Allergic Rhinitis and Non-allergic Rhinitis
Phenotypes and Endotypes of Allergic Rhinitis

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Allergic rhinitis

IgE-mediated inflammation of the nasal mucosa after allergen exposure and presents with the 3 cardinal symptoms of sneezing, nasal obstruction and rhinorrhea

Phenotype and Endotype

“Phenotype” describes subtypes of a disease defined by a ‘clinically observable characteristics’.

“Endotype” describes subtypes of a disease defined by a ‘distinct pathogenetic mechanism’. (genetic, pharmacologic, physiologic, biologic and immunologic)
Phenotypes of allergic rhinitis

• Disease severity
  Mild, Moderate/Severe
• Disease duration
  Intermittent, Persistent
• Seasonality
  Seasonal, Perennial
• Sensitization pattern
  Systemic, Local
• Age
  Pediatric, Adult, Geriatric
• Dominant symptom
  Sneezers, Runners, Blockers
• Presence of comorbidities
  With asthma, With sinusitis, etc.
Phenotyping based on disease Severity and Duration -ARIA classification-

4 phenotypes

- Mild Intermittent
- Mild Persistent
- Moderate/Severe Intermittent
- Moderate/Severe Persistent

Japanese cedar/cypress pollinosis: JCCP

- JCCP is the most popular seasonal allergic rhinitis in Japan.
- JCCP is caused by huge exposure to Japanese cedar and Japanese cypress pollen.
- These pollens disperse for approximately 3 months in spring (from February to May).
- About 1/4 of Japanese suffer from JCCP with substantial impairment in QOL, now called as the “National Affliction”.


Japanese cedar pollen

Cryptomeria japonica

Japanese cypress pollen

Chamaecyparis obtusa
Phenotyping of Japanese cedar/cypress pollinosis based on ARIA classification

- Mild Intermittent (4.6%)
- Mild Persistent (4.4%)
- Moderate/severe Intermittent (23.8%)
- Moderate/severe Persistent (67.2%)

n = 3,382


Seasonal AR (Pollinosis) ≠ Intermittent AR
Perennial AR ≠ Persistent AR
Phenotyping based on Age -characteristics of pediatric allergic rhinitis-

• High prevalence of comorbid allergic diseases such as asthma
• High prevalence of comorbid ENT diseases such as otitis media
• Less complaint of symptoms compared with objective findings
• Characteristic physical signs due to itch
  • allergic salute, allergic shiner, facial mannerism, etc.
Comparison between complaint and objective finding of rhinorrhea in pediatric AR

Double proportion of severe rhinorrhea in objective finding

Phenotyping based on Symptoms -mechanisms for the onset of allergic rhinitis-

**Early phase reaction**
- Sensory nerve
- Medulla
- Sneeze
- Gland
- nucleus salivatorius
- Rhinorrhea
- Hypersecretion
- Stasis
- Congestion
- Exudation, edema

**Late phase reaction**
- Inflammatory cell infiltration
- Eosinophils, Neutrophils
- Basophils, Lymphocytes
- Release of Pro-inflammatory mediators
- Mucosal swelling
- Congestion

**Reactions**
- Non-specific hypersensitivity
- Repeated reaction
- Irreversible mucosal swelling

**Chemokines**
- IL-4, IL-5, IL-13, GM-CSF, IFN-α
- LTα, LTB4, PAF, TXA2
- eotaxin, TARC, RANTES, IL-8

**Cell Types**
- Mast cells
  - Mucosal type mast cells
  - Connective tissue type mast cells
- Th2 cells
- B cells
- Epithelial cells
- Endothelial cells
- Fibroblasts

**Mediators**
- Histamine (Hi)
- Leukotrienes (LTs)
- Thromboxane A2 (TXA2)
- Prostaglandin D2 (PGD2)
- Platelet activating factor (PAF)

**Phenotyping based on Symptoms**

Sneeze in allergic rhinitis

- A pure neural reflex
- Stimulation of H1 receptor on sensory nerve by histamine
  → Principal sensory nucleus of trigeminal nerve
  → Sneezing nucleus in medulla
  → Reflecting constriction of respiratory muscles
- Enhanced by hypersensitivity of nasal mucosa

**Hypersensitivity of nasal mucosa**

- Augmented reaction to not only allergen-specific but also non-specific stimulation such as histamine, methacholine and cold

  **Priming effect**
  Once the disease has developed, the antigen level required for expression of similar symptoms decreases to 1/10-1/100.

