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Summary HTA

HTA-Report | Summary

Therapy of atopic eczema
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Background

The treatment of atopic dermatitis (AD) includes different interventions which should be individually selected in each patient. The management of AD should include the reduction and avoidance of the individual provocation factors and adapt symptom-orientated therapy. A special challenge is the treatment of the intense pruritus.

In Germany the therapy of the AD is performed in an outpatient setting. In the comparison to the UK, where the last HTA report has been written (Hoare et al.) a higher number of specialists (dermatologists, specially educated pediatrics, allergologists, who can perform a differentiated diagnosis and therapy) are available in Germany. In outpatient clinics and day care clinics complex therapeutical interventions can be performed. Reasons for hospitalisations are severe flares of the AD or severe complications (eczema herpeticatum, bacterial superinfections of the skin) or the evaluation of provocation factors (e.g. by provocation tests).

A number of substances and therapeutical procedures are available. A change of the therapy can be useful after a given period of time (as in other chronic diseases). The specific anti-inflammatory therapy is completed by the basic therapy. Different symptomatic treatment approaches are outlined and discussed in this HTA report in detail.

Objective

The HTA report gives systematically a summary about controlled clinical studies of the years 1999 to 2004 and a published HTA report of the year 2000 for the treatment of atopic dermatitis. Controlled clinical studies which were published after 2004 were also regarded. It is the aim to evaluate the medical effectiveness and the economical effectiveness for Germany with the help of the current literature about the controlled studies.

Medical Assessment

Methods

The medical evaluation focuses on randomised controlled clinical studies. Only prospective studies were considered in the evaluation. This report is a continuation of the HTA report from Hoare et al. Therefore this report – like the HTA report by Hoare et al. – does not discuss the whole clinical reality in the field of atopic dermatitis, which is not only based on controlled clinical studies but also on experienced knowledge which has not been evaluated by controlled clinical studies and will probably not be ensured by such studies in the near future.

The electronic database research on which this previous report based is shown in detail in the attachment. Additionally searches for 2004 and 2005 and for the years 2005 and 2006 have been performed in the database Medline with the keywords “clinical study” and “investigations in the human beings”.

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Topical cortico steroids and topical calcineurin-inhibitors are the principal substances which are currently used for anti-inflammatory therapy in atopic dermatitis. These substances have shown a significant therapeutic efficacy in controlled studies. Interestingly, only a limited number of standardized controlled studies are available for topical corticosteroids although these substances have been available for a longer time than topical calcineurin-inhibitors. This points a principal problem of the current principles of Evidence-based-medicine (EBM). In general, clinical studies on older commonly used and effective substances are methodological more insufficient than studies on newer substances. This could lead to negative assessment in case of a new evaluation of some older substances.

In newer controlled studies no difference was observable when corticosteroids were applied once or more than once daily onto the skin. Moreover, there is now one controlled study available which points to the fact that an interval therapy with a stronger topical corticosteroid over a limited time (some weeks) may lower the risk of recurrent flares of atopic dermatitis. Studies on the effect and side-effects of interval therapy topical corticosteroids over a longer time are still lacking.

Oral corticosteroids are used quite often to interfere in acute flares of atopic dermatitis. Controlled studies on the longer application of systemic corticosteroids compared to other systemic immunosuppressant are lacking for patients with atopic dermatitis. A longer application of systemic corticosteroids should therefore not be performed in patients with atopic dermatitis.

Both topical calcineurin-inhibitors pimecrolimus and tacrolimus have shown a significant therapeutically efficacy in a number of placebo-controlled prospective studies. The wealth of data is high for these substances. Both substances have been shown to be efficient in infants, children and adult patients with atopic dermatitis. The substances did not lead to a higher rate of skin infections in controlled studies. The most common side effect of tacrolimus is stinging and burning of the skin at the site of application. In spite of controversial discussions the EMEA draws a current conclusion which is in line with the conclusion of most dermatological societies. This says that there no conclusive data available which show an enhanced risk of an oncogenic potency of topical calcineurin-inhibitors in men (which is discussed in particular for spinocellular carcinoma of the skin and for lymphoma) and that there is a positive benefit / risk ratio for these substances. The EMEA proposes however, to use topical calcineurin-inhibitors as a second line therapy in atopic therapy.

Topical tar which has been used in the past contains an anti-inflammatory mixture of substances. In the timeframe starting at 1999 no controlled study has been published on this group of substances which may be taken as an indirect indicator that tar is now of less clinical relevance.

