DOI: 10.1111/j.1468-3083.2012.04636.x JEADV

GUIDELINES

Guidelines for treatment of atopic eczema (atopic dermatitis) Part II

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Abstract

The existing evidence for treatment of atopic eczema (atopic dermatitis, AE) is evaluated using the national standard Appraisal of Guidelines Research and Evaluation. The consensus process consisted of a nominal group process and a DELPHI procedure. Management of AE must consider the individual symptomatic variability of the disease. Basic therapy is focused on hydrating topical treatment, and avoidance of specific and unspecific provocation factors. Anti-inflammatory treatment based on topical glucocorticosteroids and topical calcineurin inhibitors (TCI) is used for exacerbation management and more recently for proactive therapy in selected cases. Topical corticosteroids remain the mainstay of therapy, but the TCI tacrolimus and pimecrolimus are preferred in certain locations. Systemic immune-suppressive treatment is an option for severe refractory cases. Microbial colonization and superinfection may induce disease exacerbation and can justify additional antimicrobial treatment. Adjuvant therapy includes UV irradiation preferably with UVA1 wavelength or UVB 311 nm. Dietary recommendations should be specific and given only in diagnosed individual food allergy. Allergen-specific immunotherapy to aeroallergens may be useful in selected cases. Stress-induced exacerbations may make psychosomatic counselling recommendable. 'Eczema school' educational programs have been proven to be helpful. Pruritus is targeted with the majority of the recommended therapies, but some patients need additional antipruritic therapies.

Conflict of interest

A. Alomar has been speaker for Almirall, Astellas, Leti. T. Bieber has been advisor, speaker or investigator for ALK Abelló, Astellas, Bencard, Galderma, Glaxo SmithKline, Leo, Novartis, Stallergenes. U. Darsow has been speaker, investigator and/or been a member of advisory boards for Allergopharma, ALK Abelló, Bencard, GSK, Hermal, Novartis Pharma, Stallergenes, Stiefel. M. Deleuran has been a speaker, participated in clinical trials and/or been a member of advisory boards for Merck, Novartis, Astellas, Leo Pharma, NatImmune, Pergamum, Pierre Fabre and Janssen-Cilag. A.-H. Fink-Wagner received honorarium from Pharmaxis and Chiesi during the last 3 years and was employed before that by Nycomed. J. Ring has been advisor, speaker or investigator for ALK Abelló, Allergopharma, Almirall-Hermal, Astellas, Bencard, Biogen-Idec, Galderma, Glaxo SmithKline, Leo, MSD, Novartis, Phadia, PLS Design, Stallergenes. S. Ständer was or is advisor, speaker and/or investigator for Aesca Pharma, Almirall/Hermal, Astellas Pharma, Beiersdorf AG, Birken, Essex Pharma, GSK, Pierre Fabre, Maruho, 3M Medica, Mundipharma, Novartis Pharma, Serentis, and Serono. Z. Szalai is investigator of clinical trials for Astellas, Novartis, Pfizer, Abbott, Pierre Fabre. A. Taïeb has received consulting and clinical trial honoraria from Pierre Fabre, Astellas, Almirall/Hermal, Leo and Novartis. T. Werfel has been advisor, speaker or investigator for ALK Abelló, Astellas and Novartis. A. Wollenberg has received research funding and lecture honoraria from, conducted clinical trials for, or is a paid consultant to Astellas, Basilea, GSK, Loreal, Merck, Novartis, MSD. Other authors declared no conflict of interest.

Phototherapy

As most patients affected by AE improve during the sunny summer season, artificial UV radiation is frequently employed in the treatment of AE.

A recent study has confirmed that 74.4% of the patients affected by mild-moderate AE had complete resolution during summer holidays, 16.3% had improvement and only 9.3% had no modification of AE severity, confirming the seasonability of the disease, with improvement during summertime and worsening in the other seasons: More, seaside holidays produced a significantly greater improvement than mountains holidays, with complete resolution of the disease in 91.2% vs. 11.1% of patients ($P < 0.01$).[1] While this difference cannot be explained on the sole basis of UV exposure, these data support the hypothesis on the positive effect of UV radiation on AE.

Various pathways and means through which the energy of UV radiation from natural or artificial sources is ultimately transformed into biological effects within the skin have been suggested, including cutaneous sensory nerves, neuropeptides, neurotrophins and certain nerve-related receptors.[2] The known mechanism of action targets immunomodulation through apoptosis of inflammatory cells, inhibition of Langerhans cells and alteration of cytokine production.[3] In addition, UV has an antimicrobial effect reducing the colonization of *S. aureus*,[4] due to its anti-inflammatory effect and improves skin barrier.[5] A different explanation could be supported by the role of Vitamin D: a recent study demonstrated that a 2-week course of heliotherapy significantly improved vitamin D balance by increasing serum calcidiol concentration, and caused a marked healing of AE.[6]

Present UV sources include equipments able to emit selective spectres of radiations:

- UVA + UVB (approx. 280–400 nm).
- Broadband ultraviolet B (BB-UVB = approx. 280–320 nm).
- Narrow-band UVB (nbUVB = peak: 311–313 nm).
- UVA1 (340–400 nm).

Treatment with longer wavelengths has not been sufficiently studied for AE and should therefore not be applied. When prescribed, phototherapy is usually a part of a total treatment plan, i.e. a second-level treatment used especially in adults and much less in children. Phototherapy in children younger than 12 years should not be applied.

As a rule, phototherapy is not indicated in the acute stage of AE (except UVA1, which is also effective in managing AE flares), but is more apt to treat chronic, pruritic, lichenified forms and should not be prescribed in those patients who experience a worsening of their dermatosis during sun exposure. In practise, the choice of a certain UV treatment is limited by the availability of the phototherapy equipments: e.g. UVA1 devices are expensive to buy and to maintain. The biggest drawbacks of UV therapy are that the patient must travel between three and five times per week and for 6–12 weeks to a site that offers this therapy. In addition, UV light does not effectively treat hairy areas as scalp and skin folds.

In short, taking into account the individual tolerability, narrow-band UVB has been indicated for chronic moderate forms of AE[7] and is currently preferred to broadband UV because it is less erythemogenic, whereas high dose UVA1 has been prescribed for more severe phases.[8] Medium-dose UVA1 appears to be similar in terms of efficacy as narrow-band UVB.[9] Furthermore, as highlighted in a recent study, there is a small but significant proportion of psoriasis and AE patients who do not tolerate

narrow-band UVB, but demonstrate an excellent clinical response to broad-band UVB.[10]

Topical steroids and emollients should be considered at the beginning of phototherapy to reduce a possible flare-up, whereas topical immunosuppressors as tacrolimus and pimecrolimus should be avoided. UV can also be combined with a previous (oral or topical) administration of photosensitizing drugs (psoralens): the so called PUVA (photochemotherapy). All UV treatments and, even more, photochemotherapy pose a long-term risk for development of skin cancer, together with the proven prematurely ageing of the skin. UV therapy has to comply with special requirements with regard to personnel, documentation, UV protection especially of the eyes, contraindications and technical aspects. Photochemotherapy is not the first choice for AE because of the proven carcinogeneity and the fact that most AE patients are young. During systemic photochemotherapy, patients must wear UVA-blocking sunglasses and also after treatment for some time when exposed to sunlight because psoralens are eliminated slowly. Although simple UV regimens are generally well tolerated (a transient sensation of warmth should be considered normal), PUVA has a number of side effects, which may include nausea, headache, fatigue, burning skin, itching and irregular skin pigmentation as well as an increased risk of skin cancer,[11] so the risk-benefit ratio of this treatment must be carefully weighted. However, it has been demonstrated that PUVA provides a better short- and long-term response than medium-dose UVA1 in patients with severe AE.[12] It has been recently observed that PUVA therapy may reduce epidermal hyperinnervation of AE by normalization of axonal guidance molecules as semaphorin 3A and nerve growth factor in the epidermis.[13]

Photopheresis is used in some centres for treatment of selected cases. Possible effects in patients with severe refractory AE have been described.