**Minimal persistent inflammation (MPI)**
Even exposure to antigen to an extent not causing symptoms leads to mucosal infiltration by inflammatory cells.
Rhinorrhea in allergic rhinitis

- Parasympathetic nerve reflex induced by histamine (85-95%)
  Sensory nerve → Principal sensory nucleus → nucleus salivatorius → parasympathetic nerve → glands and vessels

- Direct effect of chemical mediators (Hi, LTs, PAF) on glands and vessels

The effect of unilateral vidian neurectomy on the amount of nasal secretion from ipsilateral and contralateral nasal cavities induced by unilateral antigen challenge on the vidian neurectomized nasal mucosa in patients with perennial allergic rhinitis

<table>
<thead>
<tr>
<th></th>
<th>Before vidian neurectomy</th>
<th>After vidian neurectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Antigen challenge</td>
<td>Antigen challenge</td>
</tr>
<tr>
<td>Amount of nasal secretion, mL/10 min</td>
<td>Vidian neurectomized nasal cavity</td>
<td>Contralateral nasal cavity</td>
</tr>
<tr>
<td></td>
<td>1.593±0.71</td>
<td>1.17±0.52</td>
</tr>
<tr>
<td></td>
<td>0.03±0.02(^a)</td>
<td>1.08±0.64(^b)</td>
</tr>
</tbody>
</table>

\(^a\) P<0.0001 versus before vidian neurectomy
\(^b\) Not significant versus before vidian neurectomy
\(^c\) P<0.0001 versus before topical anesthesia using 10% cocaine

(Konno A, Curr Allergy Asthma Rep 10: 105, 2010)
Congestion in allergic rhinitis

**Early phase reaction**
- Direct effect of mediators on vessels
  - (LTs>TXA$_2$=PAF>PGD$_2$>Hi)
- Neural reflex
  - (NO>>SP, VIP, CGRP)

**Late phase reaction**
- Allergic inflammation
  - Inflammatory cell infiltration (Eo, Th2 etc.)
  - + pro-inflammatory molecules (cytokines, granule proteins etc.)

Allergic inflammation in the nose
Systemic allergic reactions (positive skin test or positive serum antigen specific IgE antibody) are absent, but allergic reactions (positive nasal mucosa antigen challenge test or positive nasal discharge antigen specific IgE antibody) are visible locally in the nasal mucosa alone.

Possibly diagnosed as vasomotor rhinitis (idiopathic rhinitis) or hypereosinophilic rhinitis in the past.

Responding to treatment with nasal antihistamines or INS (+ allergen immunotherapy)

Still controversial whether LAR is an independent disease or the early form of allergic rhinitis.

A Case of LAR: Male, 31 years old

- Complaining of paroxysmal watery rhinorrhea and sneezing since 2 years ago.
- Perennial symptoms without seasonal aggravation.
- Negative in serum test of IgE specific to antigens (mite, animals, fungi, pollens).
- Symptoms alleviated in response to nasal steroid spraying but the patient was referred to our department for cause identification.

Nasal discharge eosinophil test: Negative
Serum total IgE level: 38 IU/ml
Serum antigen specific IgE antibody test: Negative as to insects, Trichophyton and *Staphylococcus aureus* enterotoxin.

**Nasal allergen provocation test:** HD negative, Alternaria negative, Aspergillus negative but **Candida** positive.
Nasal provocation test with Candida
## Diseases Analogous to Allergic Rhinitis

<table>
<thead>
<tr>
<th></th>
<th>Allergic rhinitis (typical)</th>
<th>Local allergic rhinitis (LAR)</th>
<th>Non-allergic rhinitis with eosinophilia syndrome</th>
<th>Vasomotor rhinitis (idiopathic rhinitis)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age upon onset</strong></td>
<td>Child - Adult</td>
<td>Adult</td>
<td>Adult</td>
<td>Adult</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>Among children, ♂ &gt; ♀</td>
<td>Unknown</td>
<td>♂ ≤ ♀</td>
<td>♂ ≤ ♀</td>
</tr>
<tr>
<td><strong>Nasal symptoms</strong></td>
<td>Typical</td>
<td>Typical</td>
<td>Atypical</td>
<td>Atypical</td>
</tr>
<tr>
<td><strong>Ocular symptoms</strong></td>
<td>Many</td>
<td>Many</td>
<td>Scant</td>
<td>Scant</td>
</tr>
<tr>
<td><strong>Skin test</strong></td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td>(serum antigen specific IgE)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Nasal discharge eosinophil</strong></td>
<td>Positive</td>
<td>Negative/Positive</td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Nasal discharge specific IgE</strong></td>
<td>Positive</td>
<td>Positive</td>
<td>(Negative)</td>
<td>(Negative)</td>
</tr>
<tr>
<td><strong>Nasal mucosa challenge test</strong></td>
<td>Positive</td>
<td>Positive</td>
<td>Negative</td>
<td>Negative</td>
</tr>
<tr>
<td><strong>Nasal hypersensitivity</strong></td>
<td>Enhanced</td>
<td>Slightly enhanced</td>
<td>Slightly enhanced</td>
<td>Slightly enhanced</td>
</tr>
<tr>
<td><strong>Frequency</strong></td>
<td>About 90%</td>
<td>Unknown</td>
<td>About 2%</td>
<td>About 7%</td>
</tr>
</tbody>
</table>

