Summary HTA

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HTA-Report | Summary

Specific immunotherapy (SIT) in the treatment of allergic rhinitis

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Scientific background

Allergic rhinitis (AR), also called allergic cold, is defined as an inflammation of the mucosa of the nose and the upper airways due to substances capable of causing allergies (allergens). The AR is a common, world-wide and apparently increasing disease with a prevalence of approx. 20 % in Germany. The patients suffer from bothering symptoms, like blocked, itchy or running nose and a large percentage of these patients is impaired in their daily activity and productivity. The disease occurs frequently already in infancy, whereby about each tenth child is affected. There are some indications, that an untreated AR leads to allergic asthma. The AR and its comorbidity cause enormous costs in the health care system. The expenditures for AR in the ambulatory sector are estimated to be DM 75 million in 1996. There are most of all the direct costs caused by medications. The Federal Statistical Office quotes DM 350 million for antiallergics in 1996, which amount to approx. 75 % of the total expenditures for AR. Also the indirect costs, caused by inability to work because of AR are substantial with an amount of DM 29 million in 1996. The total costs of AR (direct and indirect costs) are quoted at DM 467 million in 1996. In 2000 the costs for the German health care system are estimated to be approx. Euros 240 million. The specific immunotherapy (SIT) is considered as the only potentially causal therapy. The goal of SIT is the clinical tolerance against the specific allergens which can be attained by the administration of gradually rising doses of the specific allergen. How far and in which indications the two administration forms of SIT, subcutaneous specific immunotherapy (SCIT) and sublingual specific immunotherapy (SLIT), are effective and/or cost effective, is unclear.

Research questions

Medical evaluation

Regarding the medical evaluation the following questions are to be answered:

1. What is the quantity of information on the medical effectiveness of the different forms of SIT in the treatment of AR?
2. Which administration forms of the SIT are effective with which indications? How are the medical effectiveness and complication rates of the different forms of SIT to be estimated?

Health economic evaluation

In the economic part the following questions are addressed:

1. What is the quantity of information on the cost effectiveness of the different forms of SIT in the treatment of AR?
2. How is the cost effectiveness of the application of different forms of SIT in the treatment of AR?

Within the scope of the

Bundesministerium für Gesundheit

Ethical, social and legal evaluation

With respect to the ethical, social and legal evaluation the following question is to be answered: Which specific ethical, social and legal implications are to be considered in the application of different forms of SIT in the treatment of AR?

Methods

The literature search is conducted in February 2008 in the medical electronic data bases MEDLINE, EMBASE, SciSearch, BIOSIS, ETHMED, INAHTA, NHS CRD DARE, NHS-EED, SOMED, Cochrane DATA base. The search is limited to the years starting from 2003 as well as to the languages German and English. The evaluation of the literature takes place in three steps (title, summaries, full text). Two independent reviewers are involved in the selection of the relevant publications.

Medical evaluation

Due to the large amount of existing information, the medical evaluation is conducted with systematic reviews based on randomised controlled trials (RCT) with their main focus on the treatment of AR. Abstracts, expert statements, narrative reviews, systematic reviews not based on RCT, systematic reviews without separate evaluation of patients with AR and asthma as well as single studies are excluded.

Health economic evaluation

In the health economic evaluation only systematic reviews of health economic analyses or primary health economic studies on the basis of RCT comparing SIT with placebo, symptomatic therapy and/or different SIT medicines among themselves are included in the evaluation. In the description and evaluation of the relevant economic studies the following aspects are considered: study design, medical and health economic assumptions, methodical aspects of conducting the study, medical and health economic results. The incremental cost effectiveness relationship (ICER) per quality-set year of life (QALY) is deemed to be the most important health economic parameter in the studies.

