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
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
Safety and Tolerability outcomes

Incidence rates per patient week for
- Adverse events (AEs)
- Serious adverse events (SAEs)
- Withdrawals because of AEs or SAEs
Efficacy and safety of systemic treatments for moderate-to-severe atopic dermatitis: A systematic review

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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

<table>
<thead>
<tr>
<th>Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>High</td>
<td>Further research is <strong>very unlikely to change</strong> our confidence in the estimate of effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>Further research is likely to have an important impact on our confidence in the estimate of effect and <strong>may change</strong> the estimate.</td>
</tr>
<tr>
<td>Low</td>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is <strong>likely to change</strong> the estimate.</td>
</tr>
<tr>
<td>Very low</td>
<td>Any estimate of effect is <strong>very uncertain</strong>.</td>
</tr>
</tbody>
</table>
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 $\rightarrow$ -1; 2+ items “high” $\rightarrow$ -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 $< 100$: $\rightarrow$ -1; $< 20$ $\rightarrow$ -2
- Publication bias: strong evidence (funnel plot): -2; ALL studies $<100$ AND funded by industry AND AND in favor of investigated drug: -1

UPgrading:
- Dose-response relationship present: +1
34 RCTs included 12 different types of systemic treatments (*):
- CsA (14)
- TCHM (4)
- Montelukast (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

Legend:
- Low risk of bias
- Unclear risk of bias
- High risk of bias
## Results

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trials (n)</th>
<th>Benefits (mean improvement in signs score)</th>
<th>Harms (weekly rate of AE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cyclosporin A (CsA)</td>
<td>14</td>
<td>52-95%</td>
<td>1-28%</td>
</tr>
<tr>
<td>Azathioprine (AZA)</td>
<td>3</td>
<td>26-43%</td>
<td>6-23%</td>
</tr>
<tr>
<td>Methotrexate (MTX)</td>
<td>1</td>
<td>48%</td>
<td>24%</td>
</tr>
<tr>
<td>IVIG</td>
<td>3</td>
<td>11-30%</td>
<td>1-3%</td>
</tr>
<tr>
<td>Systemic steroids</td>
<td>3</td>
<td>43%, 2x</td>
<td>0-20%, rebounds</td>
</tr>
<tr>
<td>Mycophenolate</td>
<td>1</td>
<td>maintenance</td>
<td>5%</td>
</tr>
<tr>
<td>IFN-γ</td>
<td>2</td>
<td>36-44%, n.r.</td>
<td>n.r.</td>
</tr>
<tr>
<td>Montelukast</td>
<td>4</td>
<td>24-51%</td>
<td>n.r.</td>
</tr>
<tr>
<td>TCHM</td>
<td>4</td>
<td>1-10%</td>
<td>1-10%</td>
</tr>
<tr>
<td>Mycobacterium vaccae</td>
<td>1</td>
<td>n.r.</td>
<td>n.r.</td>
</tr>
<tr>
<td>Pimecrolimus</td>
<td>1</td>
<td>35-47%</td>
<td>8%</td>
</tr>
<tr>
<td>Thymopentin (TP-5)</td>
<td>1</td>
<td>21%</td>
<td>n.r.</td>
</tr>
</tbody>
</table>
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

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

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

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

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

M. Hotze¹, H. Baurecht¹,², E. Rodríguez¹, N. Chapman-Rothe³, M. Ollert⁴, R. Fölster-Holst¹, J. Adamski⁵,⁶, T. Illig⁷, J. Ring⁴ & S. Weidinger¹

- Subgroup might benefit → Investigation 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
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 be 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
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 countries
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’
Choice of treatment by 244 dermatologists from 8 European countries

- MMF
- Methotrexate
- Azathioprine
- Corticosteroids
- Ciclosporin

First line | Second line | Third line | Not used
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

- Keine topische Therapie: 17.7%
- Pflegepräparate: 27.0%
- TCS (ges.): 63.1%
- TCS Klasse 1: 11.4%
- TCS Klasse 2: 18.0%
- TCS Klasse 3: 46.8%
- TCS Klasse 4: 3.4%
- Pimecrolimus: 7.9%
- Tacrolimus: 3.4%
- Teere: 0.9%
- UV-Therapie: 1.8%
- Magistralrezepturen: 46.6%
- Antihistaminika: 34.5%
- Ciclosporin: 10.2%
- Systemic Corticosteroids: < 0.1%

(TCS = Topische Kortikosteroide)

