadequate and not standardized
- Mean change vs. Response rate?
- Key head-to-head comparisons are missing
- Long-term trials are missing
- Trials in children are missing

Oral phosphodiesterase inhibitor -Apremilast -

- Pilot study in 16 adults
- EASI 11+
- 20mg bid vs. 30mg bid
- 19% and 39% EASI decrease at wk 12
- Benefits also in itch and qol
- Nausea in 33% and 90% after treatment initiation

Samrao et al. Arch Dermatol. 2012 Aug;148(8):890-7.

Methotrexate versus cyclosporine in children with severe AD

- Multicenter study from Egypt on 40 children
- Methotrexate (7.5 mg/week)
- Cyclosporine (2.5 mg/kg/day).
- 45% and 44% SCORAD decrease at wk 12
- Mild and reversible AEs in both groups

El-Khalawany MA et al. Eur J Pediatr. 2013 Mar;172(3):351-6.

Mycophenolate sodium as maintenance treatment

55 adults with severe AD; Induction treatment with CsA (5 mg/kg) over 6-weeks

→ Randomization

- CsA (3 mg/kg) vs EC-MPS (1440 mg; n = 24)
- 30 wks long-term treatment + 12 wk FU
- Until wk10 oSCORAD higher and more frequently rescue medication in MPS group
- No difference in disease activity in maintenance phase
- FU: increase in disease activity only in CsA group
- Tolerability similar, AEs mild and transient

Haeck IM et al. J Am Acad Dermatol. 2011 Jun;64(6):1074-84.

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Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

BRIEF COMMUNICATION

Increased efficacy of omalizumab in atopic dermatitis patients with wild-type filaggrin status and higher serum levels of phosphatidylcholines

M. Hotze[1], H. Baurecht[1,2], E. Rodríguez[1], N. Chapman-Rothe[3], M. Ollert[4], R. Fölster-Holst[1], J. Adamski[5,6], T. Illig[7], J. Ring[4] & S. Weidinger[1]

- Subgroup might benefit → Investigatoin of 20 adults with severe AD to explore predictors of response
- Prospective uncontrolled investigation over 28 weeks
- 14 cycles of 150 mg omalizumab eow; increase to 300mg at wk 14 if SCORAD25 not reached
- 4 Patients met SCORAD50, 4 SCORAD25, 5 no change, 7 patients worsened
- All 7 patients with FLG did NOT respond

→ Patients without primary skin barrier deficiency might benefit from Omalizumab

Allergy 2014; **69**: 132–135.

Dupilumab

- blocks the IL-4/IL-13 receptor/ligand system
- European RCT Dupilumab 300 mg + TCS (n=21) vs. Placebo + TCS (n=10)
- Moderate-to-severe AD (SCORAD >20)
- AEs tended to me more frequent in Dupilumab group, no SAEs in Dupilumab group
- EASI50 response by ~60% after 2 weeks, 100% after 4 weeks in Dupilumab group
- 40 – 50% response in placebo group

Diamant Thaçi, EADV 2014

PAEDIATRIC DERMATOLOGY

BJD
British Journal of Dermatology

The European treatment of severe atopic eczema in children taskforce (TREAT) survey

L.E. Proudfoot,[1] A.M. Powell,[1] S. Ayis,[2] S. Barbarot,[3] E. Baselga Torres,[4] M. Deleuran,[5] R. Fölster-Holst,[6] C. Gelmetti,[7] A. Hernández-Martin,[8] M.A. Middelkamp-Hup,[9] A.P. Oranje,[10] K. Logan,[11] M. Perkins,[11] A. Patrizi,[12] G. Rovatti,[7] O. Schofield,[13] P. Spuls,[9] Å. Svensson,[14] C. Vestergaard,[5] C.-F. Wahlgren,[15] J. Schmitt[16,17] and C. Flohr;[1] in collaboration with the European Dermato-Epidemiology Network (EDEN)

[1]St John's Institute of Dermatology, and [2]Division of Health and Social Care Research, Guy's and St Thomas' NHS Foundation Trust, London SE1 9RT, U.K.

