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Human Medicines Development and Evaluation

Report of the expert meeting on paediatric asthma

20 October 2010, 09:30 - 15:30

Chair: Daniel Brasseur

Vice chair: Irmgard Eichler

Table 1. List of participants

List of participants	
Jonathan Grigg	Barts and The London Children's Hospital.
Peter Helms	Department of Child Health University of Aberdeen
Gunilla Hedlin	Astrid Lindgren Children's Hospital Stockholm and Centre for Allergy Research, Karolinska Institute
Jorrit Gerritsen	Beatrix Children's Hospital University Medical Center Groningen
Eugenio Baraldi	Azienda Ospedaliera di Padova
Attilio Boner	Department of Paediatrics, University of Verona
Sally Seymour	Food and Drug Administration
Mª Luisa Suárez Gea	Medicines and Health Products Agency,Spain (AEMPS)
Birka Lehman	Paediatric Committee
Paolo Rossi	Paediatric Committee
Karen Thornoe	Paediatric Committee
Marek Migdal	Paediatric Committee
Emma Sala Soriano	European Medicines Agency
Janina Karres	European Medicines Agency
Dobromir Penkov	European Medicines Agency

Introduction

This meeting was organised to involve experts in the field of paediatric asthma to provide input for i) the EMA/CHMP guideline on asthma which will be revised and will contain a dedicated chapter to asthma in children and ii) for several Paediatric Investigation Plans on asthma.

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Several experts participated over the phone.

The meeting started with a welcome by Daniel Brasseur, chair of PDCO, followed by a short introduction of all participants.

After a brief background information on the European Paediatric Regulation which mandate that any marketing authorisation application for a new medicinal product should include either the results of studies conducted in compliance with an agreed paediatric investigation plan (PIP), or an EMA decision on a waiver or on a deferral, Irmgard Eichler presented an overview of all PIPs submitted to the Agency for the condition "treatment of asthma". Since July 2007 16 PIPs have been submitted for various classes of anti-asthmatic drugs:

- β2-adrenergic receptor agonists;
- Muscarinic receptor antagonists;
- Leukotriene modifiers/inhibitors;
- Prostaglandin antagonists;
- monoclonal antibodies (anti Ig or anti-interleukins).

The experts were asked to comment on the questions/issues listed below. The morning session focused on children below 5 years; in the afternoon more general issues with regard to development of anti-asthmatic medicinal products were discussed.

Children 5 years and below:

1. Definition of the paediatric target population:

- - asthma phenotypes
- - diagnostic criteria
- - inclusion and exclusion criteria

Q1: Is there a need for clinical trials in children below 5 years of age?

All participants unanimously agreed that

- There is a high need to study pre-school children with recurrent episodes of wheezing (age group below 5 years) because of only minimal evidence of efficacy on which to make treatment decisions.
- In this age group the term "asthma" should only be used with caution and must include a careful description of the definition of the study population or be avoided as "classical asthma" suggesting allergen induced asthma cannot reliably be diagnosed. Alternatively, the term "pre-school wheezing" could be used.
- The lead symptom should be doctor's diagnosed wheeze; additional symptoms should include dry cough, particularly nocturnal cough and cough and/or wheeze associated with exercise.
- To allow a better post-hoc definition of the heterogeneous group of pre-school wheezers, patients included in clinical trials must be well characterised with regard to:

- age at onset of symptoms;
- history of typical symptoms;
- history of exacerbations, severity of exacerbations;
- presence/absence of atopy and co-morbidities (atopic dermatitis, allergic rhino-conjunctivitis);
- family history of atopy, particularly maternal history of atopy and IgE mediated allergic disease;
- exposure to tobacco smoke;
- day-care attendance;
- prematurity*;
- exclusion of differential diagnoses, such as cystic fibrosis, anatomical abnormalities of the airways, bronchomalacia, gastroesophageal reflux, etc.

- Only with this careful patient characterisation it might be possible to potentially identify those children who may or may not respond to treatment.

Q2: Cut-off age for including pre-school children in clinical trials: Should infants be included? If yes, from what age (6 months, 1 year, 2 years)?