Reproduced with modifications from the Guideline for the Management of Allergic Rhinitis in Japan (2016 Version)
## Summary
- Phenotypes of AR and suggested medicine-

<table>
<thead>
<tr>
<th>Clinical observation</th>
<th>Phenotype</th>
<th>Suggested medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severity and Duration (ARIA classification)</td>
<td>Mild Intermittent</td>
<td>AH (oral, nasal) etc.</td>
</tr>
<tr>
<td></td>
<td>Mild Persistent</td>
<td>AH (oral nasal) And/or INS, LTRA etc.</td>
</tr>
<tr>
<td></td>
<td>Moderate/Severe Intermittent</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Moderate/Severe Persistent</td>
<td>INS</td>
</tr>
<tr>
<td>Seasonality</td>
<td>Seasonal</td>
<td>AH (oral nasal) etc.</td>
</tr>
<tr>
<td></td>
<td>Perennial</td>
<td>LTRA etc.</td>
</tr>
<tr>
<td>Sensitization pattern</td>
<td>Systemic</td>
<td>Nasal AH, INS</td>
</tr>
<tr>
<td></td>
<td>Local</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>Pediatric</td>
<td>Care for impaired performance and growth</td>
</tr>
<tr>
<td></td>
<td>Adult</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Geriatric</td>
<td>Care for drug metabolism</td>
</tr>
<tr>
<td>Symptom</td>
<td>Szeezers/Runners</td>
<td>H1RA</td>
</tr>
<tr>
<td></td>
<td>Blockers</td>
<td>LTRA, INS</td>
</tr>
</tbody>
</table>

AH: anti-histamine, INS: intranasal corticosteroid, LTRA: leukotriene receptor antagonist
### Endotypes of allergic rhinitis

<table>
<thead>
<tr>
<th>RHINITIS ENDOTYPES</th>
<th>NON-TYPE 2</th>
<th>TYPE 2</th>
<th>NEUROGENIC</th>
<th>EPITHELIUM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONGESTION</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinorrhea</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyposmia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sneezing</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Itching</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NHR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMMON COLD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RHINITIS PHENOTYPES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>severity / duration / sensitization pattern / co-morbidities</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RHINITIS PHENOTYPES</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rhinitis of the ELDERLY</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR with NHR</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Precision Medicine
Non-type 2 endotypes of allergic rhinitis

-Role of IL-17A on inflammation-

IL-17A

Epithelial cells
- IL-6, IL-8, CCL1, CXCL6
- ICAM-1, β-defensin2
- CCL20, G-CSF
- MUC5B, MUC5AC

Fibroblasts
- IL-6, IL-8, IL11
- CXCL1, ICAM-1, C3
- Factor B, G-CSF
- RANTES (by TNF)
- GM-CSF (with IL-1β or TNF)
- Mitogenic activity (with bFGF, HGF, VEGF)

Endothelial cells

Smooth muscle cells
- IL-6, IL-8
- CCL11, CXCL1

Macrophages
- IL-1β, TNF, MMP-9

Keratinocytes
- IL-6, IL-8, β-defensin2
- B-defensin3, S100A8, S100A8, S100A9
- CCL27 (by TNF)

Granulopoiesis

Neutrophils

Dendritic cells

CCL17/TARC

Non-type 2 endotypes of allergic rhinitis - Role of IL-17A on inflammation -

Epithelial cells
- IL-6, IL-8, CCL1, CXCL6
- ICAM-1, β-defensin2
- CCL20, G-CSF
- MUC5B, MUC5AC

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- B-defensin3, S100A8, S100A8, S100A9
- CCL27 (by TNF)

Granulopoiesis

Neutrophils

Dendritic cells

CCL17/TARC
Expression of IL-17A on human nasal mucosa from patients with allergic rhinitis

Control (rabbit IgG)  IL-17 A

Clinical significance of local IL-17A expression in AR

Comparison of numbers of IL-17A+ cells in nasal mucosa

\[ \text{IL-17A+ cells (cells/field)} \]

- NAR: Non-allergic hypertrophic rhinitis, \( n=13 \)
- NARES: Non-allergic rhinitis with eosinophilia syndrome, \( n=7 \)
- PAR: Persistent allergic rhinitis, \( n=21 \)

\[ \text{p=0.002} \quad \text{p=0.843} \quad \text{p=0.021} \]