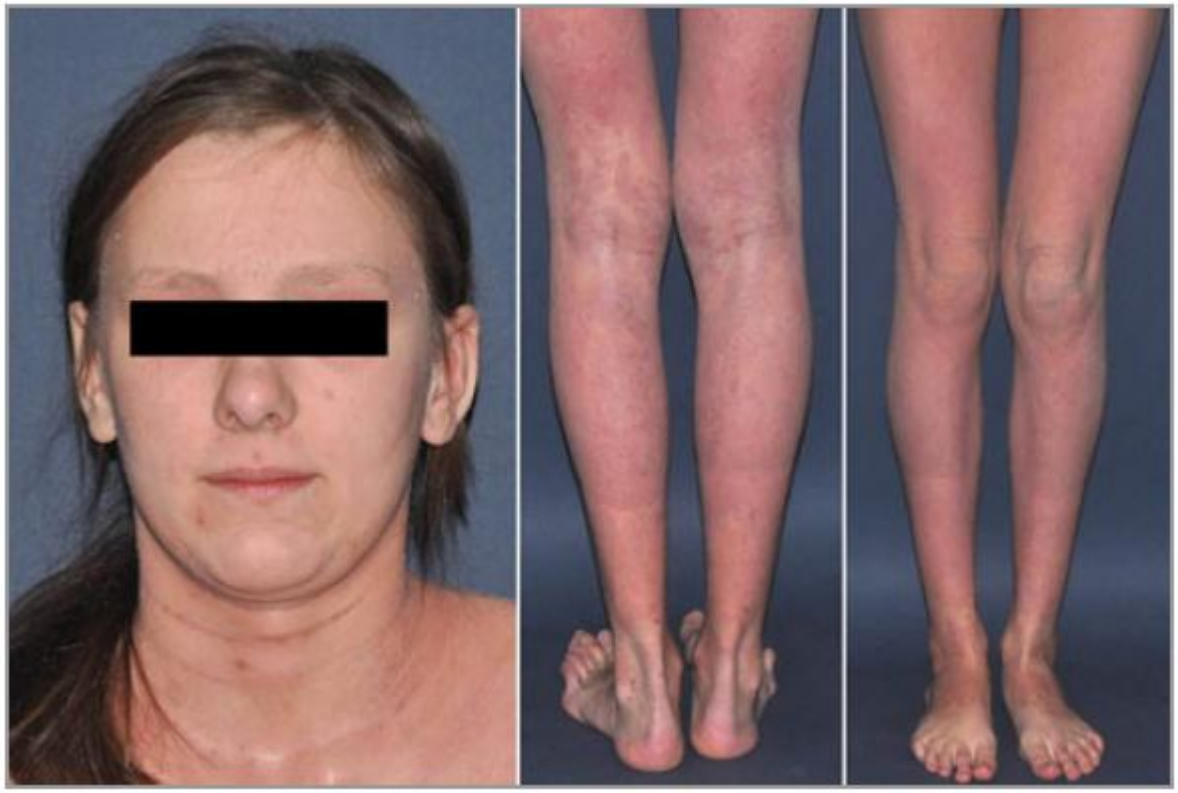
Webbased survey among 343 consultant physician members of paediatric dermatology societies and interest groups of eight European countries

Use of systemic agents in refractory paediatric atopic eczema?

>70% of participating dermatologists initiate systemic immunosuppression for children with severe atopic eczema

