Allergen Immunotherapy in Asthma: Now and in the Future

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Management of asthma

<table>
<thead>
<tr>
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<th>Allergic</th>
<th>Nonallergic</th>
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<tbody>
<tr>
<td>Avoidance</td>
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<td>Pharmacotherapy</td>
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<td>Allergen immunotherapy (AIT)</td>
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A case of SCIT in allergic asthma

• Patient: 24 yrs, Male

• Diagnosis: HDM-allergic asthma with rhinitis

• Vaccine: Der p 50% + Der f 50% (Novo-Helisen Depot)

• Build-up: Conventional schedule

• Maintenance: 4-week intervals
FEV<sub>1</sub> (% pred.)

- Fluticasone 50 µg/day
- No medications for asthma and rhinitis

Dates:
- 9-Apr-13
- 7-May-13
- 6-Aug-13
- 11-Jun-14
- 20-Aug-14
- 4-Mar-15
- 22-Mar-16
SPT wheal size (A/H ratio, %)

- Der p: Blue line
- Der f: Orange line

Date: 3-Nov-10: 617
Date: 8-Jul-14: 259
Date: 5-Jul-16: 162
Current AIT...

• Severity: Mild-to-moderate asthma

• Allergen: HDM, animal, pollen, Alternaria (Allergy 2015;70:897)

• Route: SCIT and SLIT

• Duration: at least 3 – 5 yrs
Advantages of AIT...

• Long-lasting effect after discontinuation
  ✓ Effect of pharmacotherapy is transient

• Prevention of new allergen sensitization
**Long-lasting effect**

- Methacholine AHR improvement has been maintained at least 6 – 8 years after discontinuation in 3 SLIT groups compared to controls.

*JACI* 2010;126:969
Prevention of new sensitization

✓ At least 1 new skin sensitization was reduced in 3 SLIT groups compared to controls
Extended indication for AIT in asthma

• Well controlled asthma (regardless of severity) is not a contraindication

• Uncontrolled asthma is an absolute contraindication

• Partly controlled asthma is a relative contraindication

Allergy 2015;70:897 position paper
Role of AIT for stepping down medication

• Asthma medication: stepwise approach

• Non-pharmacological strategies to step down medication: add-on-AIT
SCIT to reduce ICS dose

- 54 HDM-allergic adult asthmatics
- SCIT
- 3 yrs

![Graph showing the reduction of ICS dose with SCIT and placebo over 3 years.](Allergy 2006;61:843)
SLIT to reduce ICS dose

- 604 HDM-allergic adult asthmatics

ICS dose/day

AQLQ score

ACQ score

Resp Med 2014;108:1430
SLIT to reduce asthma exacerbation

N=834

Period 1
Screening

5-7 weeks

Randomization

Period 2
Intervention as add on to ICS

7-12 months

Period 2A

Period 2B

Period 3
ICS reduction

6 months

End of trial

HDM tablet 12 SQ-HDM

HDM tablet 6 SQ-HDM

Placebo

ICS 50% reduction

ICS 100% withdrawal

50% ICS Reduction

100% ICS Reduction

Probability of First Moderate or Severe Asthma Exacerbation, %

Time During ICS Reduction, d

JAMA 2016;315:1715
In step 3 and 4, add-on-SLIT can be considered in HDM-allergic adult asthmatics with exacerbations despite ICS treatment, provided FEV$_1$ is > 70% pred.
Induction of Treg and Breg cell during AIT

World Allergy Organ J 2015;8:17

JCI 2014;124:4678
Limitations of AIT

• Effect: not so big

• Safety: anaphylaxis

• Treatment duration: long

• Uncontrolled asthma: contraindication
New approaches to increase AIT efficacy

- Change to a more efficient route of administration
  - Epicutaneous
  - Intralymphatic
- Increase the dose of allergen by reducing allergenicity by
  - Chemical modification (allergoid)
  - Recombinant modification
  - Not-IgE binding peptides
- Use of Th1 or Treg promoting TLR ligand
  - CpG oligonucleotides
  - MLP
- Suppression of Th2 response
  - Th2 cytokine antagonist
- Adjuvants
  - Probiotics
  - Vitamin D

Allergy Asthma Proc 2016;37:268
Treg or Breg cell-promoting agent & AIT

• AIT modulate immune reaction through increased production of Treg or Breg cells

• A new agent that generates Treg or Breg cells could be a potent adjuvant for the development of more effective and safe AIT
Flagellin, TLR5 ligand: A candidate to induce Treg cells

A Bacterial Flagellin, *Vibrio vulnificus* FlaB, Has a Strong Mucosal Adjuvant Activity To Induce Protective Immunity
Flagellin suppressed OVA-induced asthma

A. Experimental protocol

B. AHR

C. BAL

D. Lung tissue

JACI 2016;137:426
Flagellin decreased Th2/Th1 cytokines but increased Treg cell cytokines

E  BAL fluids

F  Bronchial LN cultures

JACI 2016;137:426
Flagellin induced Foxp3+ Treg cells

CD4+ T cells from bronchial LN
Flagellin generated regulatory DC

CD11c+ DC from bronchial LN

[Graphs showing IL-10, IL-12, TGF-β, and TNF-α levels with and without FlaB treatment for OVA+OVA and PBS+PBS conditions.]

[Bar graphs showing relative expression of IL-10, iDO, and COX-2 genes with and without FlaB treatment for OVA+OVA and OVA+OVA/FlaB conditions.]

[Graph showing ³H-thymidine incorporation with and without OVA peptide treatment for different concentrations of OVA peptide.]

JACI 2016;137:426
Effect of flagellin on human immune cells

- HDM-allergic adult asthma patients
- PBMC → monocyte-derived CD11c+ DC, CD4+ T cells
- Co-culture (DC+T cell + HDM extract)
Intracellular cytokines

Effect of flagellin on regulatory DC and Treg cell was reproduced in peripheral blood from asthma patients

JACI 2016;137:426
Summary of flagellin experiments

• Flagellin induced regulatory DC and Treg cells in mouse and human asthma

• Flagellin-adjuvanted AIT could maximize AIT efficacy by robust generation of Treg cells
Breg cell-promoting probiotics & AIT

- 60 HDM-allergic adult asthmatics
- SCIT for 6 m
- Probiotics: *Clostridium butyricum* (CB)
- 4 groups: AIT, AIT/CB, CB, Placebo

Am J Transl Res 2016;8:5256
Breg cell-promoting probiotics enhanced the effect of AIT in asthma patients

Am J Transl Res 2016;8:5256
Conclusions

Now

• AIT can be done if asthma is well controlled, regardless of asthma severity (Allergy 2015;70:897).

• AIT(SLIT) can be added to GINA step 3 or 4 to control asthma (GINA 2017).

Future

• Treg and Breg cell-promoting agents may be potent adjuvants for more effective and safe AIT vaccine.

• Flagellin, TLR5 ligand, may be one of the useful candidates.