The cut-off age for inclusion of children into clinical trials evaluating anti-asthmatic drugs, was discussed at some length. There was consensus that inclusion of children below 6 months, is not recommended as both, classic asthma as well as episodic wheezing triggered by viral infection require an opportunity to observe the clinical pattern with time:

- for multi-trigger wheeze or assumed “classic asthma”: persistence of symptoms in infection-free periods and generally a response to therapy;
- for episodic (viral) wheeze: symptomatic "episodes" separated in time by asymptomatic periods, and typically displaying an association with intercurrent respiratory infections and with a concentration of episodes in the winter months.

It was further discussed whether a lower cut-off age of 8 or 10 months would be preferable to a 6 months cut off; however all three proposals are rather arbitrary as no hard evidence is available to support either of them. The majority of participants therefore thought that 6 months could be recommended. A further sub-division by age (e.g. 6 months to 2 years, 2-5 years) was not considered necessary.

Q3: How to best differentiate / stratify the various phenotypes: Is there a need to differentiate / stratify between viral induced wheezers and atopic wheezers?

An European Respiratory Society (ERS) task force recommended to differentiate between episodic (viral) and multi-trigger wheeze. Other publications recommend differentiating between atopic asthma, viral wheeze or obstructive bronchitis and recurrent wheeze due to disturbed airway development.

* One participant proposed to exclude children with a history of prematurity (i.e birth < 36 weeks of gestational age) because of evidence showing that they represent a separate phenotype of wheezers, completely different from “Viral wheezers” and” Multi-trigger wheezers”. Thus, preterm wheezers should be evaluated in separate studies.

It was discussed that the differentiation relates to risk of asthma persisting into later childhood but it's relation to response to treatment is less clear. Therefore, it should be recorded for post-hoc analyses but not as inclusion/exclusion criteria.

Jonathan Grigg, a member of the above mentioned ERS task force, pointed out that the concept of various phenotypes (i.e. episodic (= viral) wheeze versus multiple-trigger wheeze (Brand et al, ERJ 2008) was driven by medication response.

There was consensus that it is important to document atopy, however, no general consensus was reached whether patients should be stratified according atopy – non-atopy. While stratification was supported by many participants with atopy defined as documented sensitization to inhalant allergens and potentially also to hen's egg, some experts expressed their concern that stratification by atopy – non-atopy is too restrictive and might not cover the wide range of this heterogeneous group of patients; furthermore some patients may become atopic at a later age (after inclusion) and therefore would be missed; thus a broader stratification in viral vs. multi-trigger (including atopy) was felt more accurate.

Concern was expressed that stratification beyond predominant viral versus multi trigger wheeze might not be possible as with a strict stratification at entry the numbers of enrolled patients in some groups, particularly the atopic group, might be rather small. Furthermore such a stratification requirement would not be able to account for children who subsequently expressed atopy, as pointed out above. However detailed characterisation at trial entry would allow several pre-specified subgroup analyses, e.g. viral versus multi-trigger wheezers and, on trial completion, atopic versus non-atopic children. Therefore, it is important to document atopy (symptoms, sensitisation, heredity) in the background data of each child included in a drug study (see answer to Q1 above).

It was also pointed out that in view of the high population prevalence of pre-school wheeze such "post hoc" stratification should be possible and allow meaningful numbers for inclusion in the various subgroups. In this context it was considered important to avoid "small studies", which do not allow meaningful conclusions but to conduct clinical trials (CTs) with sufficiently large study populations with the power to answer the pertinent questions.

Q4: Should patients with different phenotypes be studied separately? If yes, are separate trials feasible?

Separate trials were not considered feasible by all experts.

Q5: Need to evaluate novel (biologic) therapeutics in pre-school children?

Yes, there is a need to evaluate them in children with severe attacks (while for studies with other drug classes, children with mild to moderate symptoms should be included). Extrapolation from older children to pre-school children was not considered possible, as pre-school children presenting with severe attacks are very different from older children presenting with severe asthmatic attacks. There was consensus, that novel biologic medications should first be evaluated in children with "significant exacerbations", suggested to be defined as exacerbations requiring systemic corticosteroids for > 3 days, before potentially considering evaluation in less severe patients (severity staggered approach).

In addition, there was general consensus that novel biologic therapeutics would have to have significant advantages over established therapies considering their increased costs and their potential side-effects, particularly those with pleiotropic mechanisms of action.