New devices as 308 nm monochromatic excimer light expand the therapeutic options in patients with localized and therapy-resistant AE, even though they can treat only limited surfaces.[14,15] There are no prospective trials on AE patients comparing narrow-band UVB and UVA1 with more complex regimens, such as heliotherapy, balneophototherapy, psoralen plus UVA (PUVA) and extracorporeal photophoresis.[16] Pulsed-dye laser for the treatment of chronic AE is still experimental.[17]

In conclusion, phototherapy can improve and even clear AE; it can decrease bacterial colonization and reduce the strength and/or the amount of topical anti-inflammatory drugs needed, but the beneficial effects vary from person to person.

Recommendations

Narrow-band UVB is to be preferred to broad-band UVB (1a, A).

Medium-dose UVA1 is similar in efficacy as narrow-band UVB (1b, A).

High dose UVA1 is to be preferred in severe phases (1b, A).

Topical steroids and emollients should be considered at the beginning of phototherapy to reduce flare-up (C).

All UV treatments pose a long-term risk for development of skin cancer (2a, B).

PUVA therapy is not a first choice therapy. It provides a better short- and long-term response than medium-dose UVA1 (1b, A).

New devices as 308 nm excimer laser expand therapeutic options, but have been not assessed properly in AE (-, D).

Systemic immunosuppressive treatment

Oral glucocorticosteroids

Oral glucocorticosteroids are used in many European countries for treatment of AE. Well known side effects limit their use especially for long-term treatment. Funding of expensive clinical trials in the near future is unlikely.

Controlled clinical trial data demonstrating efficacy There is one controlled trial available that demonstrates equal efficacy of therapy with systemic glucocorticosteroids as ciclosporin.[18] Broad experience from clinical use by many experts indicates efficacy.

Evaluation summary Short-term treatment with oral glucocorticosteroids is effective (-, D).

Recommendations

Systemic steroids have a largely unfavourable risk/benefit ratio for treatment of AE. (-, D).

Short-term (up to 1 week) treatment may be an option to treat an acute flare in exceptional cases of atopic eczema. Restrictive use, largely limited to adult patients with severe atopic eczema, is recommended (-, D).

The recommended daily dose should be adjusted to body weight.

Long term use in AE patients is not recommended. The indication for oral steroids in children should be handled even more cautiously than in adults (-, D).

Ciclosporin A

Ciclosporin is licenced in many European countries for treatment of AE. Ciclosporin inhibits the production of NF-AT dependent proinflammatory cytokines in T cells.

Controlled clinical trial data demonstrating efficacy

Ciclosporin vs. placebo – meta-analysis A meta-analysis of pooled data from eight RCTs[19] clearly demonstrated the efficacy of ciclosporin in AE. Body surface area, erythema, sleep loss and glucocorticosteroid use were reduced in the ciclosporin group. The authors concluded that ciclosporine is more effective than placebo, but there is prompt relapse if ciclosporin is stopped. All scores are back to pretreatment values 8 weeks after end of ciclosporin therapy.

Three RCTs have been published after this meta-analysis:[19]

Ciclosporin dosis finding study for AE treatment in adult patients A fixed dosage ciclosporin regimen was evaluated in 106 adults with severe AE.[20] Initial treatment was performed with 300 mg/day or 150 mg/day and reduced after 2 weeks to 50% of the initial daily dose until a final evaluation was performed after 8 weeks. Clinical efficacy was detectable after 2 weeks in both treatment groups, but the higher dose was significantly more effective ($P < 0.05$). The authors recommended to start therapy with 150 mg/day because this regimen showed a lower incidence of serum creatinine increase.

Continuous or intermittent ciclosporin therapy study of AE in children Forty children aged 2–16 years were randomized to either a continuous long-term or an intermittent short-term ciclosporin regimen.[21] Both groups showed significantly better results in clinical scores and quality of life assessments. Enhanced sustained improvement was seen in the continuously treated group. As the intermittent therapy was sufficient in some patients but associated with a lower cumulative ciclosporin dose, the authors recommended choosing the regimen on an individual basis.

Ciclosporin or UV Therapy for AE Ciclosporin was tested against a combined UVA/UVB regimen in a 1 year, open label, multicenter trial involving 72 patients.[22] Ciclosporin therapy induced a significantly higher number of days in remission, as compared to UV therapy.

Compounding of Ciclosporin Microemulsions of ciclosporin show an earlier onset and higher peak value of efficacy compared with traditional formulations.[23] The clinical efficacy evaluated after 8 weeks of therapy was identical for both formulations.

Drug safety profile of ciclosporin Patients receiving ciclosporin should be monitored for blood pressure and renal parameters, as ciclosporin is known to induce structural and organic kidney damage. Nephrotoxic effects are more likely to occur if the daily dose exceeds 5 mg/kg body weight, serum keratinine values are elevated or elderly patients are treated.

Summary of evidence-based data Many RCTs indicate the efficacy of ciclosporin vs. placebo in AE (1a, A).

The duration of therapy is guided by clinical efficacy and tolerance of the drug. Both short-term and long-term therapy may be useful in AE (-, D).

Dose reduction should be considered according to clinical efficacy. Long-term treatment prescribing the lowest clinically useful dose may be advisable in selected cases (-, D).

Side effects of cyclosporin argue against a long-term treatment of AE with ciclosporin – cessation of therapy should be attempted after 2 years of therapy (-, D).

Self-willed reduction in the recommended ciclosporin dose may reduce the clinical efficacy of ciclosporin and is not recommended (2b, B).

A microemulsion of ciclosporin has the advantage of an earlier onset and peak level of clinical efficacy, which may be useful in short-term treatment (1b, A).

Ciclosporin is effective in children and adolescent atopic eczema patients (2b, B). As an intermittent dosage regimen will lead to lower cumulative doses of ciclosporin and is effective in some AE patients, an individualized dosage regimen is recommended for underage patients (-, D).

Long-term intermittent ciclosporin therapy for 1 year is more effective than an intermittent UVA/UVB therapy following a two to three time weekly regimen (1b, A).

Recommendations

Ciclosporin may be used in chronic, severe cases of AE in adults (1a, A).

Well known side effects of ciclosporin limit its use in AE (-, D).

An initial daily dose of 2.5–3.5 mg/kg/day and a maximal daily dose of 5 mg/kg/day, divided upon two single doses, are recommended. A dose reduction of 0.5–1.0 mg/kg/day every 2 weeks is recommended, as indicated by clinical efficacy (-, D).

Ciclosporin trough levels do not need to be assessed during therapy (-, D).

Ciclosporin may be used 'off label' in children and adolescent patients showing a refractory or severe course of disease (2b, B). A detailed patient monitoring, especially of the renal status, is advisable.

