Systemic immnosuppressive agents are recommended for patients with atopic eczema in whom disease activity cannot be controlled adequately with topical treatments. Guidelines do not give clear advice which agents to prefer. We systematically reviewed clinical trials on systemic treatment for severe atopic eczema to provide evidence-based treatment recommendations. Standardized literature search, independent standardized assessment of eligibility and data abstraction was performed by 2 reviewers. Twenty-seven studies totalling 979 patients were included. Eleven studies consistently showed effectiveness of cyclosporin. Cyclosporine is recommended as first option for patients with atopic eczema refractory to conventional treatment. Evidence from randomized controlled trials also exists for interferon-γ and azathioprine. Although frequently used in clinical practice, systemic glucocorticosteroids have not been assessed adequately in studies. Mycophenolate mofetil showed effectiveness in 2 small uncontrolled studies. Intravenous immunoglobulins and infliximab are not recommended based on published data. Key words: atopic dermatitis; evidence-based medicine; immunosuppressive therapy; immunomodulator; systemic treatment.

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With a prevalence of up to 20% in children and 1–10% in adults living in industrialized countries, atopic eczema (AE) is among the most common dermatological conditions (1–4). AE imposes a high economic burden, both in terms of total cost and out-of-pocket expenses (5, 6). Although most cases of AE are mild in terms of objective clinical activity, this condition adversely affects most aspects of everyday life in the majority of patients (7–9). Most patients can be treated effectively with emollients and topical anti-inflammatory agents such as topical corticosteroids and the topical calcineurin inhibitors (1, 10).

There is a broad consensus that topical treatments should be used as first-line therapy. Systemic treatment modalities are limited to the subgroup of patients in whom the activity of skin lesions and concurrent symptoms cannot be controlled sufficiently with conventional topical treatments and phototherapy (10–12). For those patients published treatment guidelines recommend agents such as systemic glucocorticosteroids, cyclosporin A (CyA), methotrexate, azathioprine (AZT), interferon-γ (IFN), intravenous immunoglobulin (IVIG) and mycophenolate mofetil (MMF) (10, 11).

Recommendations are based on small randomized controlled trials (RCT) or, more frequently, on uncontrolled studies, case reports and expert opinion. Different systemic treatment options have not yet been compared against each other in a RCT.

We performed a systematic review of prospective studies on systemic treatment options for patients with severe AE who could not be controlled adequately with conventional topical therapies. Our primary objective was to provide evidence-based recommendations on which systemic immunosuppressive or immunomodulatory agent to use as first and second choice treatment for these patients.

MATERIALS AND METHODS

We systematically reviewed all prospective clinical studies on the effectiveness of systemic immunosuppressive/immunomodulatory drugs in patients with severe AE. To minimize selection bias due to different baseline severity we limited our review to studies evaluating the subset of patients with severe AE, who do not adequately respond to topical treatments.

Literature search

A standardized electronic literature search was performed using MEDLINE (until August 2005) and the keywords “(atopic AND (eczema OR dermatitis)) OR neurodermatitis”, for study type “(study OR trial OR comparison) AND (treatment OR drug OR therapy)”. Specific treatment options were identified by searching for the generic names of immunosuppressive/immunomodulatory drugs discussed in current treatment guidelines (10, 11). We limited the literature search to papers on humans, papers with abstracts, and excluded reviews. A total of 213 articles matched these criteria. Eight additional papers were identified in the Cochrane Skin Group specialized register and the Cochrane central register of controlled trials and by hand-searching the reference lists of review articles on AE (Fig. 1).
Study selection
Each of these 221 articles was reviewed for eligibility by 2 independent reviewers (JS, NS) using a standardized eligibility form. Disagreements were resolved by discussion. Exclusion criteria comprised no original data reported, studies not carried out in humans, no diagnosis of AE, only subgroup of patients with AE included (e.g. extrinsic AE), no systemic treatment, patients not classified as inadequately controlled by conventional therapies, no clinical end-point, no prospective study, case reports/case series on less than 5 patients, and no full-text article (e.g. letter). A total of 31 articles met the eligibility criteria, 4 of which were secondary publications on studies that have been published previously (13–16). Thus, 27 studies were included in this systematic review (17–43) (Fig. 1).

Data extraction and quality assessment
Twenty-seven articles were abstracted using standardized data extraction and quality assessment forms. Relevant data of each study was independently extracted by 2 reviewers (JS, NS). Disagreements were resolved by consensus. Recorded data included information on study population (geographical region, number of patients enrolled, age range, inclusion criteria regarding the severity of AE), year of publication, study design (study type, dosage and duration of active treatment), concurrent treatment, clinical outcome measure (investigator-rated measurement including intensity and extent of skin lesions, if assessed), study result, safety, and study quality assessment.

Effectiveness was expressed as change in mean objective clinical severity (defined as investigator-rated measurement including intensity and extent of skin lesions) from baseline to end of active treatment. If not mentioned in the paper, the mean relative change in clinical severity was calculated using absolute scores at baseline and during treatment. In some articles the mean absolute severity scores were not reported in the text, but could be derived from a presented figure or graph. If means were not reported, the distribution of relative individual responses was abstracted. To be able to compare RCT and non-controlled studies we considered exclusively the active treatment groups of placebo-controlled studies. In cross-over RCT we considered only the study period prior to cross-over. This was done to avoid information bias due to carry-over effects. Methodological quality was assessed in terms of adequate case definition, use of validated outcome, follow-up rate of 80% or more, conduct of intention-to-treat analysis, adequateness of randomization concealment and blinding procedures (44). If no information was provided, the corresponding quality item was judged inadequate. Since quality assessment is subjective and because it is not easy to distinguish between study quality and reporting quality, we did not exclude studies that did not meet certain quality criteria. Both data abstraction and quality assessment was based solely on the methods and results sections.