There was great variation in prescription practice between coutries

British Journal of Dermatology (2013) **169**, pp901–909



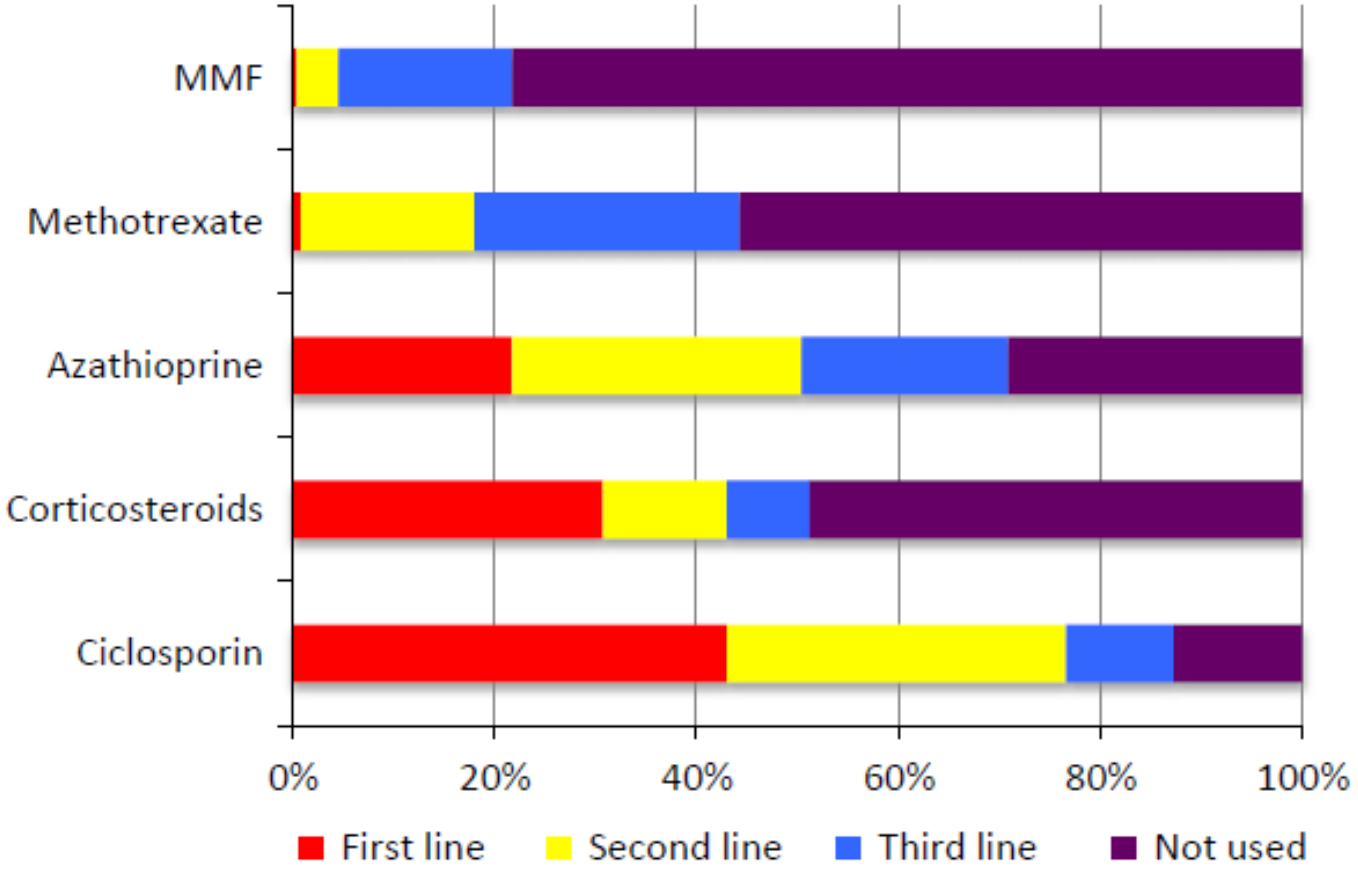
Clinical Scenario:

This 12-year-old girl has had severe atopic eczema since the age of 4-months. She is being maximally treated with antiseptic soap substitutes, emollients, potent topical corticosteroids and antihistamines and failed to respond to a course of narrowband UVB phototherapy.

Please select the first-, second- and third-line systemic medications you would employ in such a case, outside the context of an acute flare, given a selection of oral corticosteroids, ciclosporin, azathioprine, methotrexate, mycophenolate, or 'other drug'

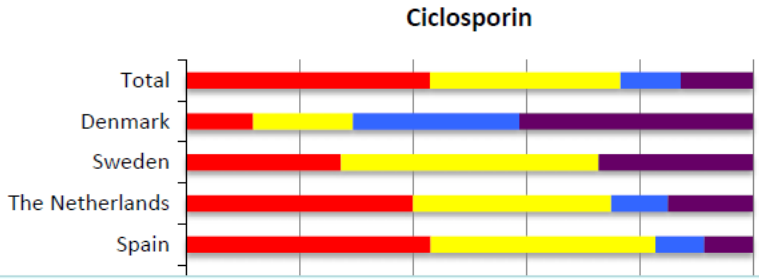
Proudfoot et al. BJD 2013

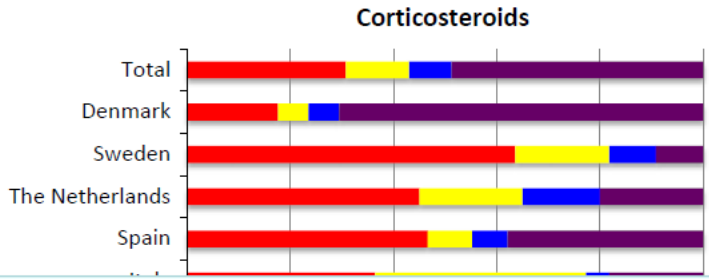
Choice of treatment by 244 dermatologists from 8 European countries