Although there are no controlled studies available regarding the efficacy of vaccination during ciclosporin therapy, there is no evidence for a failure during ciclosporin either. Hence, a traditional cessation of therapy of 2 weeks before and 4–6 weeks after vaccination seems possible. Clinically, there is no evidence for this recommendation (-, D).

A combination therapy of ciclosporin with UV therapy is not indicated because the incidence of cutaneous malignancies may be increased (-, D).

Azathioprine

Azathioprine is used since many years in Great Britain and the United States for treatment of AE in adult patients. Funding of expensive clinical trials in the near future is unlikely.

Controlled clinical trial data demonstrating efficacy Efficacy of azathioprine was tested in a randomized, controlled, 6-month, crossover clinical trial involving 37 patients aged 17–73 years.[24] The drop-out rate was high (12 patients on azathioprine, 4 patients on placebo). Azathioprine (2.5 mg/kg bw/day) or placebo was given for 3 months each in a crossover design. The SASSAD skin severity score was reduced by 26% in the azathioprine group and

3% in the placebo group ($P < 0.01$). Pruritus, sleep loss and fatigue improved significantly during azathioprine but not during placebo treatment.

Another randomized double-blinded, placebo-controlled, 12 weeks, clinical trial involved 63 outpatients with AE.[25] Following a low dose introduction phase, azathioprine was dosed in 42 patients according to the results of a thiopurine methyltransferase (TPMT) polymorphism, which may be indicative for the myelotoxicity of azathioprine – the other 21 patients received placebo. Patients with a normal TPMT activity were treated with 2.5 mg/kg bw/day azathioprine, whereas patients with a reduced TPMT activity (heterozygous phenotype) received 1.0 mg/kg bw/day azathioprine. The azathioprine regimen was clearly effective in AE, as the disease activity dropped by 37% in the azathioprine group and by 20% in the placebo group. None of the patients showed myelotoxic symptoms.

A retrospective, uncontrolled study investigated 48 children and adolescents aged 6–16 years diagnosed with severe AE.[26] After 3 months of therapy, 28 patients showed very good and 13 patients showed good improvement of their symptoms, whereas 7 patients showed little or no improvement. None of the patients showed myelotoxic symptoms, TPMT activity was determined in all patients before treatment. All patients were started on 2 mg/kg bw/day and the dose was increased to 3 mg/kg bw/day in 14 patients due to insufficient clinical response. The mean time to achieve clinical response was 4 weeks.

A retrospective, uncontrolled study in a heterogenous group of 17 children and adults from Hong Kong with a mean age of 16 years showed significant improvement of SCORAD after 3 and 6 months and significant reduction in total serum IgE levels.[27]

Drug safety profile of azathioprine The authors of the Berth-Jones study concluded that azathioprine would be an effective and clinically useful drug for treatment of severe AE, but would be associated with a high rate of unwanted drug effects.[24] Leucocyte counts and liver enzymes must be controlled during therapy. The higher dose caused gastrointestinal symptoms in 14 patients; leucopenia in two and elevated liver enzymes in eight patients.

Summary of evidence-based data Azathioprine is effective for treatment of severe atopic eczema (1b, A).

Recommendations

Azathioprine may be used (off label) in AE patients, if ciclosporin is either not effective or contraindicated (1b, A).

Patients should be screened for TPMT activity before starting azathioprine therapy to reduce the risk for bone marrow toxicity by dose adaptation. The suggested dose range is 1–3 mg/kg bw/day (1b, A).

There are no published prospective clinical trial data regarding treatment of children and adolescents (-, D).

Mycophenolate mofetil (MMF)

Mycophenolate mofetil is an immunosuppressant drug licenced in many European countries for treatment of systemic lupus erythematosus and prevention of transplant rejection.

Controlled clinical trial data demonstrating efficacy There is one controlled trial with enteric-coated MMF vs. Ciclosporin A as long-term treatment showing almost equal efficacy.[28]

In addition, uncontrolled trial data and some case reports indicate its clinical efficacy in AE.[29,30]

There is one uncontrolled retrospective report involving 14 children indicating efficacy in this age group[31]: MMF 40–50 mg/kg/day in younger children and 30–40 mg/kg/day in adolescents.

Drug safety profile of MMF Gastrointestinal adverse events, such as nausea or diarrhoea, are the most relevant side effect of MMF. They are most common during initiation of treatment and tend to disappear during long-term treatment. Leucopenia or thrombopenia may also occur.

Summary of evidence-based data Positive case reports and uncontrolled clinical trial data indicate that MMF may be effective in AE (4, C).

Recommendations

MMF may be used (off label) for treatment of AE in adults in a dose up to 2 g/day, if ciclosporin is not effective or not indicated (4, C). There are no trial data for its use in children or adolescents (-, D).

Methotrexate (MTX)

The immunosuppressant MTX is frequently used in psoriasis, but there are only little published data on its use in AE. Some clinicians are using this drug in AE with good success since many years. Funding of expensive clinical trials in the near future is unlikely.

Controlled clinical trial data demonstrating efficacy A randomized trial with MTX vs. Azathioprine showed comparable effects in severe atopic eczema.[32]

An open 24-week dose escalation clinical trial involving 12 adult patients investigated the efficacy of increasing doses MTX.[33] The starting dose of 10 mg/week was increased weekly in steps of 2.5 mg/week until clinical efficacy was seen. The skin score SASSAD improved by 52% during 24 weeks. The median dose administered was 15 mg MTX/week. Improvement remained stable in nine patients 12 weeks after the end of treatment.

An uncontrolled, retrospective report involving 20 adult AE patients treated with 10 mg/week to 25 mg/week MTX showed response in 16 patients after 8–12 weeks.[34] First improvement was observed after a period ranging from 2 weeks to 3 months (mean

9.95 ± 3.17 weeks). Treatment was more effective in adult onset AE than in childhood onset.

Drug safety profile of MTX Drug safety data for MTX are largely derived from clinical experience from other low dose indications for MTX, indicating liver toxicity and teratogenicity as main areas of concern. There are no AE specific safety data available for MTX.

Summary of evidence-based data An open, uncontrolled clinical trial indicates that MTX may be effective in AE (4, C).

Recommendations

MTX may be used (off label) for treatment of AE in adults, if ciclosporin is not effective or not indicated (4, C). There are no trial data for its use in children or adolescents (-, D).

Interferon gamma (IFN-γ)

Some interferons may interact with the dystorted immune system of AE patients. IFN gamma (IFN-γ) is a TH1 cytokine which has been shown to antagonize TH2 immune responses *in vitro*.

Controlled clinical trial data demonstrating efficacy A 12-week multicentric study involving 83 patients aged 2–65 years compared the efficacy of subcutaneous injection of 50 mg/m^2 IFN-γ with placebo in AE patients, who were allowed to continue topical glucocorticosteroid treatment.[35] Significantly more IFN-γ treated patients showed 50% improvement of the skin score compared with placebo. Erythema and scratch marks were significantly reduced by 30%, whereas induration, dryness, itch and lichenification were not.

A high dose (1.5 Mio IE) and a low dose (0.5 Mio IE) three times weekly IFG-g regimen were compared with placebo in 51 severe AE patients.[36] Both IFG-g regimen had improved the AE after 12 weeks as compared to placebo, but there was no difference between both IFN-γ treatment arms.