The skin of patients with atopic dermatitis is colonized in the majority with S.aureus, a gram-positive bacterium. Therefore, a therapeutical approach for the treatment of atopic dermatitis is the anti-bacterial or anti-septic treatment of the skin. There is some evidence for the efficacy of this approach coming from open studies. Due to the lack of randomized controlled studies there is still not final proof that antimicrobial or anti-septic treatment of non-infected eczematous skin is efficient for the treatment of atopic dermatitis. Of note, a reduction of Staphylococcus aureus is also observable.
during an anti-inflammatory treatment of the skin with topical corticosteroids and / or the topical calcineurin-inhibitor tacrolimus.

There is one controlled study available which points to the fact that antimycotic therapy may be beneficial in patients who suffer from a head, neck and shoulder dermatitis which is often colonized with the yeast Malassezia furfur.

Antihistaminic drugs which are orally applied in atopic dermatitis may support the therapy of the itching skin disease. One controlled study showed a rapid reduction of itch during the use of a non-sedating antihistaminic drug.

There are, however, no controlled studies which show the efficacy of antihistaminic drugs on the skin condition in atopic dermatitis. There is only indirect evidence on a possible effect of antihistaminic drugs on atopic dermatitis showing the reduction of the amount of applied topical corticosteroids during the therapy of atopic dermatitis.

Dietetic restrictions should be applied only after a specific allergological diagnostic clarification. The “gold standard” is still a (blinded) oral provocation test which has to show an influence of a given food on the skin condition. This should be performed before a long-lasting therapeutical elimination diet is started. Controlled studies are still lacking evaluating the effect of a long-lasting elimination diet on the skin condition of patients with atopic dermatitis (however, it is very difficult to perform such studies in a randomized controlled setting due to practical reasons). On the other hand, there is sufficient evidence that there is no general dietetic approach which shows efficacy in atopic dermatitis.

Further dietetic procedures such as the treatment with essential fatty-acids, vitamins or zinc did not lead to convincing therapeutical effects so that these approaches do not have a practical value in the treatment of atopic dermatitis. The treatment of patients with lactobacillae is still controversially discussed. Available studies which showed an efficacy show methodological weaknesses so that this approach can not be generally recommended for clinical practice at the time now.

Approaches reducing house dust mite in the surroundings of patients with atopic dermatitis can have an effect on the skin condition so that at least in mite sensitized patients this approach appears to be reasonable. The specific immunotherapy with house dust mite showed clinical efficacy in a controlled study and in some open studies. Specific immunotherapy is still not formally approved for the treatment of atopic dermatitis but can be taken as a very interesting approach for the therapy of this disease in the future. The treatment of atopic dermatitis with special clothes (particularly with clothes containing antibacterial substances) is a new and interesting approach - although available clinical studies have not been performed as randomized controlled studies.

The education of patients with atopic dermatitis or their parents is a further efficient approach in the management of this chronic skin disease. Interdisciplinary approaches in patient’s education containing also psychological elements appear to be an attractive new approach for the treatment of atopic dermatitis.

Phototherapy is a further possibility of intervention in atopic dermatitis. This approach should, however, only be used in adolescents and adults in most cases due to safety reasons. The available evidence points to the fact that UVB radiation (both small and broad spectrum), UVA-1 radiation and balneo-phototherapy are efficient therapeutical options for atopic dermatitis.

The systemic treatment with the immunosuppressive substance cyclosporine A is efficient in the treatment of severe atopic dermatitis. Cyclosporine A is approved for the treatment of adult patients with this skin disease. The immunosuppressive substance azathioprine showed a high clini-
cal efficacy in two controlled studies for severe atopic dermatitis in adults. The immunosuppressive substance mycophenolat-mofetil may efficient as shown in open trial but controlled studies are still lacking. Other anti-inflammatory substances like platelet activating factor antagonists, interferons (which may change the TH1-TH2 cytokine imbalance in atopic dermatitis), anti-interleukin-5 antibodies, thymus extracts or thymus peptides or immunoglobulines did not show any or only weak effects on the status of the skin in atopic dermatitis so that these substances do not offer therapeutical options for clinical practice.

There are still controversial results for the application of leucotriens antagonists in the treatment of atopic dermatitis: in some open studies a therapeutical efficacy was described which was, however, not reproducible in a newer controlled study.

