The Value of Real World evidence

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Wiesbaden, Germany
Disclosure

Clinical studies:
• ALK-Abello, Danmark, Allergopharma, Germany, Artu-Biologicals, Netherlands, Bencard, Great Britain, Bionorica, Germany, Biomay, Austria, Boehringer Ingelheim, Germany, Cytos, Switzerland, HAL, Netherlands, Hartington, Spain, GSK, Great Britain, Leti, Spain, Lofarma, Italy, Novartis, Switzerland, MEDA, Germany, MSD, USA, Phadia / Thermofisher, Sweden, Optima, Germany, Roxall, Germany; DFG; BMBF, EU-Kommission; VW-Stiftung; Fresenius-Stiftung; Hochschulfond BW

Lecturing fee:
• ALK-Abello, Danmark, Allergopharma, Germany, Bencard, Great Britain, Bionorica, Germany, Boehringer Ingelheim, Germany, Cytos, Switzerland, HAL, Netherlands, Hartington, Spain, GSK, Great Britain, Leti, Spain, Lofarma, Italy, Novartis, Switzerland, MEDA, Germany, MSD, USA, Phadia / Thermofisher, Sweden, Optima, Germany, Roxall, Germany

Scientific advice:
• ALK-Abello, Danmark, Allergopharma, Germany, Bionorica, Germany, Boehringer Ingelheim, Germany, Cytos, Switzerland, Hartington, Spain, GSK, Great Britain, Leti, Spain, Lofarma, Italy, Novartis, Switzerland, MEDA/Mylan, USA/Germany
<table>
<thead>
<tr>
<th>Health Research</th>
</tr>
</thead>
<tbody>
<tr>
<td>biomedical basic research</td>
</tr>
<tr>
<td>experimental, animal, preclinical, ex vivo / in vitro</td>
</tr>
<tr>
<td>experiments</td>
</tr>
<tr>
<td>clinical research</td>
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<tr>
<td>clinical studies Phase I-III</td>
</tr>
<tr>
<td>Controlled trials</td>
</tr>
<tr>
<td>healthcare research</td>
</tr>
<tr>
<td>observational studies, Public Health-research, epidemiology, Health economics</td>
</tr>
<tr>
<td>„Real-world“-trials</td>
</tr>
</tbody>
</table>
## Combined Symptom and Medication Score (CSMS)

### Daily Symptom Score (dSS)

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>eyes itch</td>
<td>☐</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>tearing</td>
<td>☐</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>nose itch</td>
<td>☐</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>sneezing</td>
<td>☐</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>runny nose</td>
<td>☐</td>
<td>☑</td>
<td>☑</td>
</tr>
<tr>
<td>obstruction</td>
<td>☐</td>
<td>☑</td>
<td>☑</td>
</tr>
</tbody>
</table>

(maximum dSS: 6 x 3 = 18/6 = 3)

### Daily Medication Score (dMS)

<table>
<thead>
<tr>
<th>Medication</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antihistamines</td>
<td>☐</td>
<td>☑</td>
<td>☐</td>
<td>☐</td>
</tr>
<tr>
<td>Nasal corticosteroids</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
<td>☐</td>
</tr>
<tr>
<td>Oral corticosteroids</td>
<td>☐</td>
<td>☐</td>
<td>☐</td>
<td>☑</td>
</tr>
</tbody>
</table>

If rescue medication of different classes used: 

\[ dMS = \text{score of the highest class} \]

(maximum dMS = 3)