A randomized, prospective case–control study involving 44 AE patients treated with IFN-α, IFN-γ, thymopentin or null therapy.[37] IFN-α was effective in 11 of 13 treated patients, whereas IFN-γ showed improvement in 2 of 10 patients. Thymopentin and null therapy were ineffective.

Drug safety profile of IFN-γ The high rate of IFN-γ induced unwanted drug effects included headache (60%), muscle pain (32%) and fever (39%), all of which were significantly more frequent compared with placebo.

Summary of evidence-based data IFN-γ seems to be moderately effective in adult patients with severe AE (1b, A).

Some uncontrolled observations and empirical knowledge do not confirm the efficacy data from clinical trials (-, D).

The high rate of unwanted drug effects and the high treatment costs are limiting the potential use of IFN-γ in chronic diseases (-, D).

Recommendations

IFN-γ and IFN-α should not be used for treatment of AE (-, D).

Alitretinoin

Alitretinoin is a retinoid binding both retinoid and rexinoid receptors, thus delivering anti-inflammatory and antiproliferative effects. It is licenced in some European countries for the treatment of chronic hand eczema irrespectively of its pathogenesis.

Controlled clinical trial data demonstrating efficacy

There is one large, multicentric randomized, placebo-controlled clinical trial involving 1032 patients with chronic hand eczema, about one third of which are probably atopic hand eczema patients.[38] Improvement of eczema symptoms was seen in 75% of the patients. The response rate of hyperkeratotic hand eczema (49%) and pulpitis sicca type patients (44%) was higher than the dyshidrosiform subtype of hand eczema (33%). The patient group suffering from atopic hand eczema has not been analysed separately, and extrapalmar symptoms have not been assessed in this trial.

Six patients with AE and prominent hand involvement have been treated with alitretinoin for 12 weeks in an uncontrolled, open label trial.[39] Palmar and extrapalmar lesions improved during the trial, as shown by the mTLSS hand eczema score and the SCORAD.

Drug safety profile of alitretinoin As alitretinoin is teratogenic, all women of childbearing potential must adhere to a strict birth control programme. Headache is the most frequent clinical side effect of alitretinoin, especially in the first 2 weeks of treatment. Serum lipid and TSH elevation may also occur.

Summary of evidence-based data Direct evidence from an uncontrolled clinical trial, as well as indirect evidence from a large, double-blinded, placebo-controlled clinical trial indicates that alitretinoin may be effective in atopic hand eczema (4, C).

Recommendations

Alitretinoin may be used for atopic hand eczema in adult patients of non-child-bearing potential unresponsive to topical steroid therapy (1b, A).

Bystander improvement of extrapalmar AE lesions is likely, if alitretinoin is used to treat chronic hand eczema (4, C).

There are no trial data for its use in children or adolescents (-, D).

Biologics

Biological agents (Biologics) present a relatively new group of therapeutics created by using biological processes that include

recombinant therapeutic proteins, such as antibodies or fusion proteins. Biologics specifically target inflammatory cells and mediators. In AE, biologics are used to reduce inflammation by modulating the number, activation and function of immune cells or the action of cytokines or disease relevant antibodies. A number of case reports, pilot studies and retrospective analyses on the effect of biologics in patients with moderate to severe AE refractory to topical and/or systemic therapy have been published recently. However, representative, randomized, placebo-controlled studies evaluating the efficacy and safety of biologics in AE are still not available.

T cells play a key pathogenic role in AE therefore targeting their activation is a major approach of biologics. Alefacept is a fusion protein of lymphocyte function protein (LFA)-3 (CD58) and immunoglobulin (Ig) G that inhibits costimulation and induces apoptosis of T cells. A 12-week course of alefacept 15 mg weekly was reported to significantly reduce skin symptoms, pruritus and concomitant topical steroid therapy.[40] Another study demonstrated a clinical improvement in six of nine patients.[41]

The anti-CD11a antibody efalizumab shown to be effective in AE by blocking the recruitment of T cells is no longer available because of the risk of progressive multifocal leukoencephalopathy (PML). Whereas early observations stated a significant improvement upon efalizumab therapy,[42] a recent retrospective analysis revealed a slight effect in 5–11 patients only.[43] The depletion of B cells by an anti-CD20 antibody, rituximab (2 × 1000 mg), resulted in a rapid reduction in skin inflammation in all patients with a sustained effect over 5 months in five of six patients. These results suggest a pathogenic role of B cells in AE.[44] However, a report on two cases of severe AE receiving rituximab could not confirm these findings.[45]

Inflammation in AE is characterized by a T-helper 2 cytokine expression including interleukin (IL) –5 and eosinophil infiltration. Upon short-term therapy with the anti-IL-5 antibody mepolizumab (2 × 750 mg), a moderate improvement of clinical symptoms was observed, although a rapid depletion of eosinophils in the peripheral blood was noted.[46] Mepolizumab had no effect on atopy patch test reactions.[47] Based on the promising results in AE and the experiences in bronchial asthma therapy, long-term trials with anti-IL-5 antibodies seem indicated.

The majority of AE patients has elevated serum IgE levels, but the pathogenic role of IgE in AE remains unknown. First case reports gave inconsistent results on the effect of anti-IgE antibody (omalizumab) treatment in severe AE.[48,49] Upon low-dose anti-IgE therapy (10 cycles of 150 mg), 6 of 11 AE patients with serum IgE levels >1000 kU/L before therapy responded as shown by a decrease of SCORAD more than 50% in two and between 25% and 50% in four patients.[50] However, in a placebo-controlled study in 20 patients, omalizumab administered for 16 weeks failed to improve AE symptoms and itch despite a depletion of free serum IgE and reduction in IgE receptor saturation.[51] Recent studies reported that accompanying AE significantly improved in patients receiving omalizumab because of severe bronchial asthma.[52–54]

Anti-TNF-alpha (infliximab) has been shown to significantly decrease skin symptoms and pruritus in patients with severe AE during induction therapy.[55] However, a sustained improvement was seen only in two of nine patients during maintenance therapy.[55] A patient with severe AE and concomitant contact allergy responded well to anti-TNF-alpha.[56] To note, some authors observed AE-like skin eruptions in patients treated with anti-TNF-alpha,[57,58] whereas others did not.[59]

None of the biologics has been approved for the therapy of AE yet. At present, the use of biologics in AE is advisable only in patients with severe AE refractory to other topical and/or systemic treatment. Beside the lack of efficacy and safety data in AE, the potential side effects as well as the costs have to be taken in account before using biologics. On the other hand, treatment with biologics provides important information on pathogenic mechanisms in AE. Today, more biologics are under investigation for treatment of allergic diseases.

Recommendations

In patients with severe AE refractory to topical and systemic treatment, a therapy with biologics (omalizumab, rituximab or alefacept) can be considered (4, C).