Relationship between numbers of IL-17A+ cells and total nasal symptom score

\[ \text{TNSS} \quad r=0.403 \quad p=0.011 \]

NAR: Non-allergic hypertrophic rhinitis
NARES: Non-allergic rhinitis with eosinophilia syndrome
PAR: Persistent allergic rhinitis

Neurogenic endotype of allergic rhinitis
-Role of TRPV1-

Transient receptor potential vanilloid 1 (TRPV1)

- A sensory nerve receptor expressed on the trigeminal sensory neurons in the nose
  - Enhanced expression in chronic inflammation

- Activated by several physiological stimuli
  - Capsaicin, heat, low pH, etc.
  - Mediators such as histamine, PGs

- Contributes to nasal hyper-responsiveness not only in non-allergic rhinitis but also allergic rhinitis
TRPV1-mediated itch in seasonal allergic rhinitis

-Alenmyr L, et al. Allergy 64: 807, 2009-

- Nasal challenge with TRPV-1 agonists were performed in patients with SAR (n=10).

- Olvanil (TRPV1-agonist) induced significant rhinorrhea, pain and itch during the pollen season but not prior to the season.

- 2-3 patients failed to respond the challenge with TRPV1-agonists.

Existence of neurogenic endotype in SAR
Type 2 endotypes of allergic rhinitis

-Role of type 2 cytokines in allergic rhinitis-

SPF Allergen Microbes
Epithelial cells IL-25 IL-33 TSLP etc.
Dsc
ILC2
Th2 cells IL-4
Naïve T cells
Basophils

Type 2 cytokines
IL-4 IL-5 IL-13 IL-31

Mast cells
IgE
Eosinophils

Inflammation

Type I allergy

Determination of pollen antigen-specific cytokine production by peripheral blood mononuclear cells (PBMCs)

Blood sampling

Isolation of PBMC by density gradient

Ag (-)

Cry j 1 (10 µg/ml)

72 hours’ Incubation

Cytokine determination (IL-5/IL-13/IL-31/IFN-γ/IL-17A)
Specific production = (Ag+) - (Ag-)
Production of IL-5 by PBMCs in response to Cry j 1

IL-31

• A newly discovered Th2 cytokine in 2004
• A member of IL-6/gp130 family cytokines
• Produced by activated CD4+ cells (particularly Th2 cells), monocytes, macrophages, mast cells, and DC

Clinical characterization of IL-31 in allergic diseases
• Elevation of serum concentration in patients with bronchial asthma
• Enhancement of local expression in atopic dermatitis (AD)
• Correlation between serum concentration and clinical severity in AD

Effect of humanized anti-IL-31 receptor mAb on atopic dermatitis

- Phase I/Ib clinical trial for atopic dermatitis
- Single subcutaneous injection of anti-IL-31 receptor mAb (CIM331) or placebo to healthy controls or Japanese patients with AD
- Significant reduction of itch (approx. half) as compared with placebo

Production of IL-31 by PBMCs in response to Cry j 1

Positive responder: 18/29 (62.1%)  
Negative responder: 11/29 (37.9%)

by Mann-Whitney’s U-test
Comparison of the amounts of IL-5, IL-13 and IFN-γ between patients showing positive and negative production of IL-31

IL-5

<table>
<thead>
<tr>
<th>IL-31 production</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative (n=11)</td>
</tr>
</tbody>
</table>

[Data representation with significance levels: p=0.009, p=0.007, p=0.132]

IL-13

<table>
<thead>
<tr>
<th>IL-31 production</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative (n=11)</td>
</tr>
</tbody>
</table>

[Data representation with significance levels: p=0.007]

IFN-γ

<table>
<thead>
<tr>
<th>IL-31 production</th>
</tr>
</thead>
<tbody>
<tr>
<td>negative (n=11)</td>
</tr>
</tbody>
</table>

[Data representation with significance levels: p=0.132]

Comparison of the naso-ocular symptoms and QOL during the peak season of cypress pollen dispersion between patients showing positive and negative production of IL-31

<table>
<thead>
<tr>
<th>Symptom Score</th>
<th>QOL Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Score</td>
<td>Score</td>
</tr>
<tr>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>20</td>
</tr>
<tr>
<td>20</td>
<td>60</td>
</tr>
</tbody>
</table>

**Symptom Score**

- **Score**: 0, 10, 20
- **p-value**: 0.259

**QOL Score**

- **Score**: 0, 20, 60
- **p-value**: 0.001

---

Correlation between the naso-ocular symptoms and QOL during the peak season of cypress pollen dispersion and the amounts of Cry j 1-induced IL-31 produced by PBMCs