### Primary endpoint: CSMS = dSS + dMS (range 0-6)

## Patient needs in AR

<table>
<thead>
<tr>
<th>Needs</th>
<th>% quite/very important*</th>
<th>Mean*</th>
<th>SD*</th>
</tr>
</thead>
<tbody>
<tr>
<td>to be able to stay outdoors without symptoms</td>
<td>93.2</td>
<td>3.7</td>
<td>0.6</td>
</tr>
<tr>
<td>to no longer have a runny or stuffed up nose</td>
<td>90.4</td>
<td>3.6</td>
<td>0.7</td>
</tr>
<tr>
<td>to be healed of all symptoms</td>
<td>89.2</td>
<td>3.6</td>
<td>0.8</td>
</tr>
<tr>
<td>to be able to breathe through my nose more freely</td>
<td>88.5</td>
<td>3.5</td>
<td>0.8</td>
</tr>
<tr>
<td>to not have itching on the eyes, nose or palate anymore</td>
<td>85.4</td>
<td>3.6</td>
<td>0.7</td>
</tr>
<tr>
<td>to not have sneezing impulses</td>
<td>77.7</td>
<td>3.2</td>
<td>1.1</td>
</tr>
<tr>
<td>to have an easily applicable treatment</td>
<td>77.5</td>
<td>3.4</td>
<td>0.9</td>
</tr>
<tr>
<td>to have confidence in the therapy</td>
<td>76.7</td>
<td>3.5</td>
<td>0.8</td>
</tr>
<tr>
<td>to not have burning or watery eyes anymore</td>
<td>76.0</td>
<td>3.6</td>
<td>0.8</td>
</tr>
<tr>
<td>to feel less fatigued or groggy</td>
<td>75.5</td>
<td>3.5</td>
<td>0.8</td>
</tr>
<tr>
<td>to be able to engage in normal leisure activities</td>
<td>69.9</td>
<td>3.4</td>
<td>0.8</td>
</tr>
<tr>
<td>to be less dependent on doctor and clinic visits</td>
<td>64.1</td>
<td>3.2</td>
<td>1.1</td>
</tr>
<tr>
<td>to be able to sleep better</td>
<td>61.8</td>
<td>3.4</td>
<td>0.9</td>
</tr>
<tr>
<td>to have fewer side effects</td>
<td>61.2</td>
<td>3.2</td>
<td>1.1</td>
</tr>
<tr>
<td>to be more productive in everyday life</td>
<td>60.2</td>
<td>3.2</td>
<td>0.9</td>
</tr>
<tr>
<td>to have fewer out-of-pocket treatment expenses</td>
<td>59.2</td>
<td>3.0</td>
<td>1.3</td>
</tr>
<tr>
<td>to be able to concentrate better at work</td>
<td>56.9</td>
<td>3.3</td>
<td>0.9</td>
</tr>
<tr>
<td>to have no fear that the disease will become worse</td>
<td>50.0</td>
<td>3.2</td>
<td>1.0</td>
</tr>
<tr>
<td>to need less time for daily treatment</td>
<td>50.0</td>
<td>2.9</td>
<td>1.3</td>
</tr>
<tr>
<td>to experience a greater enjoyment of life</td>
<td>47.6</td>
<td>3.4</td>
<td>0.9</td>
</tr>
<tr>
<td>to feel less depressed</td>
<td>46.1</td>
<td>3.3</td>
<td>1.1</td>
</tr>
<tr>
<td>to feel less irritated</td>
<td>43.7</td>
<td>3.1</td>
<td>1.1</td>
</tr>
<tr>
<td>to feel more comfortable showing yourself</td>
<td>33.3</td>
<td>2.8</td>
<td>1.2</td>
</tr>
<tr>
<td>to be less burdened in your partnership</td>
<td>33.0</td>
<td>2.7</td>
<td>1.4</td>
</tr>
<tr>
<td>to be able to have a normal sex life</td>
<td>27.5</td>
<td>2.7</td>
<td>1.4</td>
</tr>
</tbody>
</table>
Economic impact of workplace productivity losses due to allergic rhinitis compared with select medical conditions in the United States from an employer perspective.
Pollen concentration in nature vs challenge chamber

Fig. 9. Fluctuation of grass pollen count during 4 h in a park setting and in the Vienna Challenge Chamber (VCC).

Fig. 10. Comparison of subjective eye itching using the conjunctival provocation test (CPT). This symptom was scored every 15 min on a 0-3 scale, in subjects studied in the Vienna Challenge Chamber (VCC) or in a park setting.
AR patients have high expectations from treatment

- 40%: expected to be cured by Tx
- 43%: expected suppression of symptoms

**Preferred therapy**
- Nasal spray: 30%
- Oral treatment: 24%
- Combination: 16%

**Approach**
- 31%: combination Tx with step-down approach
- 20%: mono-therapy with step-up approach
The AR landscape in the Real World is complex


AR: allergic rhinitis; Tx: treatment
What patients want: simplification of AR treatment