Allergen-specific immunotherapy (ASIT)

The efficacy of specific immunotherapy in AE has been shown in a number of case reports and smaller cohort studies,[60] (reviewed by Darsow *et al.*[61]) and more recently in a larger multicenter trial with subcutaneous house dust mite immunotherapy.[62] Due to these data it became clear that ASIT can be applied for the treatment of allergic rhinitis or mild asthma also in those patients who suffer in addition from AE as eczema was obviously not worsened during or after ASIT. More and larger prospective studies are now being performed which shall respond to the question whether AE alone may be an indication for the initiation of ASIT. Experience in a pair of monozygotic twins with AE (with spring and summer exacerbations) treated either with grass pollen ASIT or placebo in a double-blind fashion showed significant improvement and decrease in serum IgE in the patient treated with ASIT.[63] Several open uncontrolled study designs also demonstrated advantages of ASIT in patients with AE, these data were often published in national or non-anglosaxon journals. Some investigators in the 1970s and 1980s also showed improvement of AE in controlled trials (review[61]). A double-blind controlled trial of ASIT with *Dermatophagoides pteronyssinus* in children with AE was published in 1992 by Glover and Atherton[63a] This study failed to demonstrate superiority over placebo after a standard 8 months' course of treatment with tyrosin-adsorbed house dust mite extracts in 24 children with AE and immediate hypersensitivity to this allergen. However, in a second study phase children were randomly allocated to continue with active treatment or

placebo for a further 6 months. The numbers were too small to permit confident conclusions, but the clinical scores suggested that prolonged hyposensitization may be more effective than placebo with regards to several objective parameters of eczema severity. The authors noted that a high placebo effect led to problems in comparing the active treatment. In the placebo-controlled study of Kaufman and Roth,[64] the skin condition of 13 of 16 treated patients improved, whereas only in 4 of 10 placebo-treated patients this effect was noted. Similar results were reported by Warner *et al.*[65] and Zachariae *et al.*[66] showing improvement of eczematous skin lesions under ASIT with house dust mite extracts.

Oral ASIT for *D. pter.* was not effective in a controlled study enrolling 60 children with AE which were followed for 3 years.[67] In contrast, Mosca *et al.*[68] could show the effect of s.c. conventional ASIT ($n = 41$; 76% improved) and sublingual route immunotherapy (SLIT; $n = 48$; 64% improved). This study also reported on medication used and adverse drug reactions. The latter occurred in 15–20% (both groups). Mastrandrea[69,70] reported a 6-year study in 35 selected AE cases undergoing SLIT, with average 72% remission of AE after 2 years. However, this observational study also lacked a control group. Pajno *et al.*[71] performed a controlled study applying SLIT with house dust allergens in children with AE. The outcome of this intervention was positive only in patients with mild-to-moderate AE but not with severe AE.

Noh and Lee[72] reported in a pilot study the improvement of AE together with changes in T-cell subpopulations induced by IFN-γ pretreatment before ASIT with house dust mite allergens. Patients receiving placebo, IFN-γ only or ASIT only showed no treatment effect.

Werfel *et al.*[62] investigated 89 patients with AE showing a sensitization to house dust mite (CAP-FEIA > 4). Patients were injected weekly with three different doses of HDM allergen extract. With higher allergen doses, a beneficial SCORAD decrease occurred after 8 weeks compared to a control group with very low allergen dose. The effect was maintained over 1 year and was accompanied by lower glucocorticosteroid use. A smaller DBPC study involving 20 patients with HDM- or grass pollen sensitization also showed objective and subjective symptom relief[73] under ASIT.

Even if the results of the studies are interpreted very carefully with regard to the therapeutical effects of ASIT, it is remarkable that exacerbations of the skin disease during this specific treatment were rare. In contrast, the treatment was well tolerated in most patients. The same was true for studies in patients with coexistent AE who were treated with ASIT for respiratory atopic diseases and experienced not more often flares of eczematous skin lesions. One also has to keep in mind that eczema flares were seen in the control or placebo groups, too.

The role of allergens in the pathophysiology of AE has been proven in controlled studies on allergen avoidance and atopy patch testing.[74–76] In respiratory atopic diseases, ASIT plays an important role not only for treatment but also for the prevention of further sensitizations and progress to more severe respiratory disease (change from rhinitis to bronchial asthma).

Hypothetically, patients with a positive atopy patch test and corresponding history of eczema flares may be candidates for ASIT with the eliciting allergen. The performed studies point to the safety of ASIT also in AE, if the treatment is performed according to the guidelines. However, the final judgement on the efficacy of ASIT in this diagnosis is still not possible due to the lack of large, controlled and randomized clinical trials with modern allergen vaccines.[61] As ASIT works in the sense of a biological response modifier, it may require a longer time to exert all its effects on inflammatory reactions as usually selected for pharmacotherapeutic trials.[69] The issue of combining ASIT with immunomodulating (pre) treatment may also deserve further investigations in AE patients. Thus, the addition of anti-IgE treatment (with a monoclonal, commercially available antibody) to ASIT has been shown to result in increased improvement in patients with respiratory atopy.[77]

Recommendations

ASIT may have positive effects in selected, highly sensitized patients with AE. The best evidence so far is available for ASIT with house dust mite allergens (2a,B).

There is no contraindication of performing ASIT in patients with respiratory allergic diseases (allergic rhinoconjunctivitis, mild allergic bronchial asthma) associated with AE (2b,B).

Complementary and alternative medicine in atopic eczema

There is evidence of growing interest of so called complimentary alternative medicine (CAM) as treatment for AE.[78–80] This chapter summarizes the available RCT-based evidence on specific treatment modalities.

For that purpose the electronic database PubMed was systematically searched for available randomized, controlled trials of complementary, alternative treatment modalities used for AE. The search covered the period from 1966 up to October 2009 and included the terms 'atopic dermatitis or eczema' and 'complementary or alternative medicine' as well as specific modalities, such as 'acupuncture, homeopathy, bioresonance or phytotherapy'. Statements for the consensus process are given in bold letters at the end of each chapter. If not specified otherwise these are based on RCT (1a) evidence.

Definition

CAM has been defined as 'diagnosis, treatment or prevention which complements mainstream medicine by contributing to a common whole, by satisfying a demand not met by orthodoxy or by diversifying the conceptual frameworks of medicine'.[79]

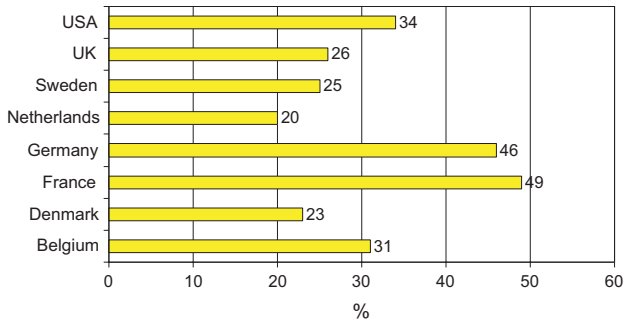

Figure 1 Results from population-based studies reporting use of complementary medicine (% of patients) in the USA and selected European countries.[82]

The underlying concept, rationale and practise of the different CAM modalities will not be described in detail. The interested reader is kindly referred to the corresponding literature.[81]

Usage of CAM in the general population

With respect to single countries, France (49%) and Germany (46%) seem to exhibit the highest usage of CAM in Europe[82] (Fig. 1). The growing interest in CAM in the public was demonstrated by a study from the United States, indicating an increase in the usage of CAM from 33.8% to 42.1% between 1990 and 1997.[83] A recently published telephone survey of the British Broadcasting Corporation revealed that 20% of a random sample of 1204 adults reported experiences with CAM in the preceding year.