Naso-ocular Symptoms

QOL

\[ \rho = 0.263, \ p = 0.207 \]

\[ \rho = 0.641, \ p < 0.001 \]

by Spearman's correlation coefficient by rank test
Proposed high type 2 endotype in allergic rhinitis

Naïve T cell → IL-5/IL-13 producing Th2 cell → IL-31 producing Th2 cell

No AR → Onset of AR → Exacerbation of AR
Epitelium endotype of allergic rhinitis
-epithelium-derived immune responses (Epimmunome)-
IL-33

A member of IL-1 cytokine family
Produced by epithelial cells and vascular endothelial cells

Receptor: ST2/IL-1RAcP
Expressed on Th2, ILC2, MC and Baso

Induces Type 2 cytokine production by Th2, ILC2 and basophils
Induces IL-6/IL-13 production by mast cells
Enhances mucin production in mouse
(Kondo Y, IL 20: 791, 2008)

Higher level of IL-33 in serum and nasal secretions in AR patients
Genetic polymorphism in IL-33 and ST2 in AR

Elevated serum IL-33 in patients with JCCP

(Sakashita M, Fujieda S, et al, CEA 38: 1875, 2008)
Expression of IL-33 on human nasal mucosa

Control

IL-33
Effect of recombinant IL-33 on Cry j 1-induced cytokine production by PBMC

- IL-5: I---p<0.001---I
- IL-13: I---p<0.001---I
- IFN-γ: I---p=0.528---I

IL-33 (5ng/ml)

PBMC

Cry j 1 (10μg/ml)

+(−) IL-33

IL-5
IL-13
INF-γ

(n=25)
by Wilcoxon’s signed rank test (unpublished data)
Enhanced expression of IL-33 mRNA in human nasal epithelial cells by TLR9 signaling

Endotypes related to treatment response

• Glucocorticoid (GC) responsive/resistant
• Leukotriene receptor antagonist (LTRA) responsive/resistant
• Anti-IgE responsive/resistant
• Anti-IL-5 responsive/resistant
• Anti-IL-4/IL-13 responsive/resistant
Endotypes related to treatment response

-GC resistant endotype-

Glucocorticoid receptor $\beta$ (GR-$\beta$):
a natural spliced variant lacking GC binding (decoy receptor)

Expression of GR-$\beta$ in nasal mucosa

Comparison of GR-$\beta^+$ cells between patients and controls

Endotypes related to treatment response
-LTRA responsive endotype-

• Allelic variant of leukotriene C₄ synthase (LTC4S) increases the synthesis of cysLT in eosinophils.

• A significant relationship between clinical response to pranlukast (LTRA) and genetic variability of LTC4S: C(-444) in Japanese asthmatic patients.

### Table 4
Multivariate regression analysis of clinical response to pranlukast (% increase in FEV₁)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Standardized partial regression coefficient †</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reversibility after salbutamol (FEV₁)</td>
<td>0.38</td>
<td>0.031</td>
</tr>
<tr>
<td>LTC₄ synthase C(-444) allele</td>
<td>0.44</td>
<td>0.018</td>
</tr>
<tr>
<td>CL/F</td>
<td>0.14</td>
<td>0.431</td>
</tr>
</tbody>
</table>

† Adjusted for gender and age.
CL/F, oral clearance; LT, leukotriene.

Endotypes related to treatment response  
-Anti-IgE responsive endotype- 

Effect of Omalizumab on Japanese cedar/cypress pollinosis 

About 1/4 of omalizumab-treated patients were symptom-free. 

## Summary

- Endotypes of AR and suggested precision medicine-

<table>
<thead>
<tr>
<th>Endotype</th>
<th>Biomarker</th>
<th>Suggested precision medicine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type 2</td>
<td>IL-5, IL-13, IL-31 etc. Nasal NO?</td>
<td>GC Immunotherapy</td>
</tr>
<tr>
<td>Non-type 2</td>
<td>IL-17A, IFN-γ?, TNF-α?</td>
<td>Macrolides??</td>
</tr>
<tr>
<td>Neurogenic</td>
<td>SP, NK TRP channels</td>
<td>Anti-choligergic Capcaisin, TRPV1 antagonist</td>
</tr>
<tr>
<td>Epithelium</td>
<td>TSLP, IL-33, IL-25 etc.</td>
<td>Nasal irrigation?</td>
</tr>
<tr>
<td>Treatment response</td>
<td>GR-β</td>
<td>GC</td>
</tr>
<tr>
<td></td>
<td>LTC4S</td>
<td>LTRA</td>
</tr>
</tbody>
</table>
Thank you for your attention.
Effect of mucosal TRPV1 inhibition in allergic rhinitis


### Table 2.

Effects of the transient receptor potential vanilloid-1 (TRPV1) blocker SB-705498 on nasal symptoms (range, 0–3) produced by capsaicin challenge in patients with seasonal allergic rhinitis (n = 12). The symptoms pain or smart and a sensation of heat were attenuated by the TRPV1 blocker.