As surrogate variables for drug safety, serious adverse events and withdrawals due to adverse events were abstracted. To be comparable across studies, safety data is provided in events per month of immunosuppressive/immunomodulatory treatment. Primarily because of small case numbers and short follow-up periods, most RCT or uncontrolled effectiveness studies are inappropriate to assess adverse drug reactions (ADR) with long latency or rare events. Additional problems derive from varying and non-standardized reporting of ADRs in clinical studies. Therefore, the presented data on safety should be interpreted with caution.

RESULTS
Overall, 27 studies met all eligibility criteria, totalling 979 patients with severe AE, inadequately controllable with topical therapies (17–43) (Fig. 1). Tables I–III detail these studies. Among those, 11 studies on CyA, totalling 498 patients were identified. The corresponding data for other treatments were: systemic glucocorticosteroids (2 studies; n=47), IFN (4 studies; n=216), IVIG
Table I. Characteristics of studies included in the systematic review

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Year</th>
<th>Study design</th>
<th>Country</th>
<th>Number enrolled (Age range years)</th>
<th>Inclusion criteria regarding disease severity</th>
<th>Drug</th>
<th>Duration of active treatment (if applicable)</th>
<th>Initial dose, comparator</th>
<th>Dose adjustments</th>
<th>Concurrent treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>37</td>
<td>1991</td>
<td>d-b RCT</td>
<td>UK</td>
<td>n = 33 (17–56)</td>
<td>Inadequately controlled by conventional therapies</td>
<td>CyA</td>
<td>8 weeks</td>
<td>5 mg/kg BW vs. placebo</td>
<td>None</td>
<td>Topical steroids</td>
</tr>
<tr>
<td>38</td>
<td>1994</td>
<td>d-b RCT</td>
<td>Netherlands</td>
<td>n = 46 (17–68)</td>
<td>Resistant to conventional therapies</td>
<td>CyA</td>
<td>6 weeks</td>
<td>5 mg/kg BW vs. placebo</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>17</td>
<td>1996</td>
<td>open RCT</td>
<td>Netherlands</td>
<td>n = 78 (18–70)</td>
<td>Resistant to conventional therapies and/or significantly disabling AE</td>
<td>CyA</td>
<td>1 year</td>
<td>3 mg/kg BW vs. 5 mg/kg BW</td>
<td>After 2 weeks stepwise adjustment to minimum effective dose</td>
<td>None</td>
</tr>
<tr>
<td>19</td>
<td>1996</td>
<td>open u-c study</td>
<td>UK</td>
<td>n = 27 (2–16)</td>
<td>Refractory to topical steroids</td>
<td>CyA</td>
<td>6 weeks</td>
<td>5 mg/kg BW</td>
<td>None</td>
<td>Topical steroids, antihistamines</td>
</tr>
<tr>
<td>18</td>
<td>1997</td>
<td>open u-c study</td>
<td>UK</td>
<td>n = 100 (≥12)</td>
<td>Disabling AE, inadequately controlled by topical steroids</td>
<td>CyA</td>
<td>48 weeks</td>
<td>2.5 mg/kg BW</td>
<td>After 8 weeks stepwise adjustment to minimum effective dose</td>
<td>Topical steroids, antihistamines</td>
</tr>
<tr>
<td>20</td>
<td>2000</td>
<td>open RCT</td>
<td>UK</td>
<td>n = 43 (2–16)</td>
<td>Refractory to topical steroids</td>
<td>CyA</td>
<td>1 year</td>
<td>5 mg/kg BW vs. 12 weeks short courses</td>
<td>After 4 weeks stepwise adjustment to minimum effective dose</td>
<td>Topical steroids</td>
</tr>
<tr>
<td>31</td>
<td>2000</td>
<td>d-b RCT</td>
<td>Germany</td>
<td>n = 106 (≥18)</td>
<td>Refractory to conventional therapies and BSA 30% or more</td>
<td>CyA</td>
<td>8 weeks</td>
<td>150 mg vs. 300 mg</td>
<td>After 2 weeks stepwise adjustment to minimum effective dose</td>
<td>Topical steroids, antihistamines</td>
</tr>
<tr>
<td>21</td>
<td>2000</td>
<td>open u-c study</td>
<td>Italy</td>
<td>n = 10 (17–45)</td>
<td>Resistant to conventional therapies</td>
<td>CyA</td>
<td>6 weeks</td>
<td>5 mg/kg BW</td>
<td>None</td>
<td>Not reported</td>
</tr>
<tr>
<td>23</td>
<td>2001</td>
<td>open u-c study</td>
<td>Germany</td>
<td>n = 10 (1–15)</td>
<td>SCORAD &gt; 50 and refractory to topical steroids</td>
<td>CyA</td>
<td>8 weeks</td>
<td>2.5 mg/kg BW</td>
<td>After 2 weeks stepwise adjustment to minimum effective dose</td>
<td>Topical steroids</td>
</tr>
<tr>
<td>22</td>
<td>2001</td>
<td>open u-c study</td>