Usage of CAM for AE or allergies

A few studies have investigated the patterns of use of CAM in patients with AE or related disorders. A study from Switzerland investigated 202 inpatients with atopic disorders of which 37% claimed to have used CAM previously. The most frequently used techniques were homoeopathy (48%), diet (35%) and herbalism (28%), autologous blood injection (28%), phytotherapy (20%) and acupuncture (18%).[84]

A study from Norway investigated 444 inpatients with AE of which 51% reported the previous use of CAM. The most popular modalities were homoeopathy (34%), herbalism (19%), food supplements (18%), diet change (18%) and acupuncture (11%).[85]

A German population-based telephone survey in adults with allergies revealed that 26.5% have used CAM.[86] The most common procedures were homoeopathy (35.3%), autologous blood injection (28.1%), acupuncture (16.6%) and bioresonance (10.0%).

Utilization of CAM by dermatologists

A British health service research survey compared the treatment patterns of dermatologists in Japan, the USA and the UK.[87] The highest prevalence of utilization of CAM was reported by Japanese dermatologists (27%). Interestingly, dermatologists over 45 years of age prescribed CAM significantly more often in the UK and the USA.

Specific CAM modalities

Essential fatty acids With respect to polyunsaturated fatty acids (PUFA), a distinction should be made between ω-3 acids like eicosapentaenoic acid and their metabolites and ω-6 acids like arachidonic acid and the corresponding metabolites. The supplementation with ω-3 fatty acids is based on the assumption that the inflammatory profile of ω-6 fatty acids and their metabolites is higher than that of ω-3 fatty acids and their metabolites and that the supplementation with ω-3 fatty acids shifts the metabolic pathway towards less inflammatory metabolites. ω-3 PUFA were studied in oral and topical administration in patients with AE. The most commonly used preparations were eicosapentaenoic acids, evening primrose oil (containing 8–10% GLA, Epogam®, Strathmann GmbH, Hamburg, Germany), borage oil (containing at least 23% GLA) and fish oil. The systematic review of treatments for AE published in 2000 summarizes available RCT evidence of supplementation with essential fatty acids.[19] The authors describe a meta-analysis of 9 RCTs[88] and another large study conducted by Bamford *et al.*[89] The meta-analysis concluded that primrose oil has a modest beneficial effect. However, several trials had not been made available to the public at this stage, which made a critical methodological appraisal impossible. Results of the two largest and well-reported studies on evening primrose oil could not show an effect superior to placebo. The further 9 published RCTs have given conflicting evidence. Further meta-analyses and systematic reviews on evening primrose oil and GLA supplementation are under way.

In a trial published by Ring and Kunz, 17 patients were treated with eicosapentanoeic acids or placebo over 3 months.[90] At the end, all clinical parameters had improved significantly in both with a slight superiority for placebo.

A study from India failed to show significant therapeutic effects of primrose oil 500 mg/day compared to 300 mg/day sunflower oil delivered in capsules over 5 months.[91]

Beside four smaller trials,[92–95] giving conflicting results, there are only two other reported RCTs on the use of borage oil in atopic eczema. In the trial published by Henz *et al.*,[96] 160 adult patients were treated with borage oil containing capsules or placebo over a 24 weeks period. No significant differences concerning the clinical response as a function of corticosteroid usage was found. However, subgroup analyses by centres or patients who demonstrated an increase in erythrocyte dihomo-γ-linolenic acids revealed significant results in favour of supplementation with borage oil. This might indicate a beneficial effect on those who absorb and metabolize GLA and justifies further trials.

A total of 140 patients, including 69 children, were treated by an English working group with either borage oil capsules or placebo over 12 weeks. No significant differences in severity, symptoms, global assessment or use of medication were observed.[97]

A study from Berlin compared the daily administration of 5.4 g docosahexaenoic acid (DHA) in 21 patients who completed the trial with an isoenergetic control of fatty acids ($N = 23$) over 8 weeks. The SCORAD dropped significantly in the DHA group, however, significant differences to control were not observed.[98]

In a comparison of dietary hempseed oil with olive oil, some parameters of skin physiology and symptoms improved under hempseed oil, but obviously without significant difference to the control group.[99]

A recent randomized trial in 20 hospitalized patients with AE comparing infusions of fish oil to soybean oil revealed marked improvements within 1 week in both groups, but a significantly greater effect in those treated with fish oil.[100] Some smaller RCTs have also indicated a beneficial effect,[101–103] although the largest and well-reported trial could show no difference between the fish oil and the placebo.[104]

Primrose oil has also been used as topical treatment. Although the pilot study has indicated some beneficial effects,[105] further studies were unable to establish a dose response relationship.[106] Further studies could not prove a beneficial effect on skin barrier function.[107] However, large trials on that issue are lacking.

Recommendations

There is not enough evidence to support the use of oral or topical applications of unsaturated fatty acids in the treatment of AE.

Phytotherapy

Herbal remedies are used either orally or topically since a long time also for skin diseases, mainly because of their anti-inflammatory and itch-relieving capacity. Detailed background information on herbal therapy in dermatology is summarized in a recent review.[108] Concerning the topical use we identified two RCTs investigating the efficacy and safety of a chamomile preparation[109] and a cream containing hypericum extract respectively.[110] The chamomile extract containing commercial cream Kamillosan® (MEDA Pharma GmbH, Bad Homburg, Germany) was compared to either 0.5% hydrocortisone cream or vehicle cream in a half-side comparison in 69 patients with AE. With respect to the major outcome parameters pruritus, erythema and desquamation, Kamillosan® was moderately superior to 0.5% hydrocortisone after a 2 week treatment and not different to the vehicle cream. Results of statistical analysis were not given in this publication. The cream containing hypericum extract standardized to 1.5% hyperforin was compared with the corresponding vehicle cream in a half-side comparison in 18 patients with mild-to-moderate AE. Over 4 weeks the modified SCORAD index improved with both therapies, but the improvement was significantly higher under active treatment. This promising result should be confirmed by larger trials and in comparison with topical standard therapy.

A further study compared a topical preparation of Mahonia aquifolium, Viola tricolor and Centella asiatica with the vehicle cream in 88 patients and could not find significant differences.[111] A subgroup analysis revealed superiority of the plant preparation under dry and cool weather conditions.

Plant extracts are prone to induce contact sensitization and subsequent contact allergy. This has been studied intensively and corresponding clinical reports exist.[112,113] It was demonstrated that so called phytocosmetic creams containing a mixture of plant extracts also contain triamcinolone acetonide as an active ingredient.[114]

Beside negative results, there is only one RCT indicating a beneficial effect of hypericum as a topical phytotherapy. No recommendation can be given based on the available evidence.

Chinese herbal medicine

Chinese herbs are part of the traditional Chinese medicine which consists of Chinese herbs administered orally or topically, acupuncture, diet and exercise.[115,116] Chinese herbal treatment is promoted as treatment for AE, taken orally as decoction, usually consisting of about 10 different herbs. The first randomized controlled trials of Chinese herbal medicine in the treatment of AE outside China were published by Sheehan and coworkers[117,118] and subsequently summarized in a systematic review.[119] In a similar crossover design, 37 children and 31 adults received either an active or a placebo plant mixture over an 8-week period. The severity scoring included erythema, surface damage and percentage area affected. The median percentage change for surface damage in the children's group was 63.1% for Chinese herbs, compared with 6.2% for placebo. In a 1-year follow-up, the 23 children who decided to stay on Chinese herbs showed overall better results than those who quit this therapy.[120] In the adult group the geometric mean for surface damage at the end of Chinese herbs treatment was 11.3 compared with 111 at the end of placebo.[121] After 1 year 12 of the 17 adults, who decided to continue the herbal treatment had a greater than 90% reduction in the clinical score which was significantly better than those of the 11 patients, who chose not to carry on taking the medication. Short-term toxicity was not observed in these trials, but prior routine checks of haematological, renal and hepatic function were recommended. Serious adverse effects including fatal hepatitis have been reported by independent investigators following these trials.[115,122–124] A further trial investigating a commercial product of Chinese herbs (Zemaphyte®, Phytopharma, UK) focused on immunological outcomes and indicated relevant immunological as well as clinical effects.[125] Zemaphyte was further evaluated and compared with placebo in a crossover trial involving 37 patients.[126] A trend towards clinical improvement was observed in both groups without significant differences between groups.