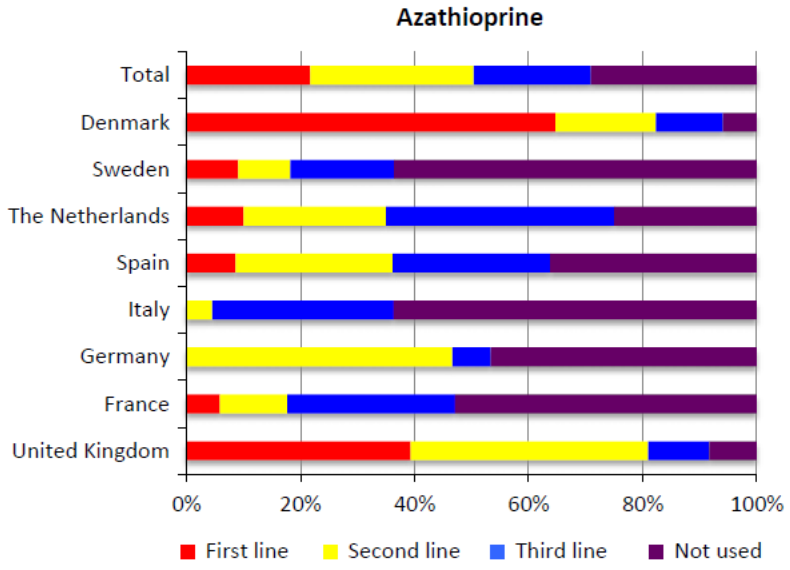
Proudfoot et al. BJD 2013

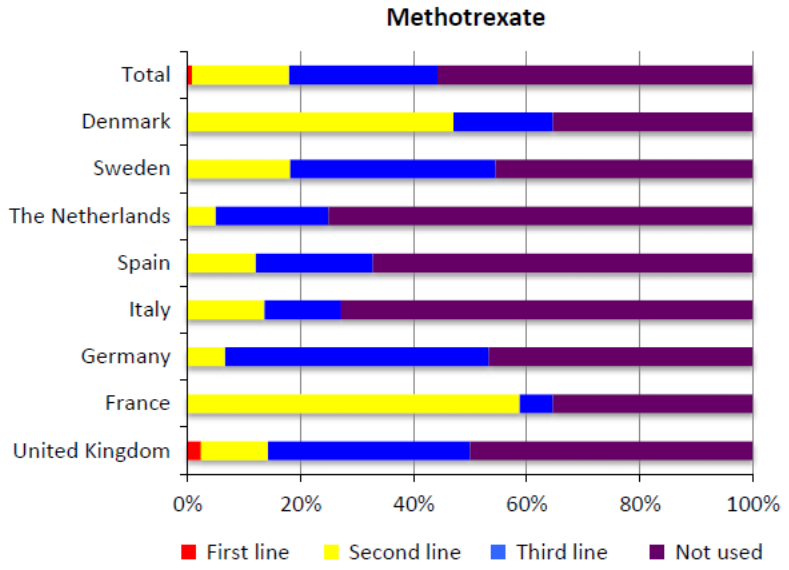
Great variation in treatment preferences between dermatologists from different European countries