<td>Italy</td>
<td>n = 15; 35.5 (median)</td>
<td>Resistant to conventional therapies</td>
<td>CyA</td>
<td>8 weeks</td>
<td>5 mg/kg BW</td>
<td>Not reported</td>
<td>Not reported</td>
</tr>
<tr>
<td>30</td>
<td>2004</td>
<td>d-b RCT</td>
<td>Italy</td>
<td>n = 30 (13–45)</td>
<td>Inadequately controlled by topical steroids</td>
<td>CyA</td>
<td>6 weeks</td>
<td>3 mg/kg BW vs. topical tacrolimus</td>
<td>None</td>
<td>Antihistamines</td>
</tr>
<tr>
<td>35</td>
<td>1984</td>
<td>d-b RCT</td>
<td>UK</td>
<td>n = 27 (3–14)</td>
<td>Inadequately controlled by conventional therapies</td>
<td>Beclomethasone-dipropionate</td>
<td>4 weeks</td>
<td>0.8 mg/day oral + 0.4 mg/day nasal</td>
<td>None</td>
<td>Topical steroids, antihistamines</td>
</tr>
<tr>
<td>42</td>
<td>1995</td>
<td>d-b RCT</td>
<td>Italy</td>
<td>n = 20 (2–6)</td>
<td>Inadequately controlled by topical therapies</td>
<td>Flunisolide</td>
<td>2 weeks</td>
<td>0.64 mg/day (age 2 years)</td>
<td>None</td>
<td>Antihistamines</td>
</tr>
<tr>
<td>36</td>
<td>1993</td>
<td>d-b RCT</td>
<td>USA</td>
<td>n = 83 (2–65)</td>
<td>Inadequately controlled by conventional therapies</td>
<td>INF-γ</td>
<td>12 weeks</td>
<td>1.5 × 106 IU/m²/day vs. placebo</td>
<td>None</td>
<td>Systemic and topical steroids, antihistamines</td>
</tr>
<tr>
<td>25</td>
<td>1993</td>
<td>open u-c study</td>
<td>Germany</td>
<td>n = 14 (22–33)</td>
<td>Inadequately controlled by topical steroids</td>
<td>INF-γ</td>
<td>6 weeks</td>
<td>5 × 2 × 106 IU in 1st week 3 × 2 × 106 IU in week 2–4 2 × 106 IU in week 5–6</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Ref.</td>
<td>Year</td>
<td>Study design</td>
<td>Country</td>
<td>Number enrolled</td>
<td>Age range (years)</td>
<td>Inclusion criteria regarding disease severity</td>
<td>Drug</td>
<td>Duration of active treatment</td>
<td>Initial dose, comparator (if applicable)</td>
<td>Concurrent treatment</td>
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</tr>
<tr>
<td>24</td>
<td>1998</td>
<td>open u-c study</td>
<td>Korea</td>
<td>n = 68</td>
<td></td>
<td>Inadequately controlled by conventional therapies</td>
<td>INF-γ</td>
<td>6 weeks</td>
<td>5 × 10^6 IU/m² in 1st week 3 × 10^6 IU/m² in week 2–4</td>
<td>None</td>
</tr>
<tr>
<td>39</td>
<td>2000</td>
<td>d-b RCT</td>
<td>Korea</td>
<td>n = 51</td>
<td>≥15</td>
<td>Inadequately controlled by conventional therapies, BSA ≥ 25%</td>
<td>INF-γ</td>
<td>12 weeks</td>
<td>1.5 × 10^6 IU/m² in week 1 vs. 0.5 × 10^6 IU/m² in week 2</td>
<td>None</td>
</tr>
<tr>
<td>26</td>
<td>1998</td>
<td>open u-c study</td>
<td>USA</td>
<td>n = 9</td>
<td>7–64</td>
<td>Inadequately controlled by conventional therapies</td>
<td>IVIG</td>
<td>7 months</td>
<td>Standard formulation of 10 herbs (Zemaphyte)</td>
<td>None</td>
</tr>
<tr>
<td>40</td>
<td>2002</td>
<td>d-b RCT</td>
<td>UK</td>
<td>n = 10</td>
<td>21–38</td>
<td>SCORAD ≥ 50 and inadequately controlled by conventional therapies</td>
<td>IVIG</td>
<td>1 cycle (evaluation at day 30)</td>
<td>2 g/kg BW by mouth</td>
<td>None</td>
</tr>
<tr>
<td>28</td>
<td>2002</td>
<td>open u-c study</td>
<td>Germany</td>
<td>n = 10</td>
<td></td>
<td>Inadequately controlled by conventional therapies</td>
<td>MMF</td>
<td>12 weeks</td>
<td>2 g/kg BW by mouth</td>
<td>None</td>
</tr>
<tr>
<td>41</td>
<td>2002</td>
<td>d-b RCT</td>
<td>UK</td>
<td>n = 10</td>
<td>19–60</td>
<td>Inadequately controlled by conventional therapies</td>
<td>Azathioprine</td>
<td>8 weeks</td>
<td>2.5 mg/kg BW by mouth</td>
<td>None</td>
</tr>
<tr>
<td>43</td>
<td>2005</td>
<td>open u-c study</td>
<td>Germany</td>
<td>n = 9</td>
<td>(17–61)</td>
<td>Resistant to conventional therapies</td>
<td>Infliximab</td>
<td>10 weeks (primary end-point)</td>
<td>5 mg/kg BW at weeks 0, 2 and 6</td>
<td>None</td>
</tr>
<tr>
<td>32</td>
<td>1999</td>
<td>d-b RCT</td>
<td>Hong Kong</td>
<td>n = 40</td>
<td></td>
<td>Adequate controlled by topical therapy</td>
<td>Chelidonium majus</td>
<td>8 weeks</td>
<td>Standardized formulation of 10 herbs (Zemaphyte)</td>
<td>None</td>
</tr>
</tbody>
</table>