The phosphodiesterase-4-inhibitor cipamphyllin was efficient in the treatment of atopic dermatitis in a controlled study but weaker than a topical class II (i.e. moderate strength) corticosterone.

The HTA assessment further describes so-called complementary therapeutical approaches such as Chinese herbs, massage, bio resonance therapy, biofeedback, homeopathy which have either not properly been studied in controlled clinical trials or which have been shown to be of no value for the treatment of atopic dermatitis.

Discussion

The spectrum of therapeutical procedures has increased for atopic dermatitis but is still not sufficient. The spectrum of established substances is much smaller compared to psoriasis, another chronic and common inflammatory skin disease. There is need for the development new substances which can be applied topically and which are aimed to treat atopic dermatitis in early childhood. Another need for new developments can be found for the treatment of severe atopic dermatitis in adults.

Economic Assessment

Methods

To answer the research questions the transferability of results of international health economic evaluations to German conditions were examined. A systematic literature review of publications of international HTA agencies and health economic evaluations in electronic databases was performed.

Results

The scientific examination of economic questions of the treatment of atopic dermatitis started in the nineties, which was concerned with different economic questions. Altogether 95 publications with an economic purchase were found, there from six full health economic evaluations which did not cover the whole therapy spectrum of atopic dermatitis.

The transferability of the study results to the German health system is limited strongly by the fact that no study was aligned to a German Setting. All studies took place in the last five years. Conflicts of interests could be excluded only in two studies.

In the cost minimizing analysis the authors Green analyzed et al. different application frequencies of topic corticosteroids. The clinical studies did not show clear effectiveness differences of application one time daily versus two times daily. Apart from the drug prices the therapy costs of the corticosteroids depend on the product and its quality, the application frequency
and quantity for each application. Whether expenditures for health could be saved, is questionable. The standard package sizes lead to the fact that many prescriptions are not used completely or spoiled, since the minimum durability time runs off. The choice of the most cost effective treatment option of topical corticosteroids depends less on application frequency, but rather on the drug price and more used or unused quantity of the standard packages, so even smallest improvements justify a more frequent application.

The authors Abramovits et al. analysed tacrolimus and pimecrolimus in direct comparison. The statement that the monotherapy tacrolimus is more cost effective than the monotherapy pimecrolimus is not clearly traceable due to different weaknesses of the health economic evaluation.

The authors Ellis et al. analyzed the cost effectiveness of monotherapy tacrolimus versus high potency topical corticosteroids (HPTC). Also this health economic evaluation shows different weaknesses. According to the authors Ellis et al. the cost effectiveness was 9.08 USD per symptom-free day for the two weeks HPTC therapy, 6.80 USD for the four weeks HPTC therapy and 6.97 USD for tacrolimus. Also this result is only limited reliable.

The authors Garside et al. provided a cost-utility analysis for pimecrolimus and tacrolimus compared with topical corticosteroids in different hypothetical adult and paediatric cohorts. Mostly only the corticosteroids gained QALY (Quality adjusted life year). Thus pimecrolimus gained incremental cost-effectiveness below 30000 GBP per QALY only in mild to moderate atopic dermatitis in comparison to emollients. The incremental cost effectiveness of tacrolimus was below 30000 GBP in children (adults) with moderate or severe atopic dermatitis at the whole body (in the face). The reliability of these results is strongly limited, because the models do not illustrate the chronic nature of atopic dermatitis sufficiently.

The authors Salo et al. compared the cost effectiveness of the treatment severe insufficiently treated atopic dermatitis in adults with intermittent therapy ciclosporin versus UVA / UVB photo therapy. The authors concluded from their results showed comparable cost effectiveness from view of health care payer and from view of societal cyclosporine was more cost-effective. These results are mostly irrelevant for insufficiently treated patients, since only few alternatives are available for them.

**Conclusions**

The spectrum of therapeutical procedures has increased for atopic dermatitis but is still not sufficient. The spectrum of established substances is much smaller compared to psoriasis, another chronic and common inflammatory skin disease. There is need for the development new substances which can be applied topically and which are aimed to treat atopic dermatitis in early childhood. Another need for new developments can be found for the treatment of severe atopic dermatitis in adults.

Due to lack of health economic evaluations therapy decisions in the treatment of atopic dermatitis must take place on the basis of clinical decision criteria. The prescription of topical corticosteroids should prefer low priced drugs. Reliable statements about the cost effectiveness of the new calcineurin-inhibitors tacrolimus and pimecrolimus cannot be given up to now.

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