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Corticosteroid therapy in the treatment of pediatric patients with atopic dermatitis

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Health political background

In developed countries around 2.5 % of the population – the majority children – is diagnosed with atopic dermatitis. In Germany already around 2 to 10 % of the population is affected. According to the guidelines of the German dermatologic society and the professional organisation of German dermatologists the prevalence of atopic dermatitis in school children has risen during the last few years. It is now between 8 to 16 %, meaning that it is the most frequent chronic skin disease at school age.

Scientific background

Atopic dermatitis has a variety of clinical presentations: Differences can be seen in the age-related course of the disease as well as in the incidence of primary and secondary signs and symptoms. For most children with atopic dermatitis the itching sensation (pruritis), which is generally most severe in the evening and at night, is the symptom which causes the most distress. There does not exist one precise cause for atopic dermatitis, but it rather develops as a result of a combination of congenital and physiological factors and environmental influences.
Current methods of treating atopic dermatitis among children focus on containing and preventing the illness's further progression. Preventing dry skin, relieving symptoms (such as pruritis and inflammation of the skin) and identifying and avoiding provocating factors are elementary goals of treatment. Successful treatment can substantially increase the children's quality of life. Possible therapies of children affected by atopic dermatitis include both topically and systemically applied pharmaceuticals. During the past ten years the use of corticosteroids has been the standard topical anti-inflammatory therapy in case of aggravating inflammations. A few years ago a new group of pharmaceutical substances (the topical calcineurin inhibitors tacrolimus and pimecrolimus) was approved for the topical anti-inflammatory treatment of patients with atopic dermatitis.
Because of its high prevalence, atopic dermatitis forms a relevant expense factor for the German health care system. In 1999 the costs of the treatment of atopic dermatitis with corticosteroids in Germany amounted to 230 million Euro. If other direct costs for the treatment of atopic dermatitis, for example for hospitalisation or doctors visits, are included the total costs amount to 3.57 billion Euro. In addition to these costs patients (or their parents) also have to pay different forms of co-payments. Based on the fact that the prevalence of atopic dermatitis continues to rise, it is expected that the costs that can be accounted to this disease will further increase.

Research questions

The central questions in this study are the following: How clinically effective are corticosteroids compared to other anti-inflammatory pharmaceuticals in the treatment of pediatric patients with atopic dermatitis? What are the risks associated with these therapies? How economically effective are corticosteroids compared to other anti-inflammatory pharmaceuticals in the

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treatment of paediatric patients with atopic dermatitis? What ethical, social and juristical aspects are to be considered?

Methods

This Health Technology Assessment was conducted by applying the methods for a systematic literature review. The systematic literature search (DIMDI-HTA-superbase as well as HTA- and Cochrane-databases) yielded 1335 abstracts. Following a two-part selection process according to predefined criteria 19 medical, five economic and eight ethical publications were included in the assessment. Relevant legal acts regarding juridical aspects were also searched. Information extraction and assessment of the selected studies were performed according to pre-defined criteria. 26 publications were added by hand search.

Results

Even though topical corticosteroids are commonly used in the treatment of paediatric patients with atopic dermatitis, a surprisingly small number of randomised controlled clinical trials evaluating their effectiveness in this group of patients were identified. Most of the studies concerning the topical application of corticosteroids on children with atopic dermatitis have been published before the year 2000 and are of poor methodological quality. Of the 19 randomised controlled clinical trials which were included in the assessment seven evaluated topical corticosteroids in comparison to placebo, other topical corticosteroids or tacrolimus, which is one of the calcineurin inhibitors.
One of these studies concluded that in the treatment of children who are older than two years the topical corticosteroid fluocinolone acetonide is more effective compared to placebo. The authors found no proof for adverse local side effects or for adrenal suppression attributable to the Fluocinolon Acetonide therapy. A second trial demonstrated that in adult as well as pediatric patients (older than three months), once the disease has been stabilized, the risk of relapse of atopic dermatitis can be significantly reduced by extended intermittent dosing with fluticasone propionate. With regard to side effects (such as skin atrophy) no differences were found between fluticasone propionate and placebo in this study. Three selected studies comprised a comparison among different kinds of corticosteroids. These studies compared Hydrocortisone with betamethasone valerate, fluticasone propionate and desonide respectively. Hydrocortisone is one of the most applied milder corticosteroids. Based on these studies, the application of hydrocortisone in the treatment of small children can be considered as safe. From one of the studies, it can be concluded that treatment with betamethasone valerate over a short period is as effective as applying the milder corticosteroid hydrocortisone over a longer time period. Compared to fluticasone propionate and desonide hydrocortisone appears to be less effective. Due to the small number of randomised controlled clinical trials of sufficient quality within this field, not all available corticosteroids were analysed in the assessment.
Two trials which were documented by the same author and which contain a comparison of corticosteroids with tacrolimus were selected. Both these studies showed, through comparing disease severity scores and affected body surface areas, that tacrolimus is more effective than hydrocortisone acetate in children with moderate to severe atopic dermatitis. However, the children treated with tacrolimus more often experienced a burning sensation on the skin. In most cases this adverse local side effect disappeared after