**Table I contd.**

- AE: atopic eczema; BSA: body surface area; BW: body weight; ChE: Chinese herbal therapy; CHT: Chinese herbal therapy; C-c-o: cross-over; C-b-b: controlled, blinded, uncontrolled; C-b-b: evaluator-blinded; CyA: cyclosporin A; INF-γ: interferon-γ; IVIG: intravenous immunoglobulin; IU: International units; MMF: mycophenolate mofetil; RTC: randomized controlled trial; SCORAD: Scoring Atopic Dermatitis Index (70).
validated measurements is likely to cause substantial bias in the studies (17, 38, 41). Less than half of the studies (n=12; 44%) measured disease severity by means of a validated outcome. The frequent use of unvalidated measurements is likely to cause substantial bias and inaccuracy (45–47). Most RCT did not report on randomization concealment (17, 20, 30, 32–34, 37–39, 41, 42). Randomization concealment was adequate in 4 RCT (31, 35, 36, 40). Blinding procedures were judged adequate in 9 and inadequate in 3 RCT (Table III).

Because of substantial qualitative heterogeneity in study type, outcome assessment, and study quality we did not pool studies on the same therapeutic agents and did not compare treatments in a meta-analysis.

In the following we will qualitatively summarize the results of the studies included by treatment type.