Q6: Inclusion criteria

The following suitable inclusion criteria were discussed and found agreeable/suitable by all experts:

- Lead symptom for inclusion: doctor diagnosed wheezing;
- For children 2 years and above: history of at least 3 episodes of wheezing symptoms with or without nocturnal cough and exercise-induced wheeze/cough thought to respond to β-agonist treatment, with two of these episodes requiring unscheduled healthcare utilization and one episode of wheeze to be doctor confirmed and one to have occurred within the 6 months prior to enrolment;
- For children 6 months to less than 2 years: a minimum number of 2 wheezing episodes requiring unscheduled healthcare utilization, each requiring β-agonist treatment, one episode needs to be doctor confirmed and one needs to have occurred within 6 months prior to enrolment.

2. Choice of endpoint

There was general consensus that the primary endpoint in the pre-school age group can only be a clinical one: asthma control, such as number of exacerbations, diary based symptom episodes, number of short acting beta-agonists (SABA) intake, number of hospitalisations for wheeze exacerbations, need for systemic corticosteroids. It was felt that rate of exacerbation within a sufficient time-window would be the most important end-point in terms of patients' perspective. The ATS/ERS joint statement: asthma control and exacerbation (Am J Respir Crit Care Med 2009; 180:59-99) also provides useful guidance for paediatric trials.

Q1: Assessment of asthma control in children - what validated tests are available? For what age ranges?

There was general consensus that:

- a standardised questionnaire must be used;
- whatever instrument is used, it must be as simple as possible, e.g. boxes to tick as these diaries may have to be used over long periods. (Please refer to duration of clinical trials below);
- must also be able to capture interval symptoms without causing too much trouble for the parents.

The childhood asthma control test (ACT) was found to work very well, as it is simple, questions are understood by both children and parents; it is validated in children down to 4 years of age; it has to be filled in only every 4 weeks. In this context it was suggested to have a nurse calling every month to remind the study participants to fill in the questionnaire.

As experience from published paediatric trials as well as from submitted PIPs demonstrates, almost every company/published trial has used different questionnaires, rendering comparison of trial results difficult. The PDCO could request including one instrument in all trials to enable validation of such an instrument (in addition to the one proposed by the applicant). It was agreed to circulate the below listed instruments identified so far among the experts to comment which one (including other questionnaires published in large clinical trials) could be considered most appropriate.

- Test for Respiratory and Asthma Control in Kids (TRACK):
- The asthma control questionnaire (validated for children down to 6 years of age)
- The Childhood Asthma Control test: (validated for children down to 4 years of age)

- The asthma therapy assessment questionnaire (validated for children 5-17 years of age)

The following feed-back was received:

Gunilla Hedlin:

“The PAQLQ is well validated and useful and has been applied in many studies. My own experience is that is does not discriminate between moderate and mild asthma - but I don't know of anything better. I think we should promote the use of this PAQLQ in drug trials.

Referring to the C-ACT and the 5 item- TRACK: C-ACT has the advantage of including the child's own opinion which is valid also in young children. TRACK has the advantage of including two questions including a longer perspective - 3 months and a year - the authors think that this addition gives more information on risk for exacerbation.

My personal opinion is that the ideal thing would be to use C-ACT and add the two "long-term" questions from 5 item-TRACK.”

Jonathan Grigg:

“1) The Childhood Asthma Control test: American way of wording. It includes a child-completed section that would not be applicable to the preschool age group. Probably not appropriate because of this.

2) Test for Respiratory and Asthma Control in Kids (TRACK): Designed for preschool children. It has the American drug names (though that is remedial) and is certainly simple and would be quick. Published in JACI, with good sensitivity/specificity.

3) The asthma control questionnaire http://www.qoltech.co.uk/paqlq.html: Again, this is for children to use, not the parents.”

Eugenio Baraldi:

“I would suggest the Childhood Asthma Control test for children 4-15 years old and the Test for Respiratory and Asthma Control in Kids (TRACK) for preschool children.”

Peter Helms:

“Looking over these they are all very similar and would be suitable as they could be administered monthly and hence are more likely to be completed over a 12 month period than daily diaries. Of those available I think TRACK is the better validated. If such an instrument were combined with data on unscheduled visits and use of B2 and OCS, my feeling is that any clinically significant effects would be identified.”

Q2: How to define exacerbation?