Ethic, social and legal evaluation

The literature search looked for publications with explicit consideration of ethical, social and legal aspects of the use of SIT. Since the literature search of the German Agency for Health Technology Assessment of the German Institute for Medical Documentation and Information (DAHTA of the DIMDI) does not result in a hit, the literature of the manual search was screened for ethical, social and legal aspects of SIT and included if applicable.

Results

Medical evaluation

Summary of the results on SCIT

The reviews consider short term and medium term effects of SCIT with grass pollen compared with placebo from several studies, of SCIT with other seasonal allergens or house dust mite allergens from clearly fewer studies and of SCIT with other perennial allergens only from particular studies. Both

reviews refer to a significant effectiveness of SCIT with seasonal allergens regarding the reduction of the symptom score and medication score. In particular for the grass pollen allergy the evidence is regarded as well-proven. Also for tree pollen allergens the SCIT is considered effective, even though on a somewhat worse data base. In the context of the included studies no deaths are observed after SCIT, however severe systemic adverse events (UE) occur rarely and local UE frequently. The reviews are not able to make a statement about long term effects and the effectiveness in children due to the lack of includable studies.

Summary of the results on SLIT

For the comparison of SLIT vs. placebo, all three reviews determine a significant reduction of the symptom score and the medication score for SLIT in the short term and in the medium term follow-up in evaluations across all allergens. The performed subgroup analyses provide an inconsistent picture. One review shows significant results for SLIT in the evaluation across all allergens in adults, but not in children (the original work assumed that the data situation is not sufficient). The subgroup analysis of seasonal vs. perennial allergens shows a significant reduction of the symptom and medication score only in the comparison of seasonal allergens vs. placebo. In the comparison of SLIT with perennial allergens vs. placebo the reduction in favour of SLIT is not significant. The subgroup analyses of the later review only on SLIT in children indicates a significant effectiveness for SLIT with seasonal allergens, but not for SLIT with house dust mite allergens. Another review of five studies reports a significant reduction of the symptom score and medication score for SLIT with grass and birch pollen allergens, as well as a significant reduction of the symptom score for SLIT with house dust mite allergens. From the three studies included in the review which are conducted in children (one on grass pollen, birch pollen or house dust mite allergens, all Alk-Abelló products), only the study on SLIT with house dust mite allergens shows a significant reduction of the symptom score. In the context of the studies included in the review no deaths or cases of severe systemic UE occur, but frequently local UE like itching and swelling of the mouth mucosa occur.

Health economic evaluation

The information about the cost effectiveness of the use of SIT in patients with AR is small. Four publications about two health economic studies are identified, one of these publications on Alutard-SQ® injections (SCIT) and three on GRAZAX® tablets (SLIT). The cost effectiveness of the use of different forms of SIT in patients with AR can not to be considered as proven from the up-to-date data. The studies provide more (on Alutard-SQ®) or less (on GRAZAX®) robust information, but not the evidence on cost effectiveness of the use of the SIT in patients with AR. A dominance can be supposed for Alutard-SQ® and a cost effectiveness for GRAZAX® comparing with placebo after nine years. The cost effectiveness of other SIT medications is not determined so far.

Ethic, social and legal evaluation

In the conducted literature search, publications with explicit consideration of ethical-social and legal aspects of the application of different SIT forms were searched. Since the search of the DAHTA does not result in hits, the identi-

fied aspects found in the manual search are only discussed.