**Cyclosporin A**

All 11 studies on CyA showed a decrease in disease activity after treatment, which was superior to placebo in all placebo-controlled RCT (17–23, 30, 31, 37, 38) (Table II). The only study which compared CyA against a different agent was performed by Pacor et al. (30). The authors reported superiority of topical tacrolimus 0.1% twice daily compared with CyA (3 mg/kg). However, due to higher baseline severity in the CyA group, the statistics presented in this paper, i.e. comparison of areas under curves, are inappropriate. After re-analysis of the data we found similar effectiveness of both agents (Table II). Seven studies measured disease activity 6–8 weeks after initiation of CyA treatment. In these studies the mean benefit was consistently a reduction in AE severity of about 50% or more (19, 21, 23, 30, 31, 37, 38). A positive dose-response relationship with 29% vs. 46% mean relative benefit after 2 weeks of treatment with 3 mg/kg vs. 5 mg/kg CyA was observed by Zonneveld et al. (17). The effectiveness of CyA was similar in studies focusing exclusively on children (n=3) (19, 20, 23) and those including only adult patients (n=5) (17, 21, 31, 37, 38). Many study protocols permitted individual adjustments to the minimum effective CyA dosage (17, 18, 20, 23, 31). Long-term effectiveness of CyA treatment was evaluated in 3 studies, each of which had a follow-up time of approximately 1 year (17, 18, 20). Mean relative improvement was about 50% in each study. However, with drop-out rates of 62% (18), 35% (17), and 28% (20) and failure to perform an ITT analysis, these results might be explained by emigrative selection bias (48). Harper et al. (20) also studied relapse-rates after discontinuation of CyA treatment. Within 9 months of follow-up a relapse (defined as increase in disease severity to more than 75% of the individual baseline score) was observed in 86% of patients. Withdrawals due to adverse events occurred on average in 0.95% patient months of CyA treatment. In 2 studies no severe adverse events (SAE) were observed (30, 31). No information on the occurrence of SAE was provided in 5 articles (19, 21–23, 38). In the remaining 4 articles a total of 22 SAE occurred, including infections, abdominal pain, acute cholecystitis, and basal cell carcinoma (17, 18, 20, 37).
<table>
<thead>
<tr>
<th>Ref. Year</th>
<th>Treatment</th>
<th>Outcome measure (clinical disease severity)</th>
<th>Results*</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>37 1991</td>
<td>CyA</td>
<td>Non-validated score including intensity and extent (mean change)</td>
<td>56% reduction in mean severity score</td>
<td>Abdominal pain ($n = 1$)</td>
</tr>
<tr>
<td>38 1994</td>
<td>CyA</td>
<td>Non-validated score including intensity and extent (mean change)</td>
<td>55% reduction in mean severity score</td>
<td>Not reported</td>
</tr>
<tr>
<td>17 1996</td>
<td>CyA</td>
<td>Non-validated score including intensity and extent (mean change)</td>
<td>46% vs. 29% reduction in mean severity score at week 2 in high-dose vs. low-dose group</td>
<td>Herpes simplex infection ($n = 1$); Acute cholecystitis ($n = 1$); both in low-dose group</td>
</tr>
<tr>
<td>19 1996</td>
<td>CyA</td>
<td>SASSAD (mean change)</td>
<td>57% reduction in mean SASSAD</td>
<td>Not reported</td>
</tr>
<tr>
<td>18 1997</td>
<td>CyA</td>
<td>SASSAD (mean change)</td>
<td>39% reduction in mean SASSAD</td>
<td>Viral infection ($n = 1$); basal cell carcinoma ($n = 1$)</td>
</tr>
<tr>
<td>20 2000</td>
<td>CyA</td>
<td>SASSAD (AUC of mean scores)</td>
<td>About 50% reduction in mean SASSAD in both groups</td>
<td>17 events reported, but explicit information only on one case of folliculitis</td>
</tr>
<tr>
<td>31 2000</td>
<td>CyA</td>
<td>Non-validated score including intensity and extent (mean change)</td>
<td>58% vs. 48% reduction in mean severity in high vs. low-dose group</td>
<td>None</td>
</tr>
<tr>
<td>21 2000</td>
<td>CyA</td>
<td>Costa’s Index (mean change)</td>
<td>54% reduction in mean Costa’s Index</td>
<td>Not reported</td>
</tr>
<tr>
<td>23 2001</td>
<td>CyA</td>
<td>SCORAD (mean change)</td>
<td>58% reduction in mean SCORAD</td>
<td>Not reported</td>
</tr>
<tr>
<td>22 2001</td>
<td>CyA</td>
<td>Extent on 4-point Likert scale (assessed by patient) (mean change)</td>
<td>About 90% reduction in mean extent score</td>
<td>Not reported</td>
</tr>
<tr>
<td>30 2004</td>
<td>CyA</td>
<td>SCORAD (mean change)</td>
<td>Similar effectiveness in both treatment groups. cyclosporin group: 88% reduction in mean SCORAD</td>
<td>None</td>
</tr>
<tr>
<td>35 1984</td>
<td>Beclomethasone-dipropionate</td>
<td>Non-validated score including intensity and extent (mean change)</td>
<td>22% decrease in mean severity score</td>
<td>Not reported</td>
</tr>
<tr>
<td>42 1995</td>
<td>Flumisolide</td>
<td>Non-validated score including intensity and extent (mean change)</td>
<td>39% decrease in mean severity score</td>
<td>None</td>
</tr>
<tr>
<td>36 1993</td>
<td>INF-γ</td>
<td>Non-validated intensity score and BSA separately (mean change), no composite severity score</td>
<td>About 30% reduction in mean intensity of lesions, no significant differences between verum and placebo</td>
<td>Not reported</td>
</tr>
<tr>
<td>25 1993</td>
<td>INF-γ</td>
<td>Non-validated score including intensity, extent, and pruritus (relative individual response)</td>
<td>58% improved &gt; 50%; 21% improved &lt; 50%; 21% did not improve</td>
<td>None</td>
</tr>
<tr>
<td>24 1998</td>
<td>INF-γ</td>
<td>Costa’s Index (relative individual response)</td>
<td>34% improved &gt; 20%; 44% improved &lt; 20%; 22% did not improve</td>
<td>Not reported</td>
</tr>
<tr>
<td>Ref.</td>
<td>Year</td>
<td>Treatment</td>
<td>Outcome measure (clinical disease severity)</td>
<td>Results*</td>
</tr>
<tr>
<td>------</td>
<td>------</td>
<td>-----------</td>
<td>---------------------------------------------</td>
<td>----------</td>
</tr>
<tr>
<td>39</td>
<td>2000</td>
<td>INF-γ</td>
<td>Non-validated intensity score and BSA assessed separately (mean change)</td>
<td>45% vs. 33% reduction in mean intensity in high-dose vs. low-dose group, 51% vs. 37% reduction in mean extent in high-dose vs. low-dose group</td>
</tr>
<tr>
<td>26</td>
<td>1998</td>
<td>IVIG</td>
<td>Investigator global assessment on a 6-point Likert scale (relative individual response)</td>
<td>Slight improvement in 56%, no change in 22%, worsening in 11% of patients</td>
</tr>
<tr>
<td>40</td>
<td>2002</td>
<td>IVIG</td>
<td>SCORAD (mean change)</td>
<td>15% reduction in mean SCORAD; no statistically significant difference between groups</td>
</tr>
<tr>
<td>27</td>
<td>2002</td>
<td>IVIG</td>
<td>modified EASI (relative individual response)</td>
<td>67% (n = 4) improvement &gt; 50%, 17% (n = 2) no change, 17% (n = 1) worsening</td>
</tr>
<tr>
<td>29</td>
<td>2000</td>
<td>MMF</td>
<td>SCORAD (mean change)</td>
<td>68% decrease in mean SCORAD</td>
</tr>
<tr>
<td>28</td>
<td>2001</td>
<td>MMF</td>
<td>SCORAD (mean change)</td>
<td>55% decrease in mean SCORAD</td>
</tr>
<tr>
<td>41</td>
<td>2002</td>
<td>Azathioprine</td>
<td>SASSAD (mean change)</td>
<td>27% reduction in mean SASSAD</td>
</tr>
<tr>
<td>43</td>
<td>2005</td>
<td>Infliximab</td>
<td>EASI (relative individual response)</td>
<td>22% (n = 2) improvement &gt; 50%, 67% (n = 6) improvement &lt; 30%</td>
</tr>
<tr>
<td>33</td>
<td>1992</td>
<td>CHT</td>
<td>Non-validated severity scores of erythema and surface damage (mean change)</td>
<td>About 80% decrease in mean erythema score and in mean surface damage score</td>
</tr>
<tr>
<td>34</td>
<td>1992</td>
<td>CHT</td>
<td>Non-validated severity scores of erythema and surface damage (mean change)</td>
<td>About 67% decrease in mean erythema score; about 70% decrease in mean surface damage score</td>
</tr>
<tr>
<td>32</td>
<td>1999</td>
<td>CHT</td>
<td>Non-validated severity scores of erythema, surface damage, lichenification, and scaling (mean change)</td>
<td>No change in mean erythema score, other outcomes about 20% decrease in mean score; no statistically significant difference between groups</td>
</tr>
</tbody>
</table>