Substantial variation also in dosing regimens and treatment duration

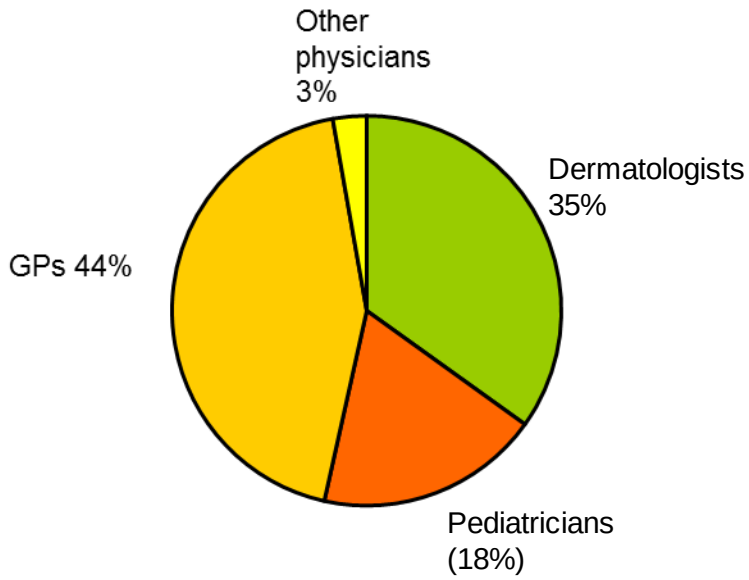




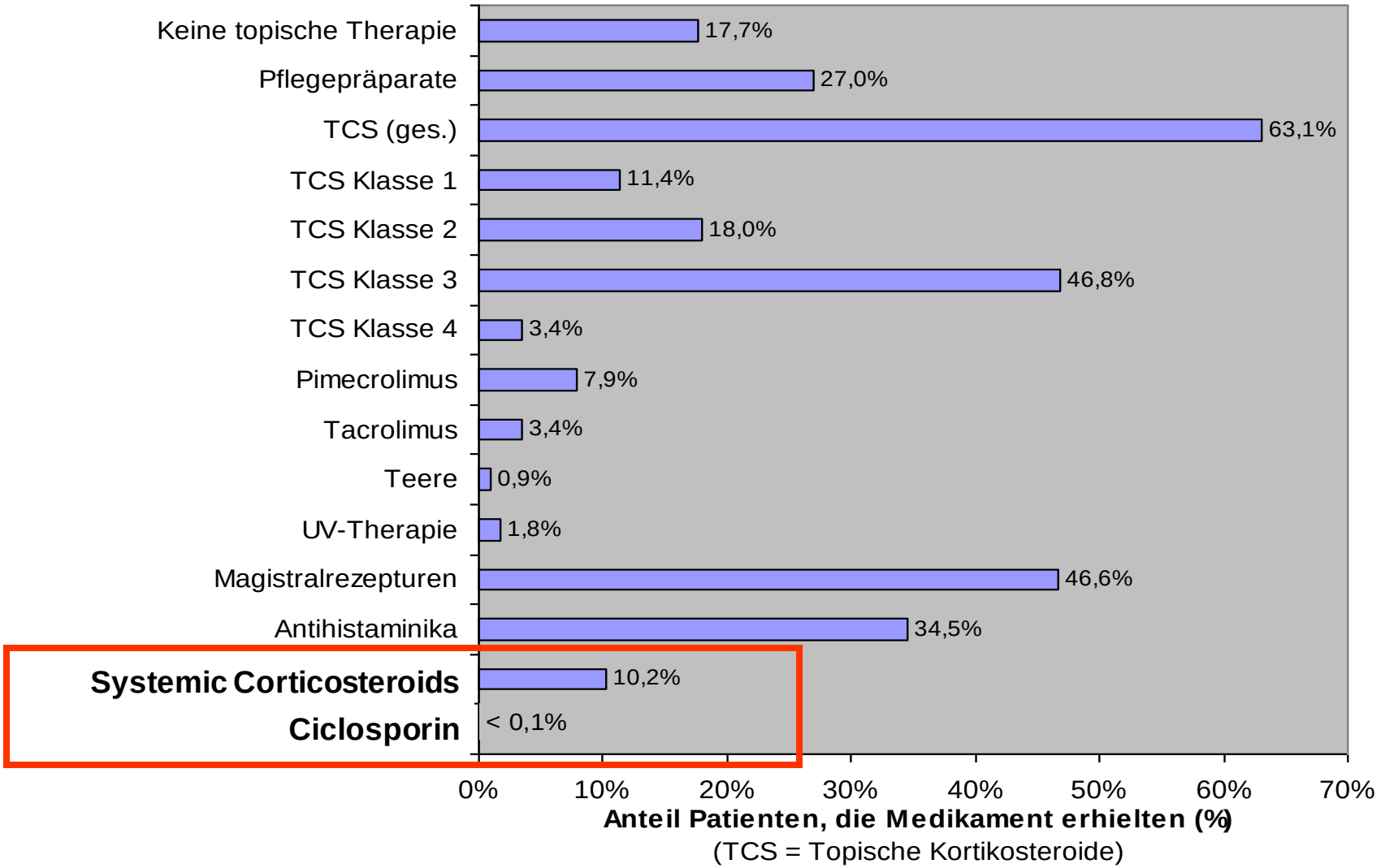
Proudfoot et al. BJD 2013

Treatment of AD in real life

97,757 patients utilizing healthcare because of AD in Germany



Treatment of adult AD in clinical routine



Schmitt J (2009) JDDG

Treatment of adults with eczema by discipline

Therapy	Proportion of patients treated (2003-2004)		
	Dermatologist (exclusively) (n=3,249)	GP (exclusively) (n=2,058)	Dermatologist and GP (n=823)
none	11,7%	32,8%	6,0%
Emollients	21,0%	11,3%	20,8%
TCS, total	68,1%	53,7%	76,6%
TCS, low potency	7,3%	8,9%	9,8%
TCS, moderate potency	23,9%	13,9%	25,8%
TCS, high potency	49,0%	37,2%	62,5%
TCS, very high potency	6,3%	3,1%	6,2%
Pimecrolimus	3,9%	2,1%	12,6%
Tacrolimus	2,2%	0,5%	7,7%
Antihistamines	26,0%	16,1%	35,4%
UV-therapy	3,0%	0,8%	3,9%
Systemic Corticosteroids	**9,1%**	**8,4%**	**12,2%**
Ciclosporin	**0,1%**	**---**	**0,3%**