- Simplification of AR treatment
- Forgiving of as-needed use
- Well-tolerated
- Rapid onset of action
- Clinically-relevant symptom relief
- Relief from all symptoms
- Clear position in guidelines
- Suitable for all aetiologies
- Forgiving of as-needed use

AR: allergic rhinitis; Tx: treatment
Disorganized AR treatment in real-life

- Perceived knowledge exceeds actual knowledge
  - 29% of patients NOT know class of allergy medication they were taking
- Changing treatments
  - 26% of patients are constantly trying different medications to find one that ‘works’
- Confusion
  - 42% of patients are confused by all the different AR medications
- Non-compliance
  - 64% of patients fail to take their AR medication consistently
  - As needed use is associated with more breakthrough symptoms


AR: allergic rhinitis

A single medication with a more rapid onset of action would be advantageous
Reasons for non-compliance

Main causes for general non-compliance\textsuperscript{1,2}

1. Frequency and complexity of treatment
2. Adverse events (real or imagined)
3. Poor communication
4. Psychosocial factors
5. Rejection of diagnosis

Improving compliance with treatment\textsuperscript{3}

1. Keep it simple
2. Deliver it effectively
3. Avoid its problems
4. Call it medicine (not drug)
5. Provide it readily (samples)
6. Review its usage
7. Link it with lifestyle
8. Put it in writing
9. Support is psychosocially
10. Minimize its cost

• **Therapeutic principals in allergies**

  • > Allergen avoidance

  • > Symptomatic therapy

  • > specific immunotherapy
Avoidance of mite allergen is not effective

- 1122 patients with asthma (18 – 50 years)
- 65% sensitization to house dust mites
- DBPC, Encasings, endpoint: PEF

<table>
<thead>
<tr>
<th></th>
<th>Intervention</th>
<th>Control</th>
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<tbody>
<tr>
<td>PEF</td>
<td>411.0 + 93.2</td>
<td>415.5 + 93.4</td>
</tr>
<tr>
<td>Symptoms</td>
<td>1.35 + 0.76</td>
<td>1.35 + 0.77</td>
</tr>
<tr>
<td>QoL</td>
<td>33.1 + 16.3</td>
<td>32.6 + 16.9</td>
</tr>
</tbody>
</table>

- PEF: $\emptyset$ difference
- Symptoms: $\emptyset$ difference
- ICS: $\emptyset$ difference
- allergen-concentration after 12 month: no difference between verum and Placebo

Conclusion: Allergen-impermeable covers, as a single intervention for the avoidance of exposure to dust-mite allergen, seem clinically ineffective in adults with asthma.
Evidence exists in the literature for:

- Determinants of treatment outcomes\(^1,2\)
- Determinants of treatment compliance\(^3,4\)
- But NOT what constitutes a simple treatment

What we prescribe: Continuous treatment

AR treatments are most often prescribed for continuous use during the whole allergy season.
Breakthrough symptoms

- Patients frequently experience breakthrough symptoms whilst on therapy\(^1\)
  - Need for a more rapidly acting AR treatment for fast relief when symptoms breakthrough

\(^1\) Price et al, Clin Transl Allergy, 2015; \(^2\) Canonica et al, Allergy 2007; \(^3\) Schatz et al, Allergy 2007

- In Europe 32.8\% of patients report moderate-to-severe nasal and ocular symptoms on therapy\(^2\)
- In the U.S. 44.0\% of patients report suffering from nasal and ocular symptoms on treatment
  - 23.7\% report symptom severity as moderate/severe\(^3\)


Tx: treatment; rTNSS: reflective total nasal symptom score; rTOSS: reflective total ocular symptom score
Patients co-medicate searching for better & faster symptom relief

% moderate/severe patients on ≥ 2 AR medications

Reason for co-medicating:
- Increased nasal efficacy: 41%
- Increased ocular efficacy: 29%
- Faster nasal response: 16%
- Faster nasal response: 8%
- Other: 7%

Price et al, Clin Transl Allergy 2015
AR: allergic rhinitis
Rapid AR treatment switching in real life

- The true AR world as revealed by Allergy Diary
- AR treatment options and VAS scores from User 1 (Sweden)