The oral application of a combination of *Eleutherococcus, Achillea millefolium* and *Lamium album* was not superior to placebo after 2 weeks.[127]

Although earlier reports indicated beneficial effects of Chinese herbal medicine in the treatment of AE, consecutive trials could not confirm these findings and further studies including larger sample sizes are certainly needed.

Recommendations
There is not enough evidence to support the use of Chinese herbs in the treatment of AE.

Acupuncture
Acupuncture has not been studied systematically or within randomized controlled trials as a treatment for AE. Case series of patients including those with AE indicate some beneficial effects, but studies implying a rigorous methodology are needed.[128–130]

Recommendations
There is absence of evidence to support the use of acupuncture in the treatment of AE.

Autologous blood therapy
We located one RCT comparing the reinjection of 1–3 ml autologous blood over 5 weeks to the injection of the equivalent amount of sterile saline solution.[131] Patients were recruited via press advertisement and finally 30 subjects participated. Over a 9 weeks period, eczema severity as measured by SASSAD dropped significantly in the verum group from 23.2 to 10.4 and did not change in the placebo group (21.0–22.5). Significant differences were not observed in health related quality of life and the subjective assessment of pruritus skin appearance and sleep quality. The data suggest a beneficial effect of autologous blood therapy with respect to the severity score. This finding should be confirmed in larger trials and different settings.

Recommendations
There is no evidence to support the use of autologous blood therapy in the treatment of AE.

Bioresonance
One RCT has been published so far, comparing bioresonance with a sham procedure in 36 children with AE attending a specialized rehabilitation unit in Davos, Switzerland.[132] After 4 weeks, severity score has improved in both groups with slight superiority of the active group (differences 12.5 vs. 8.7). Statistical significant differences between groups did not occur. Although small benefits cannot be excluded, this study could not demonstrate a substantial clinical effect and further studies under more usual outpatient conditions are needed.

Recommendations
There is no evidence to support the use of bioresonance in the treatment of AE.

Homoeopathy
Large case series illustrating the therapeutic benefits have been published as papers or books.[133,134] A recent uncontrolled trial of 17 patients with longstanding AE in Japan revealed a marked improvement after the introduction of homoeopathic treatment.[135] A classical randomized placebo-controlled trial was initiated in Germany including 60 patients.[136] There was no difference between placebo and verum homoeopathy in the outcome of AE.[137]

Recommendations
There is absence of evidence to support the use of homoeopathy in the treatment of AE.

Massage therapy/aroma therapy
The effect of additional massage therapy applied daily for 20 min over a 1-month period compared to standard therapy alone was investigated in a randomized trial in 20 children.[138] Greater degrees of improvement in anxiety scores, tactile defensiveness and coping index were reported by parents of children in the active group. Furthermore, clinical signs such as scaling and excoriation improved significantly in the massage group. However, appropriate statistical comparisons between groups were not performed. A further small crossover trial in eight children compared massage with essential oils (aroma therapy) to conventional massage.[139] Both treatment groups improved significantly without significant differences between groups. Given the small sample size, conclusions on the beneficial effects of additional aroma therapy cannot be drawn.

Recommendations
There is insufficient evidence to support the use of massage/aroma therapy in the treatment of AE.

Salt baths
Salt bath has been used for a long time to control chronic inflammatory skin diseases, especially psoriasis. Based on this experience and anecdotal evidence, salt was recently recommended also in the treatment of AE. The efficacy of salt bath alone, however, has not been studied systematically in AE. In the current reports, salt baths were investigated as part of a complex climatotherapy or in combination with UV therapy.[140,141] A large clinical observation of 1408 patients with AE, who stayed 4–6 weeks in the Dead Sea area revealed complete clearance of lesions in 90% of the patients.[142]

In another study from the Dead Sea area of 56 patients with AE, bathing in diluted Dead Sea water was compared with bathing in sweet water (20 min, twice a day) as part of the climatotherapy regimen. As a result the severity index improved significantly in both groups without significant differences between groups.[143]

Another uncontrolled trial investigated the use of narrow-band UVB and bathing in Dead Sea salt solution. Significant improvement according to the SCORAD score was reported in per-protocol analysis ($N = 143$) or intention to treat analysis ($N = 615$).[144] In a small trial from Germany, 12 patients were treated with UVA/B monotherapy and compared with 16 patients who underwent UVA/B phototherapy plus salt water baths.[145] After 20 treatments, the SCORAD score improved markedly and significantly in the balneophototherapy group and only a marginal

improvement was observed in the UVA/B monotherapy group. The patients of this small trial, however, were not randomized and the baseline severity indicates that SCORAD of the patients in the combination therapy group was much higher. In another German trial, Dead Sea salt bath plus phototherapy were compared with salt bath alone.[146] However, results of the eight patients included with AE were not given separately.

In a randomized trial from Japan, 100 patients were assigned to get either Deep Sea water or physiological saline sprayed on the skin for every 10 min, every day for 1 week.[147] Clinical improvement was small in both groups and not statistically different.

Recommendations

At the moment there is not enough RCT evidence to support the use of salt baths in the treatment of AE.

Vitamins and minerals

A total of six trials were identified investigating vitamins or minerals in the treatment of AE.[148–153] A recent study from Italy studied 96 patients who were randomized to either 400 IU of vitamin E taken orally once a day, or placebo over the period of 8 months.[152] According to the subjective assessment of the clinical outcome after 12 months, marked differences between groups were observed. A great improvement was reported by 46% in the vitamin E group compared with only 2% in the placebo group and correspondingly, 87% of the placebo group reported worsening and 8% did so in the vitamin E group. Unfortunately results of statistical tests are not given in the publication. Similarly, a smaller study of 49 patients comparing vitamin E plus vitamin B2 to vitamin E or vitamin B2 alone revealed a superiority of the combination treatment with respect to the physician's assessed overall usefulness and global rating.[150]

A further trial in 60 adults with AE compared selenium or selenium plus vitamin E vs. placebo over a 12 weeks period.[149] The AE severity score fell in all 3 study arms without significant differences. A Hungarian study compared multivitamin supplementation in 2090 pregnancies to trace element supplementation in 2032 pregnancies over a 17-month period.[148] AE occurred more frequently in the multivitamin group (0.7% vs. 0.2%). Although this unexpected result could be a chance finding as suggested by the authors, detailed studies in the prospective setting are needed.

A small trial has investigated the zinc supplementation vs. placebo in 15 children over a 2-month period.[154] The severity score increased in both study groups without significant differences.