<table>
<thead>
<tr>
<th></th>
<th>SB-705498</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pain or smart</td>
<td>0.0 (0.0)</td>
<td>1.5 (1.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Heat</td>
<td>0.0 (0.0)</td>
<td>1.0 (1.0)</td>
<td>0.008</td>
</tr>
<tr>
<td>Sneezes or itch</td>
<td>0.0 (0.0)</td>
<td>0.0 (1.0)</td>
<td>0.180</td>
</tr>
<tr>
<td>Secretion</td>
<td>1.0 (1.0)</td>
<td>1.0 (0.0)</td>
<td>0.157</td>
</tr>
<tr>
<td>Blockage</td>
<td>0.5 (1.5)</td>
<td>1.0 (1.0)</td>
<td>0.480</td>
</tr>
</tbody>
</table>

Interquartile ranges are given within parenthesis.

### Table 3.

Effects of the transient receptor potential vanilloid-1 (TRPV1) blocker SB-705498 on total nasal symptoms (TNSS; range, 0–9) in patients with seasonal allergic rhinitis (n = 26). When the patients received placebo, the allergen challenge series produced moderate to marked post-challenge symptoms and mild around-the-clock symptoms. The TRPV1 blocker did not affect these symptoms.

<table>
<thead>
<tr>
<th></th>
<th>SB-705498</th>
<th>Placebo</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evening symptoms</td>
<td>1.5 (1.7)</td>
<td>1.0 (1.3)</td>
<td>0.130</td>
</tr>
<tr>
<td>Morning symptoms</td>
<td>1.7 (1.3)</td>
<td>1.0 (1.3)</td>
<td>0.203</td>
</tr>
<tr>
<td>Post-challenge symptoms</td>
<td>4.8 (1.7)</td>
<td>5.0 (2.4)</td>
<td>0.370</td>
</tr>
</tbody>
</table>

Interquartile ranges are given within parenthesis.
Production of IL-31 by PBMCs in response to Cry j 1

Correlation between amounts of IL-31 and Th1/Th2 cytokines produced by PBMCs in response to Cry j 1

IL-5

\[ \rho = 0.680 \]
\[ p < 0.001 \]

IL-13

\[ \rho = 0.692 \]
\[ p < 0.001 \]

IFN-\( \gamma \)

\[ \rho = 0.353 \]
\[ p = 0.109 \]

by Spearman's correlation coefficient by rank test

Amounts of Japanese cedar/cypress pollen dispersion in Okayama, Japan

Year

1997
1998
1999
2000
2001
2002
2003
2004
2005
2006
2007
2008
2009
2010
2011
2012
2013
2014

pollens/cm²/season

Cedar
Cypress
岡山大学における2011年のスギ・ヒノキ花粉の飛散

スギ花粉（□---□）
本格飛散開始日:2月23日
最大飛散日:3月15日
総飛散数:1,384.1個/cm²

ヒノキ花粉（○---○）
本格飛散開始日:3月28日
最大飛散日:4月26日
総飛散数:589.3個/cm²
IL-5

A member of Th2 cytokines
Produced by CD4\(^+\) Th2 cells, mast cell and eosinophils

Receptor: IL-5R\(\alpha\)
mainly expressed on eosinophils

Effect on eosinophils
Enhances differentiation, proliferation and survival

Effect on B cells
Enhances Ab production (IgM in human)

Effect on basophils
Enhances degranulation

Central role in airway eosinophilia

Production of IL-5 by PBMCs in response to Cry j 1


Non-SIT
SIT

by Mann-Whitney’s U-test
IL-13

A member of Th2 cytokines
Produced by CD4^+ cells, CD8^+ cells, basophils, mast cells, etc.