Discussion

Medical evaluation

The topic of the current report is very broad in scope, so that the evidence is summarised from the identified systematic reviews. A potential problem of the inclusion of systematic reviews is the missing cover of search periods and therefore the risk that relevant studies are not included in the evaluation. In the present case the systematic reviews are likely to cover the literature on SCIT continuously until 2003 for all allergens and for seasonal allergens until 2006. For SLIT the covered period is until 2006 for seasonal and perennial allergens as well as for applications in adults and children. All three reviews on SIT with an information synthesis in form of a meta analysis show a large statistic heterogeneity of the studies. This clearly limits the validity of the statements. A division in manufacturers and products in order to be able to make evidence-based medical decisions is not carried out, even though requested by the medical societies. Also the questions about the optimal dose and duration of the treatment remain open to a large extent. It is often regarded as a substantial advantage of SLIT that serious UE arise clearly less frequently compared to SCIT. Despite the very small to missing occurrence of serious UE arising with the administration of SLIT, mild local UE such as swelling and itching of the mouth mucosa arise frequently. It is to be considered that the SLIT in contrast with SCIT will be administered at home without medical monitoring and therefore it might be that UE will not be treated immediately. SLIT is an application form particularly attractive in the treatment of children, since it works without “syringes“ and can be administered at home. Nevertheless, the proof of effectiveness for SLIT in children is not consistent and in particular for SLIT with non-grass pollen allergens convincing studies in children are missing. A special review particularly of the data on SLIT in children including all new published studies is demanded in the guidelines of the German Society for Allergology and clinical Immunology and also recommended by the authors of the present overall review. The prevention of asthma and new sensitisations in patients with AR is a substantial goal of SLIT. However, the reviews included in the current HTA-report cannot supply reliable information about the preventive effect of SLIT, since no appropriate studies can be included. From the included reviews only two studies with a direct comparison between SCIT and SLIT can be identified, but both studies have substantial methodical flaws. Therefore further studies with direct comparison of the two application forms, which are planned and conducted according the recommendations of the World Allergy Organization Taskforce, appear urgently needed.

Health economic evaluation

The included health economic studies show different methodical flaws. The largest potential bias is the projection of the magnitude of the medium term clinical effects on the time period of nine years. This projection is justified by the authors of the study with the results of clinical studies; some of these studies have a lower evidence level or do not provide a quantitative effect estimate. A completely equal clinical effect of the medication after nine

years is hardly to be expected.

Ethic, social and legal evaluation

Since the literature search does not result in publications with explicit consideration of ethical-social and legal aspects, the ethical aspects of the application of SIT are only discussed. The current medical evaluation implies that SIT can be associated with substantial side effects. Therefore the informed consent of the patient is important and is to be documented accordingly. In contrast to the certified SIT-proprietary medical products, the quality, effectiveness and safety of individual prescriptions is not proven in the same way. Hence from an ethical-legal point of view proprietary medical products should be given preference, if the sensitisation spectrum of the patients permits it.

Conclusions

The effectiveness of SIT in AR is not proven equally for all SIT forms and allergens. For SCIT and SLIT with grass pollen allergens the short and medium term effectiveness can be regarded as proven. These therapy forms should be used in appropriate indications and if no contraindications are present. Also SCIT and SLIT with other seasonal allergens such as tree pollen allergens can be an effective treatment option, but with a certain restraint because of poorer data; in particular on SLIT. For both SCIT and SLIT with house dust mite allergens and other allergens, no consistent proofs of effectiveness are to be determined from the available information. The effectiveness of SIT with these allergens should be examined further before widespread usage. Since the available information from the systematic reviews enable a broad but rather surveying report, further detail-oriented analyses are recommended. The authors state a substantial need for further research particularly in the field of non-grass pollen-associated SIT, allergen and manufacturer-specific evaluations as well as a more detail-oriented examination of the effectiveness of SIT in children, particularly in terms of asthma prevention. For SIT with house dust mite allergens, a current review on the basis of primary studies is recommended. The question about the optimal dose and duration of treatment should be further examined in particular for SLIT. Due to the lack of evidence the use of SIT cannot be seen as cost effective in patients with AR. To provide such evidence, further health economic studies, especially with reliable long term follow-up data, are needed. Furthermore, the cost effectiveness of the SIT medication which is not examined in previous studies should also be investigated. Since the SIT can be associated with substantial side effects, the informed consent of the patient is important and should be documented accordingly. Due to better examination of their quality, effectiveness, and safety, certified proprietary SIT products should be preferred, if the sensitisation spectrum of the patients permits it.