There is one published RCT comparing pyridoxine (vitamin B6) vs. placebo in 41 children over a 4 weeks period.[151] The median severity score increased in the pyridoxine group, whereas an improvement was observed in the placebo group. None of the differences were statistically significant.

In the only pilot study on Vitamin D so far, five children were treated daily with 1000 IU for 1 month. Compared to six controls the EASI score improved, but without statistical significance.[153]

Recommendations

There is preliminary evidence that vitamins, especially vitamin E and D, are useful in the treatment of AE, but further trials are needed before an evidence-based recommendation can be given.

Topical Vitamin B12

There are two smaller studies with half-side comparisons, which indicate a beneficial effect of a preparation containing 0.07% vitamin B12 in avocado oil compared with a placebo preparation. After application over 8 weeks in 41 adults the modified SASSAD score dropped significantly more in the verum area. Similarly, the global patients and physicians assessments were significantly better for the area which was treated by verum in this German study.[155] In the US, the preparation was tested in a similar design in 21 children and showed a significant superiority over placebo with respect to the SCORAD.[156] Large-scale studies should follow to confirm these results.

Recommendations

The committee feels that these studies do not provide enough evidence to recommend this treatment.

Harms

Contrary to widespread assumptions of the public, CAM is not free of side effects. Dietary regimens involving strong restrictions can lead to harmful sequels in terms of malnourishment. Therapeutic procedures involving organic material from plants or animals can be associated with severe toxic or allergic reactions.

Psychosomatic counselling

Psychological and emotional factors are well known to influence the clinical course of AE, which is reflected by the name 'neurodermitis' in some countries for this disease. The itch-scratch cycle is especially vulnerable to psychological influences and can show a tendency to self-perpetuation.[157–159]

It is also known that stress can elicit severe exacerbations of eczematous skin lesions.[160]

At the same time psychosomatic disease in the sense of anxiety or depression can be comorbidity features of AE.[158]

Quality of life is severely impaired in AE patients.[161]

Therefore, a variety of psychotherapeutic approaches including psychosomatic counselling and behavioural therapy have been studied.

Two randomized controlled trials compared the use of topical corticosteroid alone with steroids together with a behavioural therapy programme which led to a significantly pronounced improvement of skin condition and itch-scratch behaviour.[162]

Autogenic training together with cognitive behavioural therapy was studied in a standardized educational programme (see chapter 'Education').[163]

Behavioural therapy against itch was studied by Niebel[164] showing a significant improvement in symptoms after 1 year.

Psychosomatic counselling and psycho education with regard to relaxation techniques and behavioural therapeutical programmes are part of several educational programmes used in AE (see 'Education').

Intrafamiliar psychodynamics are also well-known factors influencing the clinical course of AE.[165,166]

Most psychological training programmes include relaxation techniques, habit training for social competence and communication as well as coping behaviour and improvement of self-control with regard to disrupting the itch-scratch cycle.

Recommendations

Psychosomatic counselling can be a helpful adjuvant procedure in the management of patients with AE including psychotherapeutical approaches and behavioural therapy techniques (3b, B).

Individual psychotherapeutic approaches can be helpful in individual patients (-, D).

Psychological and psychosomatic interventions are an essential and helpful part of educational programmes (1a, A).

Educational interventions for atopic eczema

Psychological and educational interventions enhance the effectiveness of conventional therapy for children with AE. These interventions are focused on the process of acquiring new knowledge or skills through teaching and learning activities. Information and formal teaching lead the recipients to become more accurately informed about the condition, and therefore better equipped to understand the need for medical treatments and good disease management. This improvement in disease control will restore family dynamics, the patient and family will cope better and have an overall improvement in quality of life. In addition, education should aim to reduce doctor's visits, facilitate a better partnership between the doctor, and the patient, and the parent. This leads to a decrease in the long-term costs of chronic disease treatment.

Educational service delivery models

There are different educational programmes running all around the world. These differ in number and certification of the educator, number of participants, age of patients, duration and frequency of interventions. The outcome of the patient education depends on the education techniques, the skills of the educator and the composition of the participants.

Multidisciplinary age related structured group training educational programmes: There is evidence that structured age related programmes are significantly improving severity score, improving coping behaviour, parents handling their affected children and increasing disease knowledge.[167–171]

Eczema workshops: Significantly more patients from the eczema workshop improve from moderate-to-mild severity score.[172,173] There is greater adherence to eczema management (coping behaviour, parent's handling their effected children) in the eczema school compared with the standard dermatologist-led clinic.[171]

Atopic eczema educator: There is no evidence that this kind of intervention improves the severity, the quality of life or the disease outcome. Itch-scratching cognitions are improving and parents deal with their effected children better. The additional psychological benefit in the training group does not only depend on the greater improvement of SCORAD values, the disease knowledge is increasing.[171,174,175]

Nurse-led eczema workshops, single nurse-led interventions, nurse-led care: The self-management techniques are improving. There is evidence, that the benefits of nurse interventions are the reduction in the severity of the condition and the use of topical therapies are more effective. There is a reduction in referrals to the general practitioner or dermatologists, and the disease knowledge is increasing.[171,172,176]

Structured lay-led self-management education training programmes: They lead to a small statistically significant reduction in disease status (pain/itch, disability, fatigue) and a small statistically significant improvement in depression, small improvement in psychological well being, there was no difference in quality of life.[177] No evidence that such programmes improve psychological health.[178–180]

Forms of educational intervention tools

There are numerous kinds of intervention tools, which help to improve understanding, and knowledge. The different health systems have different backgrounds.[181,182]

There is evidence that a special educational school enhances better knowledge of the disease, and has positive effects.[183–185]

There is no evidence that demonstrations, lectures, question and answer sessions and relaxation techniques result in significant improvement of disease severity.[186] The patient's perceptions of conventional medicine is improved.[187]

Direct telephone access to a nurse leads to a better understanding of self-management.[184]

Video-based education, films, audiotapes, books booklets, leaflets, handouts, questionnaires improve the disease knowledge, but the evidence of usefulness needs further investigation.[188–191]

There are no available controlled clinical trials in case of the use of written action plans, the effect on adherence in paediatric AE needs further investigation.[184,192]

Website information for educating patients is not sufficient because the internet is not generally accessible. Internet access is not common everywhere and the information is not necessarily credible among adult patients. The current status needs further investigations in each country.[193,194]

The health systems and possibilities are differing in each countries. Personal contact and the structured programmes such as the educational schools show the most benefit.

Recommendations

Educational programmes (training programmes, 'eczema schools') for AE in children and adults are highly efficient and established already in many countries. The multidisciplinary age related structured group training educational programmes are improving coping behaviour, parents handling their children. The skin symptoms improve, and there is less need for medication. These programmes have the most benefit and are therefore recommended as an adjunct to conventional therapy of AE (1a, A).

The eczema workshops lead to the improvement in severity scores, there is greater adherence in eczema management, itch-scratching cognition and there is additional psychological benefit (2a, 2b B).

The nurse-led programmes result in more effective use of topical therapies and improvement in severity scores, but there is a narrow range in their roles, although it is remarkable that this intervention is sparing doctor's time (2a, 2b B).

There is no evidence of change in severity scores due to the programmes led by an AE educator, nor the lay-led self-management education programmes, which have weak effect in improvement, but the disease knowledge is increasing (-, D).

Acknowledgements

The work was supported by Christine Kühne-Center for Allergy Research and Education (CK-CARE) Davos, Munich, Zurich.

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