Receptor: IL-13Rα1 (with IL-4Rα) / IL-13Rα2
Signal transduction: JAK1/JAK2 - STAT6

Effect on B cells
  Enhances IgE production

Effect on vascular endothelia cells
  Enhances ICAM-1/P-selectin expression

Effect on airway smooth muscles
  Enhances TARC expression, airway constriction

Effect on fibroblasts
  Induces fibrosis

Effect on airway epithelial cells
  Induces goblet cell hyperplasia and mucin production

Airway hypersensitivity
Airway remodeling
Production of **IL-13** by PBMCs in response to **Cry j 1**

By Mann-Whitney's U-test: Median

SIT: Specific immunotherapy

Pathological changes in AR

- Epithelial cell
- Goblet cell
- Gland
- Basement membrane
- Fibroblast
- Vessel
- Mast cell
- MC (sensitized)
- Eosinophil
- Neutrophil
- Basophil
- T cell
- B cell
- Dendritic cell
Congestion (swelling of nasal mucosa)
Dilation of vessels + edema by plasma exudation 血漿漏出

Early phase reaction
Direct effect of mediators on vessels
(LTs>TXA$_2$=PAF>PGD$_2$>Hi)
Neural reflex
(NO>>SP, VIP, CGRP)

Late phase reaction
Allergic inflammation
Inflammatory cell infiltration (Eo, Th2 etc.)
+ pro-inflammatory molecules (cytokines, granule proteins etc.)
Congestion (swelling of nasal mucosa)
Dilation of vessels + edema by plasma exudation 血漿漏出

Early phase reaction
- Direct effect of mediators on vessels
  (LTs > TXA$_2$ = PAF > PGD$_2$ > Hi)
- Neural reflex
  (NO >> SP, VIP, CGRP)

Late phase reaction
- Allergic inflammation
  - Inflammatory cell infiltration (Eo, Th2 etc.)
  - + pro-inflammatory molecules (cytokines, granule proteins etc.)
くしゃみの発現メカニズム

・純粋な呼吸反射
・ヒスタミンによる知覚神経終末H1受容体の刺激
  →三叉神経主知覚核→くしゃみ中枢→呼吸筋の反射的収縮
・鼻粘膜過敏性の亢進に伴い増幅される

鼻粘膜過敏性

・特異的刺激（抗原）あるいは非特異的刺激（ヒスタミン、メサコリン、寒冷など）に過敏に反応すること
・プライム効果：いったん発症すると、同程度の症状発現に必要な抗原量は10〜100分の1に減少する。好酸球や肥満細胞を中心とした炎症細胞浸潤と、炎症細胞からのメディエーター（LTなど）放出が関与する。
・最小持続炎症（Minimal persistent inflammation : MPI）：症状を発現させない程度の抗原曝露でもアレルギー炎症は誘導され、過敏性は亢進する。
Seasonal AR ≠ Intermittent AR
Perennial AR ≠ Persistent AR
Study Design

- A placebo-controlled, randomized, double-blind, parallel-group comparison -

0W (Feb 1, 2011)
2W (Feb 15)
4W (Mar 1)
6W (Mar 15)
8W (Mar 29)
10W (Apr 12)
12W (Apr 26)

Registration

Recollection

Random allocation/background variables

Patients with cedar/cypress pollinosis

Consent acquisition

Delivery of nasal allergy diary to each subject

Consent acquisition

Placebo nasal solution

Placebo nasal solution

MFNS

12 weeks

MFNS

8 weeks

Placebo nasal solution

12 weeks

Second generation antihistamines (possible to us as rescue drugs)

*: Each used once daily

Time Course of Total Nasal/Ocular Symptom Score (TSS)

Day of switch

Day on start of full-scale pollen spread

Placebo group (n=24)
Placebo→MFNS switched group (n=25)
MFNS group (n=25)
Density of spreading cedar pollen
Density of spreading cypress pollen

Start of treatment
2 weeks
4 weeks
6 weeks
8 weeks
10 weeks
12 weeks

Production of IL-33 by PBMCs in response to Cry j 1

 yıllar

Healthy controls

Non-SIT

SIT

JCCP patients

---p=0.273---

|---p=0.087---|

(by Mann-Whitney's U-test)
Local expression of IL-17A is correlated with nasal eosinophilia and clinical severity in AR

-Makihara S, Okano M, et al. Allergy Rhinol 5: e22, 2014-

Expression of IL-17A in nasal mucosa

Comparison of IL-17+ cells among disease phenotype

Non-allergic Hypertrophic rhinitis

NARES

Perennial AR
Local expression of IL-17A is correlated with nasal eosinophilia and clinical severity in AR
-Makihara S, Okano M, et al. Allergy Rhinol 5: e22, 2014-

Expression of IL-17A+ cells in nasal mucosa and pathophysiological characterizations of AR
IFN-γ

A member of Th1 cytokines
Produced mainly by T cells, NK cells and DC

Receptor: IFNGR1 / IFNGR2
Signal transduction: JAK1/JAK2 – STAT1

Effect on B cells
  Suppressed IgE production
Effect on T cells
  Suppresses Th2 cells
Effect on macrophages
  Enhances superoxide and NO production
  Enhances MHC class I expression
Effect on vascular endothelial cells
  Induces IDO, CD95 and caspase-1 expression