*In active treatment group: AE: atopic eczema; AUC: area under curve; BSA: body surface area; CHT: Chinese herbal therapy; Costa’s Index: Costa’s Index of severity of atopic dermatitis (70); CyA: cyclosporin A; EASI: Eczema Area Severity Index (72); INF-γ: interferon-gamma; IU: international units; IVIG: intravenous immunoglobulin; MMF: mycophenolate mofetil; SASSAD: Six Area Six Sign Atopic Dermatitis Score (69); SCORAD: Scoring atopic dermatitis Index (71).
Systematic review of systemic treatments for atopic eczema

Systemic glucocorticosteroids

Two small RCT evaluating systemic glucocorticosteroids in severe AE were identified (35, 42). In both studies only children were included. After 4 weeks of treatment with beclomethasone dipropionate (0.8 mg/kg oral + 0.4 mg/kg nasal) mean severity of AE decreased by 22%. One patient was withdrawn because of whooping cough (35). After 2 weeks of treatment with flunisolide (age-adjusted dose, see Table II) mean clinical severity could be reduced by 39%. Within the short observation period of 3 weeks after discontinuation of treatment no relapses (not defined) were observed (42). In both studies no SAEs were observed (35, 42) (Table II). No data was identified for prednisolone, which is the standard systemic glucocorticosteroid used in clinical practice.

Interferon-γ

Two RCT and 2 uncontrolled trials were identified on IFN (24, 25, 36, 39). Both RCT included adults and children treated for 12 weeks, did not meet important quality criteria, and did not use a composite score to measure clinical disease severity. IFN was superior to placebo in both RCT (36, 39) (Table II). Jang et al. (39) observed a positive dose-response relationship, with about 50% mean reduction in intensity and extent of AE lesions in the high-dose group (1.5 × 10^6 IU/m^2 body surface area (BSA) 3 times weekly). Hanifin et al. (36) reported a mean decrease in the intensity of AE lesions of about 30% (dosage: 1.5 × 10^6 IU/m^2 BSA/day). In both uncontrolled studies the IFN dosage was tapered off over a treatment period of 6 weeks (24, 25). In the study by Noh & Lee (24), which met all quality criteria, response rates were relatively low. A low serum IgE level was a positive predictor for response.

Intravenous immunoglobulins

Overall, the 3 small studies on IVIG eligible for this review did not show pronounced effectiveness (26, 27, 40). However, some of the patients studied in these trials were resistant not only to topical treatments, but also to systemic steroids and/or AZT (26, 27). Hypertension, haematuria, and transient serum creatinine increase were observed in one patient, serum sickness-like reaction in another patient treated with IVIG (26).

Mycophenolate mofetile

The evidence of the effectiveness of MMF in AE is limited to 2 uncontrolled studies including a total of 20 patients