Emergency room visits; unscheduled healthcare utilization; need of short (3 day or more) course of oral corticosteroids (OCS);

Mild to moderate exacerbation: need of (additional) SABA

Q3: Duration of clinical trials?

The study duration would depend on the primary treatment goal:

- for treatment of acute exacerbation: a short term study would be sufficient;

- for maintenance treatment to achieve good asthma control (i.e. prophylactic treatment to prevent exacerbations): need for long-term studies.

As many wheezing episodes will be triggered or aggravated by intercurrent respiratory infections, which usually occur most frequently in winter months, recruitment and evaluation should cover all seasons: i.e. 6-12 months recruitment, 12 month follow-up. During the trial it would be necessary to document in what season the wheezing episodes occur.

The majority of experts agreed that any period shorter than 12 month would not provide meaningful results in light of the primary endpoint i.e. exacerbations, rate of exacerbation. The experts considered 12-month treatment trials feasible.

However, this was not shared by all experts, commenting that continuous treatment during the summer months is frequently stopped as the number of exacerbations is low.

Q4: Regarding follow-up for potential safety issues:

In general, all safety follow-up measures will depend on a specific drug's mechanism of action (MOA).

While for authorised ICS the available evidence on impact on growth in children above 5 years of age was considered sufficient, this does not hold true for children below 5 years of age. The use of any ICS in this age group should be followed for at least 2 additional years after cessation of treatment period within the context of the PIP or risk management plan (RMP).

For all new ICS growth would have to be monitored – some experts thought/proposed until achievement of final adult height. However, this was considered unrealistic by others. One proposal was to follow for e.g. 2 years:

- if the child has not deviated from his/her growth spurt during 2 years, looking for final height most likely will not add a lot;
- if the child has lost some SDS after 2 years, a longer follow-up would be needed.

For LABA (only to be administered as fixed drug combination with ICS): there is a high need to evaluate long-term safety.

Additionally, experts were in agreement, that there is a need to follow-up all pre-school children enrolled in therapeutic trials to see who will go on to have true asthma (persistent, atopic, multi-trigger wheeze.) There is some evidence suggesting that distinctive phenotypes respond differently to treatment: viral induced wheezing not responding to systemic corticosteroids in contrast to atopic "asthma like" attacks. A sufficiently long follow-up is expected to clarify the question whether a thorough characterisation before treatment start and long enough follow-up might help to differentiate the different phenotypes at an earlier stage and consequently tailor the treatment regimen accordingly. This is not possible, at present.

This long-term follow-up could be done outside the PIP context, as part of open label extension studies.

Q5: What surrogate endpoints and biomarkers could be used? Are they validated for all paediatric age subsets?

All experts unanimously agreed that for the pre-school age-group no validated surrogate endpoints and biomarkers are available. Neither lung function, nor NO measurements or airway hyper-reactivity would add relevant information. Lung-function measurements as exploratory endpoint in a subgroup of

patients in centres with experience to perform pre-school lung function measurements could be considered.

Q6: Is there a need for dose-finding studies in this age group?

Although there was general agreement that there is a need to determine the appropriate dose, no clear recommendation could be provided on how to perform dose-finding studies because of lack of validated PD parameters available for this age group.

In this context the need to develop and validate appropriate biomarkers was stressed. At present candidate biomarkers, e.g. measurement of interleukins, are not correlated with clinical outcomes and are not well validated. It would be an urgent task for learned societies to address this unmet need and stimulate the required studies.

The example of paediatric dose-ranging studies for montelukast was discussed: based on PK data the paediatric doses were selected that provided overall drug exposures similar to that in adults assuming that the pathophysiology, symptoms, and treatment of asthma are similar between children and adults. Acknowledging that this assumption may not apply to pre-school wheezing, nevertheless the final conclusion after some lengthy discussion was that the only feasible way would be to conduct PK studies in adults first and children in a second step. The use of modelling simulations, child friendly sampling techniques and sparse sampling methodologies is to be encouraged.

Children 5 years and older and general issues:

3. Study design

Q1: Are placebo-controlled studies needed and justified? Are 3-arm studies to be requested (placebo, active comparator, test drug)?

Depending on the drug to be tested both, placebo- controlled or 3-arm studies would be needed.