Schmitt J (2009) JDDG

THERAPEUTICS

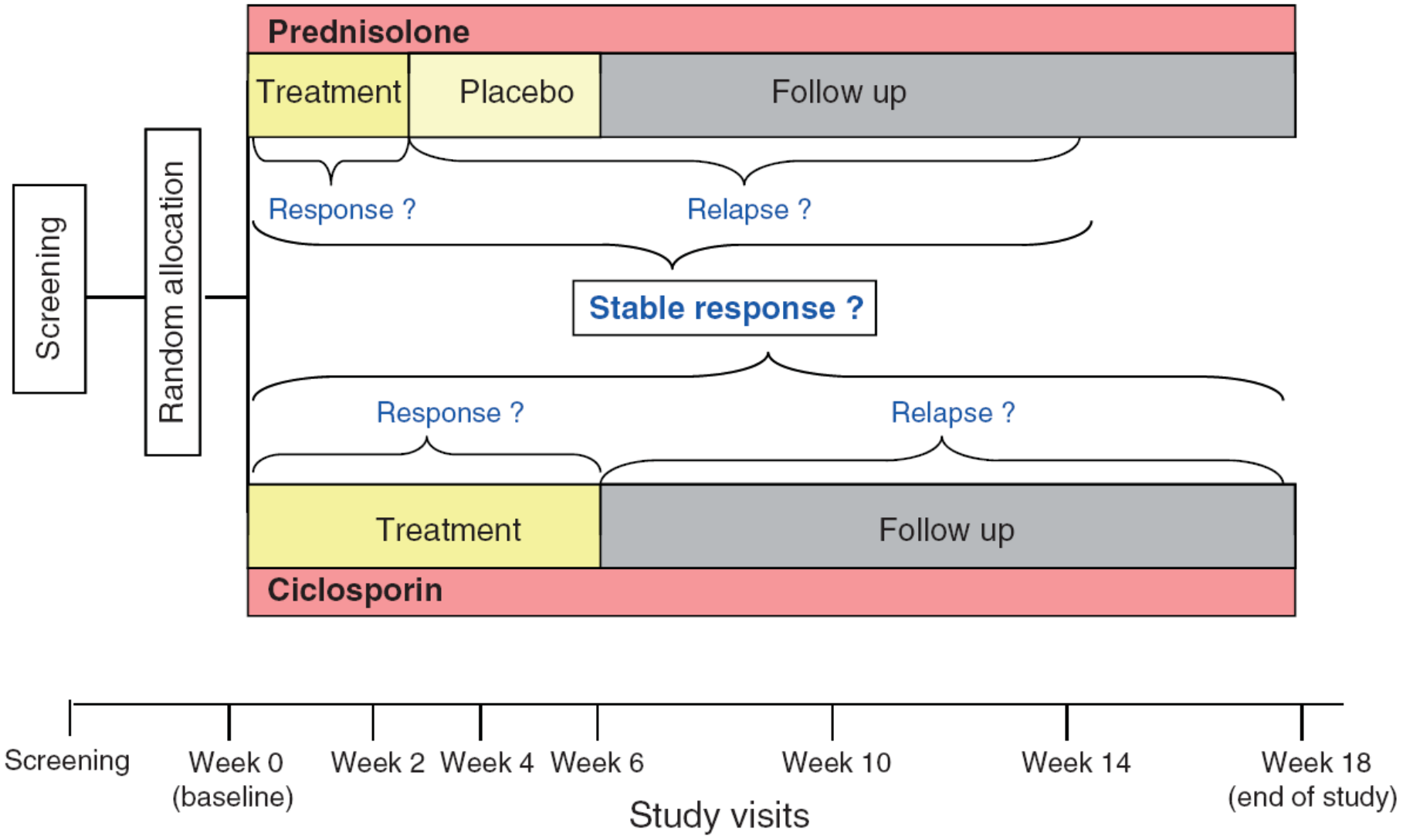
BJD
British Journal of Dermatology

Prednisolone vs. ciclosporin for severe adult eczema. An investigator-initiated double-blind placebo-controlled multicentre trial

J. Schmitt, K. Schäkel, R. Fölster-Holst,* A. Bauer, R. Oertel,† M. Augustin,‡ W. Aberer,§ T. Luger¶ and M. Meurer

Investigator initialted multi-centre trial

Prednisolone vs. Ciclosporine in Severe Atopic Eczema - **PROVE - Studie**