<table>
<thead>
<tr>
<th>Date</th>
<th>No treatment</th>
<th>INS</th>
<th>MP-AzeFlu</th>
</tr>
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<tbody>
<tr>
<td>2015-10-29</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>2016-06-06</td>
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<td>2016-06-12</td>
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<td>2016-06-18</td>
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<tr>
<td>2016-09-30</td>
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</table>

- Patients **rapidly switch** AR treatment
  - If it’s not working they switch
- **Lack of control on INS** monotherapy
- AR control achieved on MP-AzeFlu
- Users stop treatment when symptoms are well-controlled
- Users do not log symptoms every day

Patients need a treatment which has a more rapid onset AND is more effective than an INS

Scadding et al, Rhinol 2018;In press
AR: allergic rhinitis; VAS: visual analogue scale; INS: intranasal corticosteroid
Rapid switching & poly-pharmacy in real life

- AR treatment options and VAS scores from User 2

- **Polypharmacy** use
  - AH + INS

- **Rapid switching**

- Control achieved with MP-AzeFlu

- Lack of control on AH + INS or INS monotherapy

Patients need a single treatment which has a more rapid onset AND is more effective than an INS

Bachert et al, Clin Transl Allergy 2018; In press

AR: allergic rhinitis; VAS: visual analogue scale; AH: anti-histamine; INS: intranasal corticosteroid
ARIA Phase 3: The *Allergy Diary* strengthens change management

- Patient empowerment & the finger approach
Efficacy of continuous vs on demand treatment is debated

- % symptom-free days in favour of INS on demand (30% vs 22%)
- % symptom-free eye symptoms significantly in favour of INS on demand (40% vs 56%)
- INS on demand group used 61% less fluticasone (p<0.0001)

An on-demand INS strategy has the advantage of a lower overall corticosteroid exposure and less costs

Wartna et al, Allergy 2017
INS: intranasal corticosteroid; AH: anti-histamine
Pollen concentration vs symptoms

courtesy Petra Zieglmayer, Vienna
## Current state of play: onset of action by drug class

<table>
<thead>
<tr>
<th>Drug Combinations</th>
<th>Onset of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>OAH</td>
<td>LOR: 75 mins&lt;sup&gt;1&lt;/sup&gt; CET: 60 mins&lt;sup&gt;1&lt;/sup&gt; DES: 150 mins&lt;sup&gt;2&lt;/sup&gt; FEX: 60 mins&lt;sup&gt;3&lt;/sup&gt; BIL: 60 mins&lt;sup&gt;4&lt;/sup&gt;</td>
</tr>
<tr>
<td>INAH</td>
<td>AZE: 15 mins&lt;sup&gt;1&lt;/sup&gt; OLO: 30 mins&lt;sup&gt;5&lt;/sup&gt;</td>
</tr>
<tr>
<td>INS</td>
<td>FF: 8 hrs&lt;sup&gt;6&lt;/sup&gt; FP: 8 hrs MF: 12 hrs&lt;sup&gt;7&lt;/sup&gt; BUD: 12 hrs&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
<tr>
<td>INS + OAH</td>
<td>FP + LOR: 150 mins&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
<tr>
<td>MP-AzeFlu</td>
<td>MP-AzeFlu: 5 mins&lt;sup&gt;9&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

SLIT in (uncontrolled) Asthma

Time until mean or severe asthma-exacerbation

Hazard-Rate (% Risko-Reduktion)

12 SQ-HDM: 0.66 (34%), p=0.017
6 SQ-HDM : 0.69 (31%), p=0.028

MITRA-Studie: EudraCT Number: 2010-018621-19
Excellent cost effectiveness of Allergen-Immunotherapy (AIT) in Allergic Rhinitis
Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: A randomized, double-blind, placebo-controlled trial

Background: Investigations meeting current standards are limited for the effect of house dust mite (HDM) allergy immunotherapy in asthmatic patients.
Standardized quality (SQ) house dust mite sublingual immunotherapy tablet (ALK) reduces inhaled corticosteroid use while maintaining asthma control: A randomized, double-blind, placebo-controlled trial

Background: Investigations meeting current standards are limited for the effect of house dust mite (HDM) allergy immunotherapy in asthmatic patients.

Conclusion: Efficacy in mild-to-moderate asthma of 6 SQ-HDM relative to placebo was demonstrated by a moderate statistically significant reduction in the ICS dose required to maintain asthma control.