Schmitt J (2009) JDDG
## Treatment of adults with eczema by discipline

<table>
<thead>
<tr>
<th>Therapy</th>
<th>Proportion of patients treated (2003-2004)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dermatologist (exclusively)</td>
</tr>
<tr>
<td></td>
<td>(n=3,249)</td>
</tr>
<tr>
<td>none</td>
<td>11,7%</td>
</tr>
<tr>
<td>Emollients</td>
<td>21,0%</td>
</tr>
<tr>
<td>TCS, total</td>
<td>68,1%</td>
</tr>
<tr>
<td>TCS, low potency</td>
<td>7,3%</td>
</tr>
<tr>
<td>TCS, moderate potency</td>
<td>23,9%</td>
</tr>
<tr>
<td>TCS, high potency</td>
<td>49,0%</td>
</tr>
<tr>
<td>TCS, very high potency</td>
<td>6,3%</td>
</tr>
<tr>
<td>Pimecrolimus</td>
<td>3,9%</td>
</tr>
<tr>
<td>Tacrolimus</td>
<td>2,2%</td>
</tr>
<tr>
<td>Antihistamines</td>
<td>26,0%</td>
</tr>
<tr>
<td>UV-therapy</td>
<td>3,0%</td>
</tr>
<tr>
<td><strong>Systemic Corticosteroids</strong></td>
<td><strong>9,1%</strong></td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>0,1%</td>
</tr>
</tbody>
</table>

Schmitt J (2009) JDDG
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
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

53 patients screened
15 not included
12 did not meet inclusion criteria
3 refused to participate

38 randomised

Early study termination as proposed by data monitoring and safety board

and were analysed by intention-to-treat

11 patients withdrew
10 rebound/exacerbation
1 pregnancy

10 completed study per protocol

and were analysed by intention-to-treat

6 patients withdrew
5 rebound/exacerbation
1 unable to attend visits (eczema in remission)

11 completed study per protocol
# Results

<table>
<thead>
<tr>
<th>Treatment group</th>
<th>Prednisolone (n = 21)</th>
<th>Ciclosporin (n = 17)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable remission&lt;sup&gt;a&lt;/sup&gt;, n (%)</td>
<td>1/21 (5)</td>
<td>6/17 (35)</td>
<td>0.031</td>
</tr>
<tr>
<td>Secondary endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response rate&lt;sup&gt;b&lt;/sup&gt;, n (%)</td>
<td>9/21 (43)</td>
<td>11/17 (65)</td>
<td>0.180</td>
</tr>
<tr>
<td>Relapse rate&lt;sup&gt;c&lt;/sup&gt;, n (%)</td>
<td>8/9 (89)</td>
<td>5/11 (45)</td>
<td>0.043</td>
</tr>
<tr>
<td>Mean ± SD relative change in SCORAD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline until end of active treatment</td>
<td>42.7 ± 24.8</td>
<td>54.5 ± 24.0</td>
<td>0.149</td>
</tr>
<tr>
<td>Baseline until end of 12-week follow-up</td>
<td>17.2 ± 29.2</td>
<td>28.4 ± 31.7</td>
<td>0.265</td>
</tr>
<tr>
<td>Investigator’s global assessment of disease severity: proportion with mild/almost clear/clear eczema, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At end of active treatment</td>
<td>8/21 (38)</td>
<td>8/17 (47)</td>
<td>0.578</td>
</tr>
<tr>
<td>Until end of 12-week follow-up</td>
<td>0/21 (0)</td>
<td>1/17 (6)</td>
<td>1.00</td>
</tr>
<tr>
<td>Quality of life: proportion with significant reduction in DLQI (≥ 5 units), n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline until end of active treatment</td>
<td>15/21 (71)</td>
<td>13/17 (76)</td>
<td>0.726</td>
</tr>
<tr>
<td>Stable improvement until end of 12-week follow-up</td>
<td>4/21 (19)</td>
<td>7/17 (29)</td>
<td>0.269</td>
</tr>
<tr>
<td>Patient satisfaction&lt;sup&gt;d&lt;/sup&gt;, mean ± SD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At end of active treatment</td>
<td>69.4 ± 28.4</td>
<td>70.3 ± 24.3</td>
<td>0.917</td>
</tr>
<tr>
<td>At end of 12-week follow-up</td>
<td>39.1 ± 33.5</td>
<td>46.3 ± 26.8</td>
<td>0.476</td>
</tr>
</tbody>
</table>

<sup>a</sup>SCORAD<sub>50</sub> (≥ 50% improvement in SCORAD compared with baseline) at end of active treatment and no relapse (≥ 75% of baseline SCORAD) within 12-week follow-up.  
<sup>b</sup>SCORAD<sub>50</sub> at end of active treatment.  
<sup>c</sup>Relapse within 12-week follow-up after initial response.  
<sup>d</sup>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.
Issues for future research

→ Undertake qualitative research on physicians‘ rationally 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

Phyllis Ira Spuls,
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Michael Meurer
Matthias Augustin
Regina Fölster-Holst
Thomas Luger

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