Prednisolone
Treatment
Placebo
Follow up
Response ?
Relapse ?
Screening
Random allocation
Stable response ?
Response ?
Relapse ?
Treatment
Follow up
Ciclosporin
Screening
Week 0 (baseline)
Week 2
Week 4
Week 6
Week 10
Week 14
Week 18 (end of study)
Study visits

Dosage

Ciclosporin (6 weeks) 2.7-4.0 mg/kg

Prednisolone (2 weeks + 4 weeks placebo)

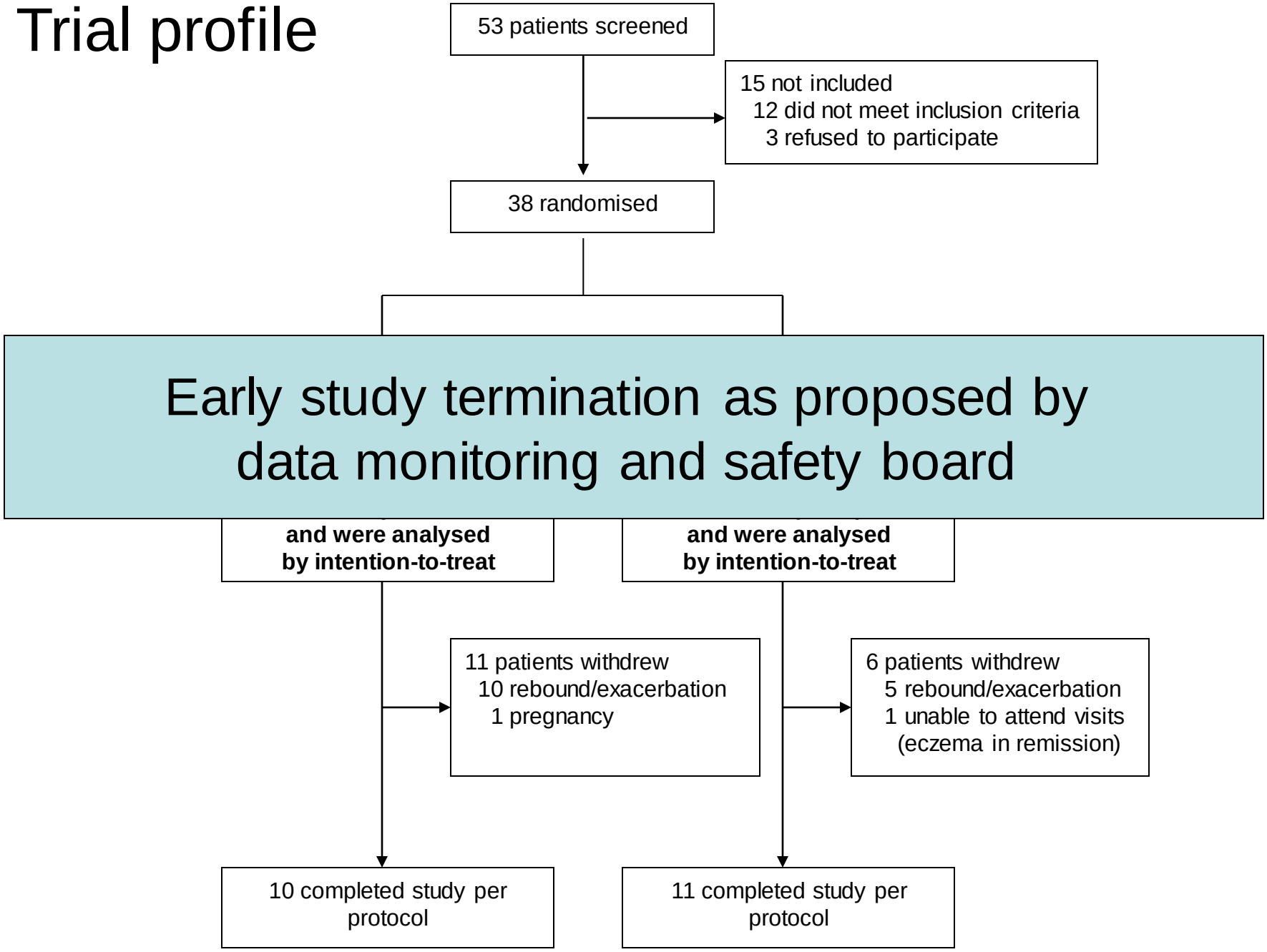
50-74.9 kg: 40mg (7d) 20mg (3d) 10mg (4d) (0.53-0.8 mg/kg)