three to four days of treatment. Other side effects showed no differences between tacrolimus and hydrocortisone acetate. No studies comparing corticosteroids with pimecrolimus in the treatment of paediatric patients with atopic dermatitis were found.
Two studies showed that in treating children with moderate to severe atopic dermatitis tacrolimus is significantly more effective than placebo. On the other hand, in one of the two studies the incidence of a burning skin, of varicella and of pruritis was higher in the group of patients treated with tacrolimus. No differences were measured between the three available concentrations of tacrolimus. The observed tacrolimus blood concentrations in these studies were consistent with minimal absorption of the substance through the affected skin.
Seven of the included studies compared the calcineurin inhibitor pimecrolimus with placebo. Some of these studies also included children under two years of age, whereas in Germany pimecrolimus is currently only authorized for the treatment of children aged above two years. In three studies the median reductions of the disease severity scores were larger following treatment with pimecrolimus compared to placebo. In three other studies the effectiveness of pimecrolimus was assessed on the basis of the incidence of disease flares and the time passed between the onset of the therapy and the occurrence of the first flare. In all three studies the number of patients not experiencing a flare within six or twelve months after therapy start was significantly larger in the pimecrolimus group. Likewise, the median time passed until the first flare was significantly longer in the pimecrolimus group compared to the placebo group. With regard to treatment side effects no differences were found. In addition, the authors of two of the studies conclude that intermittent treatment with pimecrolimus can reduce the need for topical corticosteroids. Only one study directly compared tacrolimus with pimecrolimus. No significant differences were found between the two calcineurin inhibitors in this study.
Two studies analysed possible changes in the quality of life experienced by the children affected by atopic dermatitis or by their parents due to the treatment with tacrolimus or pimecrolimus. More than half of the children treated with tacrolimus reported positive effects of the therapy on their quality of life. Treatment with pimecrolimus appeared to have a beneficial effect on the parents' quality of life.
Fourteen publications were used for the description of the economic background, of which nine were engaged with the costs of atopic dermatitis. Of the five other studies that were included two are systematic reviews. One of these two systematic reviews included only studies considering cost-effectiveness in paediatrics, which were all available as original papers. The authors of the second systematic review made a comprehensive model calculation for tacrolimus and pimecrolimus compared with topical corticosteroids. From this model calculation it was concluded that Pimecrolimus, when applied in the treatment of children with mild to moderate atopic dermatitis, is inferior to topical corticosteroids, in that the costs for a treatment with Pimecrolimus are higher whereas the effect is less. The treatment with Tacrolimus appeared also to be more expensive than that with topical corticosteroids, but also more effective. The incremental costs per quality-adjusted life year varied, depending on the treatment strategy and the affected part of the body, from 9083 GBP to 35669 GBP.
The other three economic studies also contain model calculations. In one of these studies the costs and utility of pimecrolimus are evaluated in comparison to corticosteroids. In addition, they calculate the incremental costs of pimecrolimus vs. placebo per quality-adjusted life year. The authors of this study conclude that in the treatment of children with mild to moderate