<table>
<thead>
<tr>
<th>Ref. / Year</th>
<th>Treatment</th>
<th>Clear case definition</th>
<th>Validated outcome</th>
<th>Follow-up rate &gt; 80%</th>
<th>ITT analysis</th>
<th>Adequate randomization concealment</th>
<th>Adequate blinding procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>37/1991</td>
<td>CyA</td>
<td>●</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>38/1994</td>
<td>CyA</td>
<td>●</td>
<td>○</td>
<td>○</td>
<td>●</td>
<td>○</td>
<td>●</td>
</tr>
<tr>
<td>17/1996</td>
<td>CyA</td>
<td>●</td>
<td>○</td>
<td>○</td>
<td>●</td>
<td>○</td>
<td>●</td>
</tr>
<tr>
<td>19/1996</td>
<td>CyA</td>
<td>●</td>
<td>○</td>
<td>●</td>
<td>n.a.</td>
<td>n.a.</td>
<td>●</td>
</tr>
<tr>
<td>18/1997</td>
<td>CyA</td>
<td>●</td>
<td>○</td>
<td>●</td>
<td>n.a.</td>
<td>n.a.</td>
<td>●</td>
</tr>
<tr>
<td>20/2000</td>
<td>CyA</td>
<td>●</td>
<td>○</td>
<td>○</td>
<td>●</td>
<td>○</td>
<td>●</td>
</tr>
<tr>
<td>31/2000</td>
<td>CyA</td>
<td>●</td>
<td>○</td>
<td>●</td>
<td>n.a.</td>
<td>n.a.</td>
<td>●</td>
</tr>
<tr>
<td>21/2000</td>
<td>CyA</td>
<td>●</td>
<td>○</td>
<td>●</td>
<td>n.a.</td>
<td>n.a.</td>
<td>●</td>
</tr>
<tr>
<td>23/2001</td>
<td>CyA</td>
<td>●</td>
<td>○</td>
<td>●</td>
<td>n.a.</td>
<td>n.a.</td>
<td>●</td>
</tr>
<tr>
<td>30/2004</td>
<td>CyA</td>
<td>●</td>
<td>○</td>
<td>●</td>
<td>n.a.</td>
<td>n.a.</td>
<td>●</td>
</tr>
<tr>
<td>22/2001</td>
<td>CyA</td>
<td>●</td>
<td>○</td>
<td>●</td>
<td>n.a.</td>
<td>n.a.</td>
<td>●</td>
</tr>
<tr>
<td>35/1984</td>
<td>BMDP</td>
<td>○</td>
<td>○</td>
<td>●</td>
<td>●</td>
<td>○</td>
<td>●</td>
</tr>
<tr>
<td>42/1995</td>
<td>Flunisolide</td>
<td>●</td>
<td>○</td>
<td>●</td>
<td>○</td>
<td>○</td>
<td>●</td>
</tr>
<tr>
<td>36/1993</td>
<td>INF-γ</td>
<td>●</td>
<td>○</td>
<td>○</td>
<td>●</td>
<td>○</td>
<td>●</td>
</tr>
<tr>
<td>25/1993</td>
<td>INF-γ</td>
<td>●</td>
<td>○</td>
<td>●</td>
<td>n.a.</td>
<td>n.a.</td>
<td>●</td>
</tr>
<tr>
<td>24/1998</td>
<td>INF-γ</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>n.a.</td>
<td>n.a.</td>
<td>●</td>
</tr>
<tr>
<td>39/2000</td>
<td>INF-γ</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>n.a.</td>
<td>n.a.</td>
<td>●</td>
</tr>
<tr>
<td>26/1998</td>
<td>IVIG</td>
<td>○</td>
<td>○</td>
<td>●</td>
<td>n.a.</td>
<td>n.a.</td>
<td>●</td>
</tr>
<tr>
<td>40/2002</td>
<td>IVIG</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>●</td>
</tr>
<tr>
<td>27/2002</td>
<td>IVIG</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>n.a.</td>
<td>n.a.</td>
<td>●</td>
</tr>
<tr>
<td>29/2000</td>
<td>MMF</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>n.a.</td>
<td>n.a.</td>
<td>●</td>
</tr>
<tr>
<td>28/2001</td>
<td>MMF</td>
<td>●</td>
<td>●</td>
<td>●</td>
<td>n.a.</td>
<td>n.a.</td>
<td>●</td>
</tr>
<tr>
<td>41/2002</td>
<td>Azathioprine</td>
<td>●</td>
<td>●</td>
<td>○</td>
<td>●</td>
<td>○</td>
<td>●</td>
</tr>
<tr>
<td>43/2005</td>
<td>Infliximab</td>
<td>○</td>
<td>●</td>
<td>●</td>
<td>n.a.</td>
<td>n.a.</td>
<td>●</td>
</tr>
<tr>
<td>33/1992</td>
<td>CHT</td>
<td>●</td>
<td>○</td>
<td>●</td>
<td>○</td>
<td>○</td>
<td>●</td>
</tr>
<tr>
<td>34/1992</td>
<td>CHT</td>
<td>●</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>●</td>
</tr>
<tr>
<td>32/1999</td>
<td>CHT</td>
<td>●</td>
<td>○</td>
<td>●</td>
<td>○</td>
<td>○</td>
<td>●</td>
</tr>
</tbody>
</table>

●: quality criterion adequately met; ○: quality criterion not adequately met; n.a: not applicable; ITT: intention to treat analysis (44); CyA: cyclosporin A; BMDP: beclomethasone dipropionate; INF-γ: interferon-gamma; IVIG: intravenous immunoglobulins; MMF: mycophenolate mofetile; CHT: Chinese herbal therapy.
(Table I). After 8 and 12 weeks of treatment a mean decrease in disease activity by 55% and 68%, respectively, was observed (28, 29). One patient was withdrawn due to herpes retinitis, no other SAE were reported (28).

Azathioprine

Only one study on AZT met the eligibility criteria for this review (41). In a double-blind placebo-controlled cross-over RCT Berth-Jones et al. (41) observed a mean reduction in disease activity of 27% after 12 weeks of treatment with 2.5 mg/kg AZT. An ITT analysis was performed, so that the low follow-up rate appears less problematic. Four patients were withdrawn prematurely because of adverse events.

Infliximab

In a small uncontrolled study 9 patients were treated with infliximab 5 mg/kg at weeks 0, 2, and 6. At week 10 the relative individual benefit was more than 50% in only 2 patients, whereas disease activity decreased by less than 30% in 6 patients. One patient dropped out due to a serious infusion reaction (43) (Table II).

Chinese herbal therapy

Three double-blind placebo-controlled cross-over RCT evaluated the efficacy of standardized formulation of 10 herbs (Zemaphyte®, Phytopharm plc, Cambs, UK) (32–34). In these trials no composite severity score was used, so that the results cannot be reliably compared with other studies included in this review. Although the methodology was very similar in these 3 RCT, the results are conflicting: CHT was effective in the 2 studies from the UK, whereas no significant difference from placebo was observed in the study performed in Hong Kong (32–34). In the 2 studies mentioned first, the positive results might be explained by emigrative selection bias due to low follow-up rates and inadequate statistical methods (33, 34, 48).

DISCUSSION

Main findings on specific therapies

To date, CyA is the only systemic agent for which convincing evidence of effectiveness exists in patients with severe AE. All 11 studies we identified consistently showed substantial beneficial effects (17–23, 30, 31, 37, 38). We suggest using CyA for short-term or intermittent long-term therapy in patients resistant to topical anti-inflammatory agents such as glucocorticosteroids and calcineurin inhibitors. Dosages should be adjusted to minimum effective individual levels. Contraindications include hypertension, nephropathy, and history of skin or internal cancer (49–52).