In pre-school children, as extrapolation from adults or older children is not possible, and only minimal evidence for efficacy of currently available drugs is available, placebo-controlled studies are needed, even for inhaled corticosteroids (with a detailed patient characterisation – as discussed above). A pre-requisite must be clear pre-specified criteria for initiation of (standardised) rescue treatment and for drop-out/withdrawal of the study.

In above 5 year olds, in whom asthma can be reliably diagnosed, 3-arm studies were considered preferable. New biological treatments should be studied either as add-on to standard treatment in those patients uncontrolled on low-dose ICS or in comparative trials, demonstrating added benefit over standard treatment (see discussion above). However, the latter was questioned by some participants.

Q2: Inclusion criteria:

As the most frequently used inclusion criterion, i.e. >12 % improvement of FEV1 in response to short acting beta agonist inhalation is no longer seen in majority of well-controlled asthmatic children, a more suitable inclusion criterion would be a > 10% drop of FEV1 following induced bronchoconstriction and/or a 10% rise after inhaled short acting beta agonist, particularly in 5 –12 year old children.

For new biological treatments the study population should either be children not responding to low dose ICS or children on medium/high ICS dose whether it is possible to reduce ICS dose.

It was further discussed that for innovative drugs, depending on their mode of action (MOA), induced sputum with e.g. eosinophil count could be considered to identify the target population.

Q3: Choice of endpoint:

Lung function plus asthma control.

4. Exercise induced bronchoconstriction / asthma

Q: Need for separate studies?

- ***If yes: what should be the efficacy endpoint?***

- ***How to assess treatment effect in infants and toddlers?***

Separate trials were considered feasible and needed. However, the test drug should always be used as add-on to standard treatment according to current treatment guidelines.

Endpoint should be fall in FEV1 after exercise using a standardised (treadmill) exercise test. The repeatability of the test must be documented. As standardised exercise tests cannot reliably be performed in pre-school children, a lower cut-off age of 6 years was discussed to be reasonable. In addition, no validated and standardised endpoints are available in pre-school children.

One expert proposed novel devices to monitor wheeze ("wheezometers") in children younger than 6 years. However, since the standardised exercise tests cannot reliably be performed in pre-school children, a cut-off age of 6 years was agreed.

5. Choice of age appropriate device for inhaled medications:

- In pre-school children: pMDI plus spacer (with facemask in infants and toddlers)
- In children > 5 years: either pMDI plus spacer or breath actuated devices/DPI.
- It would be preferable to have the same device for all age groups (including adolescents/adults)
- Important to always ensure adequate instruction and training to confirm correct inhalation technique.
- Companies should be discouraged to develop new devices and spacer which can only be used with their own medicinal product (MP)
- The simultaneous use of different devices (e.g. pMDI for one drug and PDI for the other) was not considered to cause problems; thus no need to actively discourage it in the conduct of a trial as long as the two devices are always the same and correct inhalation technique is ensured throughout the study.

6. Specific immunotherapy (SIT) in allergic asthma

Q1: What is the place of specific immunotherapy (SIT) in allergic asthma?

(A recent Cochrane review on SIT in chronic asthma concluded that immunotherapy reduces asthma symptoms and use of asthma medications and improves bronchial hyper-reactivity *(Allergen immunotherapy for the treatment of chronic asthma. Abramson MJ, Puy RM, Weiner JM. Injection*

allergen immunotherapy for asthma. Cochrane Database of Systematic Reviews 2010, Issue 8. Art. No.: CD001186. DOI: 10.1002/14651858.CD001186.pub2))

While it was agreed that there is a need to assess the effect of SIT and that it would be important to have this topic addressed in the EMA Concept paper on the need for revision of the CHMP note for guidance on the clinical development of medicinal products in the treatment of asthma (CPMP/EWP/2922/01), which is currently under revision, conducting such trials was considered difficult, as SIT in allergic asthma

- is usually an add-on therapy;
- requires long-term treatment over several years to observe the expected immune-modulating effect;
- only stable, well-controlled patients can be enrolled in clinical trials;
- thus a large number of patients is needed to demonstrate an effect over standard therapy.

There was consensus that efficacy of SIT in allergic asthma should be evaluated in the same way as any other anti-asthmatic drug. Potential outcome measures could be:

- decreased need for controller medication,
- less exacerbations of asthma.