75-100 kg: 60mg (7d) 30mg (3d) 15mg (4d) (0.6-0.8 mg/kg)

Concomitant treatment

- emollients
- moderately potent topical steroid
- continuation of antihistamines

Trial profile



Results

	Treatment group		
	Prednisolone (n = 21)	Ciclosporin (n = 17)	P-value
Primary endpoint			
Stable remission[a], n (%)	1/21 (5)	6/17 (35)	0·031
Secondary endpoints			
Response rate[b], n (%)	9/21 (43)	11/17 (65)	0·180
Relapse rate[c], n (%)	8/9 (89)	5/11 (45)	0·043
Mean ± SD relative change in SCORAD			
Baseline until end of active treatment	42·7 ± 24·8	54·5 ± 24·0	0·149
Baseline until end of 12-week follow-up	17·2 ± 29·2	28·4 ± 31·7	0·265
Investigator's global assessment of disease severity: proportion with mild/almost clear/clear eczema, n (%)			
At end of active treatment	8/21 (38)	8/17 (47)	0·578
Until end of 12-week follow-up	0/21 (0)	1/17 (6)	1·00
Quality of life: proportion with significant reduction in DLQI (≥ 5 units), n (%)			
Baseline until end of active treatment	15/21 (71)	13/17 (76)	0·726
Stable improvement until end of 12-week follow-up	4/21 (19)	7/17 (29)	0·269
Patient satisfaction[d], mean ± SD			
At end of active treatment	69·4 ± 28·4	70·3 ± 24·3	0·917
At end of 12-week follow-up	39·1 ± 33·5	46·3 ± 26·8	0·476

[a]SCORAD50 (≥ 50% improvement in SCORAD compared with baseline) at end of active treatment *and* no relapse (≥ 75% of baseline SCORAD) within 12-week follow-up. [b]SCORAD50 at end of active treatment. [c]Relapse within 12-week follow-up after initial response. [d]Assessed using a 100-unit visual analogue scale with 0 reflecting total dissatisfaction and 100 reflecting maximal satisfaction with treatment/medical care of eczema. DLQI, Dermatology Life Quality Index.


MY OPINION BASED MEDICINE
MY WAY by Anne ecdote
Cochrane
Best Sellers
NNT forever
EBM

Issues for future research

→ Undertake qualitative research on physicians‘ rationals and barriers concerning systemic treatment for AD

→Develop methods to integrate external and internal evidence

→Coordinate local and national data collection in routine care (patient cohorts / clinical registries)

→Involve other medical disciplines in the research agenda

→Perform THE RIGHT clinical trials

→Develop quality indicators that allow to measure process quality and outcome indicators in routine care (P4P)

Thank you

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