Data on the long-term effects of sublingual immunotherapy (SLIT) are sparse, and the optimal duration of treatment is a matter of debate.
Data on the long-term effects of sublingual immunotherapy (SLIT) are sparse, and the optimal duration of treatment is a matter of debate.
Conclusions: Three years of SCIT induced significant improvement in children with dust mite respiratory allergy, **but a 5-yr course** added clinical improvement in rhinitis.
How adherent to sublingual immunotherapy prescriptions are patients?

FIG 1. Percentages of SLIT treatments still ongoing at 1, 2, and 3 years after the initial prescription. Upper panel, Percentages for pollens and house dust mite SLITs. Lower panel, Percentages according to the reimbursement modality. Significant P values are indicated above the bars.
Clinical implications: Efforts to increase persistence with allergen immunotherapy in real life are urgently needed because large amounts of money are currently being misspent as a result of premature discontinuation of treatment.
ARIA Phase 3: The *Allergy Diary* strengthens change management

- Patient empowerment & the finger approach

![Diagram showing cycle with Patient (an active role), Treatment choice, Goals, Control assessment, Education, Lifestyle, Measureable outcomes, and a finger pointing upwards.](image)
ARIA real World approach for care pathways in rhinitis and asthma

Patient with allergic rhinitis symptoms

Self-care

Pharmacist

General practitioner

Specialist

Emergency care (asthma)

Bousquet et al, Eur Respir J 2014

OTC: over the counter
Guidelines are based on evidence derived from RCTs: real life data should be considered

- **RCTs**
  - Continuous treatment
  - Defined treatment start and end time points
  - Homogenous patient population
  - Adherence to protocol is required
  - Success of treatment
    - Superiority to placebo
    - Measured using symptom scores

- **Real life**
  - Intermittent treatment
  - Heterogeneous patient population
  - Non-adherence is common
  - Success of treatment
    - ??
    - ??

Real life data should be incorporated into the next generation guidelines

RCT: randomized controlled trial
Treatments received in MASK

MACVIA: Contre les Maladies pour un Vieillissement Actif; MASK: Mobile Airways Sentinel Network
Adherence to treatment

2,850 users
Adherence
≥ 5 days
70% same treatment
6% users

Most patients use their treatment for ≤ 4 days and are non-adherent

Bousquet et al, Allergy 2018
mHealth approach for care pathways

Goals
1. Develop for each step an mHealth tool
2. cell phone for self-care
3. interoperable tablet for pharmacists and physicians
4. Patient’s personal data with maintained privacy

Bousquet et al, Eur Respir J 2014
Stepwise approach for next generation care pathways

**Goals**
1. For each step develop a document with a 4-pages pocket-guide
2. Include mHealth for each step
3. From one step to the next one
4. When to go to the next step
5. Stepwise approach for management
6. Develop machine learning to optimize ICPs

**Diagram**
- **Patient with allergic rhinitis symptoms**
- **Self-care**
- **Pharmacist**
  - Incorrect diagnosis Severity
  - OTC medication
  - Improvement
  - Failure
  - Check For asthma
- **General practitioner**
  - Incorrect diagnosis Severity
  - Treatment
  - Improvement
  - Failure
- **Specialist**
- **Emergency care (asthma)**

**Annotations**
- Improvement in care pathway design to enhance patient participation, health literacy and self-care through technology assisted ‘patient activation’
- ARIA in the pharmacy
- Next-generation ARIA-WAO guidelines

**Note**
OTC: over the counter; ICP: integrated care pathway
Embedding environment in next generation care pathways

**Goals**

1. Embedding environmental data
2. Prevention of symptoms and asthma (self-care)
3. Assess if severity of symptoms is associated with allergens or pollution
4. Predict emergency care visits
5. Develop machine learning to optimize ICPs
European Rhinallergy meeting

Focus on allergen specific immunotherapy and biologicals

21 - 23 March 2019

Eastbourne, United Kingdom

- Local OC: M Shamji, S Durham, C Hopkins, G Scadding
- EAACI OC: P Gevaert, L Klimek, JL Fauquert, L Jacobsen, O Palomares Gracia, P Hellings, I Agache
- ENT Section & Interest groups: Immunotherapy & Biologicals
- EAACI congresses: C Schmidt-Weber

European Rhinallergy Meeting