Conclusions

The meeting ended with a short summary of the main issues addressed:

1. Target study population / phenotypes / inclusion criteria:

In absence of a unified phenotype classification the following is recommended

- Below 5 years:
  - Lead inclusion criterion: doctor confirmed wheezing.
  - Stratification at trial entry only for predominantly viral exacerbated (intermittent) wheeze and multi trigger wheeze (including atopy) considered meaningful due to the difficulties in either confirming or refuting atopy in this young age group and because many children express atopy well after initial presentation with wheeze. However, all study participants must be well characterised regarding atopy (symptoms, sensitisation, heredity) at study entry and again at study end to allow pre-specified subgroup analysis atopic versus non-atopic children on trial completion.
- Above 5 years:
  - Doctor confirmed “classic” asthma
  - Lung function:

    in 5 –12 year old children: > 10% drop of FEV1 following induced bronchoconstriction,

    above 12 years: same as adults.

2. End points:

Control of asthma, rate of exacerbations.

Asthma control could be defined as minimal or no symptoms, minimal or no use of rescue medication, no activity limitations as outlined in the paper (by BP Yawn et al. Assessment of Asthma severity and asthma control in children. Pediatrics 2006;118:322-329).

Gunilla Hedlin, Jontahan Grigg, Peter Helms and Eugenio Baraldi commented on available asthma control questionnaires as to which instrument appears most suitable for the PDCO to consider requesting as secondary endpoint on all asthma PIPs:

- All four recommended the use of “Test for Respiratory and Asthma Control in Kids (TRACK)” for pre-school children.
- For older children, the experts’ opinions varied:
  - One expert considered the available questionnaires very similar and suitable as all can be administered on a monthly basis and hence are more likely to be completed over a 12 month period than daily diaries.
  - Three experts considered the use of the C-ACT, potentially combined with data on unscheduled visits, the use of SABA and OCS, as well as the two "longterm" questions from 5 idem-TRACK.

In addition lung-function in all patients above age of 5 years.

In below 5 year olds: exploratory end points including lung function and biomarkers recommended in subgroup of patients in selected centres.

3. Dose finding:

There is a need to determine the correct dose for all drugs, particularly in pre-school children. However, no validated PD parameter available; thus only PK studies with paediatric specific considerations (e.g. sparse sampling) were considered feasible

4. Device:

- Below 5 years: pMDI plus spacer (with facemask in infants and toddlers);
- Above 5 years: either pMDI plus spacer or breath actuated devices/DPI;
- Same device for all age groups (including adolescents/adults) preferable;
- Companies to be discouraged to develop new devices and spacer which can only be used with their own medicinal product (MP).

5. Placebo controlled studies justified?

- Below 5 years:
  - Placebo-controlled studies needed
  - Pre-requisite: clear pre-specified criteria for initiation of (standardised) rescue treatment and for drop-out/withdrawal of the study.
- Above 5 years:
  - 3-arm comparative studies considered preferable.
  - New biological treatments should be studied either as add-on to standard treatment in those patients uncontrolled on low-dose ICS or in comparative trials, demonstrating added benefit over standard treatment

6. Exercise induced bronchoconstriction:

- Waiver below 6 years
- Endpoint: fall in FEV1 after standardised exercise testing:
  - 10% fall in FEV1 in children below 12 years of age; and
  - 12% fall in FEV1 in children 12 years and older.

7. Long-term follow-up:

Safety:

- Depending on MOA in context of risk management plan (RMP)
- For authorised ICS:
  - available evidence on impact on growth in children above 5 years of age considered;
  - sufficient – no need for long-term monitoring;
  - below 5 years of age: need for growth monitoring for at least 2 additional years after cessation of treatment period within the context of the PIP
- For all new ICS: need to monitor growth in all paediatric patients in context of RMP - for at least 2 additional years after cessation of treatment period within the context of the PIP
- For LABA (only to be administered as fixed drug combination with ICS): high need to evaluate long-term safety in context of RMP

Efficacy:

- Need to follow-up all pre-school children enrolled in therapeutic trials until age of 6 years to see who will go on to develop “classic asthma” (with subsequent expression of atopy if not atopic at trial entry).

8. Specific immunotherapy (SIT) in allergic asthma

- Clear need to include SIT in asthma guideline.
- Efficacy endpoints in clinical trials should be same as with any other anti-asthmatic drug.