AZT or IFN could be used for short-term treatment in patients who are not eligible for or unresponsive to CyA treatment. For these agents, evidence of the efficacy can be derived from RCT, although only a few patients were analysed in these studies. Compared with CyA, the benefit of AZT and IFN seems to be less pronounced (36, 39, 41). Although only one RCT evaluated its efficacy in patients with AE, AZT is frequently applied in clinical practice (53). AZT increases the risk of squamous cell carcinoma by generating mutagenic oxidative DNA damage (54, 55). Myelotoxicity of AZT is increased in patients with thiopurine methyl transferase (TPMT) deficiency. TPMT-based dosing of AZT seems to reduce toxicity without loss of efficacy (56, 57).

Although systemic glucocorticosteroids are frequently used for short-term therapy of AE in clinical practice there is insufficient evidence from clinical studies (35, 42). Studies including adult patients have not been published at all.

MMF might be a valuable treatment option, but evidence is restricted to 2 small uncontrolled studies (28, 29). From an evidence-based medicine perspective both IVIG and infliximab should be considered only in patients in whom disease activity cannot be sufficiently controlled with other systemic treatment options including CyA, systemic glucocorticosteroids, AZT, and IFN.

The results of the 3 RCT on CHT are conflicting. The 2 trials showing positive effects of CHT did not meet critically important methodological criteria: the end-points used are unvalidated and constructed qualitatively differently from the end-points applied in the majority of other studies reviewed (32–34, 48). Adequate comparison of the effectiveness of CHT and other agents is impossible. Zemaphyte® is a standardized preparation of therapeutic herbs for the treatment of AE. This is consistent with the concept of Western medicine: to treat certain diseases with certain substances. By contrast, traditional Chinese medicine prefers an individualized polypharmacology approach and emphasizes the importance of treating the whole individual rather than a certain diagnosis. Therefore, advocates of traditional Chinese medicine argue that this conceptual difference explains the failure of efficacy of Zemaphyte® in many patients (32). Reports of severe toxicity of CHT including fatal hepatitis highlight the significance of regularly monitoring patients treated with traditional Chinese medicine (58–60). Further well-designed, larger scale trials are required, but Zemaphyte® is no longer available.

Study quality

A major concern is that important quality criteria were not met in a high proportion of studies included in this review. High drop-out rates, imprecise case definition, inadequate statistical methods, inadequate randomiza-
tion concealment and/or blinding procedures, and unvali-
dicated outcome measurements are well-known threats
to internal validity (48). The use of many different,
in many cases unvalidated, outcome assessments for
disease severity was a major source of heterogeneity.
This was one reason why meta-analysis could not be
performed.

Limitations of this review

All systemic treatment options discussed are known to
be associated with potentially severe ADR (12, 49, 51,
61, 62). Small short-term clinical studies like most of
the ones discussed in this review are not appropriate
to evaluate long-term safety or rare ADRs. We used
withdrawals due to ADRs and SAEs as surrogate pa-
rameters for safety. Particular safety concerns were not
revealed. However, the reporting quality of adverse
events was inadequate in a high percentage of studies.
It is questionable whether all ADRs were disclosed.
Therefore, it was not possible to compare the benefit-
to-risk ratio of the different agents reviewed. Because
of potentially SAEs, systemic remedies should be
restricted to patients who do not adequately respond
to both topical therapies (first-line therapy for AE) and
phototherapy (second-line therapy) (10, 11, 63–66).
When administering systemic treatments in AE dif-
f erent goals may be pursued: to induce or to maintain
remission. Efficacy is typically defined as a drug’s
potential to decrease disease severity, i.e. its potential
to induce remission. Because most studies focused on
this aspect, our recommendations primarily relate to
induction of remission in severe AE.

Research recommendations

It is critically necessary to standardize outcome assess-
ments used in clinical investigation on AE. A core set of
outcomes for defined settings (e.g. RCT, clinical record
keeping) should be identified, e.g. using consensus meth-
ods (67). A standardization of outcome methodology
would enable us to approach many clinically important,
yet unanswered, questions, e.g. the additional benefit of
topical therapies and quantitative comparisons of the
effectiveness of different treatment options.

To clarify the relative importance of systemic gluco-
corticosteroids, comparative clinical studies, e.g.
against CyA, should be performed. In addition to ef-
ficacy this research should focus on relapse rates after
discontinuation of treatment, tolerability, additional
benefits of topical treatments, dosing regimens with
optimal benefit-to-risk ratio, and possible predictors of
treatment success. Additionally, studies on topical vs.
systemic steroids are encouraged.

Although the data on efficacy is convincing, CyA
may cause kidney damage and other ADR when used
as a long-term treatment. Therefore, we should evaluate
other treatment options with better safety profiles in
long-term RCT. Leflunomide might be such a therapeu-
tic alternative, but larger scale trials are required (68).

Because most studies included in this review looked
only at induction of remission, long-term studies on
remission maintenance are encouraged.

Implications for clinical practice

Current guidelines on the treatment of patients with
AE do not always reflect published evidence (10). The
International Consensus Conference on Atopic Derma-
ititis II (2003) suggested using systemic steroids,
CyA, methotrexate, or AZT for patients whose disease
is resistant to topical anti-inflammatory agents (10).
Although the evidence is very different for these treat-
ment options in terms of quality, quantity and results,
the consensus did not provide an algorithm for the
preference of systemic treatments for AE. Based on the
results of this systematic review, treatment guidelines
should be updated appropriately.

Conflict of interest: No conflict of interest to declare,

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