atopic dermatitis the application of Pimecrolimus is inferior to that of topical corticosteroids.
The two other studies provide a calculation of the cost-effectiveness of Pimecrolimus in comparison to placebo and corticosteroids. Both studies calculate in a Markov-model the incremental costs per quality-adjusted life year of pimecrolimius vs. placebo and corticosteroids. Topical corticosteroids were, in both studies, only applied in case of disease flares of a predefined severity. During the treatment with corticosteroids, Pimecrolimus was not applied. One of the studies calculated for the children included in the study population total incremental costs of 1,267 USD from the viewpoint of the Canadian legislators or 1,1185 USD from the viewpoint of the Canadian society. The incremental quality-adjusted life year was found to be 0.3. From the viewpoint of the Canadian legislators the incremental costs per quality-adjusted life year were estimated to be 40,000 USD, from the viewpoint of the Canadian society this was 38,000 USD. According to the other study, from the viewpoint of the American society the calculated incremental costs per quality-adjusted life year amounted to 34,108 USD.
The social and ethical aspects of atopic dermatitis mostly concern psychosomatics, improving of the quality of life of the patients and instructing patients and their relatives. With regard to the psychosomatic aspects the relation between the child and its parents is of particular importance. Instructing patients and their relatives can teach them how to deal with the disease and the psychosocial limitation it causes in everyday life. Regarding the quality of life it has been proven that treatment with the newer substances tacrolimus and pimecrolimus can have a positive effect.
In addition to the conventional treatment with corticosteroids and calcineurin inhibitors patients often opt for ”off label use“ pharmaceuticals. In most cases these pharmaceuticals are not reimbursed and have to be paid for by the patients, or their parents, themselves.

Discussion

For five decades topical corticosteroids has been the first choice therapy in the treatment of atopic dermatitis patients. Their effectiveness has been proven by several studies. In the treatment of children the long term application of topical corticosteroids or the application of topical corticosteroids on sensitive skin areas has been associated with side effects such as skin atrophy. Today, with the newer generations of topical corticosteroids the occurrence of these adverse side effects appears to be less frequent.
The effectiveness of the topical calcineurin inhibitors has also been proven in a number of studies. But since they have only been authorised a few years ago, experiences both tacrolimus and pimecrolimus are far less than those with topical corticosteroids. So far, the only adverse side effect of the calcineurin inhibitors appears to be a burning sensation of the skin, which tends to decrease and disappear over time. In the case of tacrolimus, the longest run time of the studies assessed was twelve weeks. Therefore, no conclusions could be drawn concerning the long-term application of tacrolimus. Likewise we lack evidence concerning the possible carcinogenicity of calcineurin inhibitors in humans.
Only two studies were identified which provided a direct comparison of calcineurin inhibitors (tacrolimus) and corticosteroids. According to the authors of these studies tacrolimus is more effective than hydrocortisone acetate in the treatment of children with moderate to severe atopic dermatitis. Randomised controlled trials comparing corticosteroids with pimecrolimus were not found. Two of the assessed studies however

concluded that the intermittent treatment with pimecrolimus can reduce the need for topical coricosteroids.
In relation to the economic aspects of the treatment of atopic dermatitis a point for discussion concerns the argument of the authors of two economic studies, who say that pimecrolimus is cost-effective because the calculated costs per quality-adjusted life year are lower than the frequently hawked value of 50,000 USD, whereas in the end it is up to policy makers to decide on the actual value of a quality-adjusted life year.
Considering the ethical and social aspects of atopic dermatitis, it is clear that atopic dermatitis can be quite burdensome on patients quality of life and that patients often face social exclusion in their everyday life. The latter could at least be reduced through providing the people who are not affected with more information about the disease, for example in school settings.
Considering juridical aspects, treatment alternatives to the already mentioned conventional treatment should be considered.

Conclusions / Recommendations

From a medical as well as an economical viewpoint, there appears to be insufficient evidence stating that inflammatory steroid-free substances are more effective and / or efficient than topical corticosteroids. Based on the results of the studies that have been included in this assessment therapies based on calcineurin inhibitors seem to constitute a good alternative in case a child is unresponsive or intolerable to topical corticosteroids and for the treatment of intertriginous areas.