Therapeutic target of Th2-type allergic diseases
Production of IFN-γ by PBMCs in response to Cry j 1

|------------------p=0.390------------------|
|-----p=0.132-----| |-----p=0.004-----|

SIT: Specific immunotherapy
by Mann-Whitney’s U-test

Effect of recombinant IFN-γ on Cry j 1-induced cytokine production by PBMC

<table>
<thead>
<tr>
<th></th>
<th>IL-5</th>
<th>IL-13</th>
<th>IL-31</th>
</tr>
</thead>
<tbody>
<tr>
<td>(−)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(+)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IFN-γ (5ng/ml)

(i−p=0.657−−−−I)

(i−p=0.001−−−−I)

(i−p<0.001−−−−I)

IFN-γ (5ng/ml)

PBMC

Cry j 1 (10µg/ml)

+/- IFN-γ

IL-5

IL-13

IL-31

(n=25)

by Wilcoxon’s signed rank test
ARIAによるアレルギー性鼻炎の重症度分類

分類

間欠性 (intermittent)
“週に4日未満”
または
”連続4週間未満”

持続性 (persistent)
“週に4日以上“
かつ
”連続4週間以上”

重症度

軽症 (mild)
以下の問題が存在しない

中等症/重症 (moderate/severe)
以下の問題が1つ以上ある

睡眠障害
日常生活、レジャー、
スポーツにおける障害
学業や仕事の障害
煩わしい症状

(ARIA 2008)
抗コリン薬がTRPV1誘導反応を抑制
Diagnosis of allergic rhinitis

Intermittent symptoms
Mild
Not in preferred order oral H1 blocker or intranasal H1-blocker and/or decongestant or LTRA

Moderate-severe
Not in preferred order oral H1 blocker or intranasal H1-blocker and/or decongestant or intranasal CS or LTRA (or cromone)

In persistent rhinitis review the patient after 2-4 wks
If failure: step-up
If improved: continue for 1 month

Persistent symptoms
Mild

Moderate-severe
In preferred order intranasal CS H1 blocker or LTRA
Review the patient after 2-4 wks
Improved
Step-down and continue treatment for > 1 month
Add or increase intranasal CS dose
Rhinorrhea add ipratropium
Blockage add decongestant or oral CS (short term)
Failure
Referral to specialist

Review diagnosis
Review compliance
Query infections or other causes

Allergen and irritant avoidance may be appropriate

If conjunctivitis
Add oral H1-blocker
# Treatment of Perennial Allergic Rhinitis

- Reproduced from the Guideline for the Management of Allergic Rhinitis in Japan (2016 Version)

<table>
<thead>
<tr>
<th>Severity</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease type</td>
<td>Sneezing/ rhinorrhea type</td>
<td>Nasal congestion type or complete type primarily involving nasal congestion</td>
<td>Sneezing/ rhinorrhea type</td>
</tr>
<tr>
<td>Treatment</td>
<td>One of (1) through (4)</td>
<td>One of (1), (2) and (3) As needed, (1) or (2) is combined with (3).</td>
<td>Steroid for nasal spraying + Second generation antihistamines</td>
</tr>
<tr>
<td>(1)</td>
<td>Second generation antihistamines</td>
<td>Anti-LT agents</td>
<td>Steroid for nasal spraying + Anti-LT agents or anti-PGD2-TXA2 agents</td>
</tr>
<tr>
<td>(2)</td>
<td>Release suppressors</td>
<td>Anti-PGD2-TXA2 agents or Second generation antihistamine + vasoconstrictor combinations</td>
<td></td>
</tr>
<tr>
<td>(3)</td>
<td>Th2 cytokine inhibitors</td>
<td>Th2 cytokine inhibitors</td>
<td></td>
</tr>
<tr>
<td>(4)</td>
<td>Steroid for nasal spraying</td>
<td>Second generation antihistamine + vasoconstrictor combinations</td>
<td></td>
</tr>
<tr>
<td>(5)</td>
<td>Second generation antihistamines + vasoconstrictor combinations</td>
<td>Surgery in cases of nasal congestion type accompanied by morphological abnormalities of nasal cavity</td>
<td></td>
</tr>
</tbody>
</table>

**Allergen immunotherapy**

**Antigen removal/avoidance**

Even when symptoms have alleviated, treatment may not be immediately discontinued but should be reduced in a step-down manner, checking stabilization for several months.
### Choice of Treatment Method for Pollinosis Depending on Severity Level

- Reproduced from the Guideline for the Management of Allergic Rhinitis in Japan (2016 Version)

<table>
<thead>
<tr>
<th>Severity</th>
<th>Initial therapy</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe/severest</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Severity</strong></td>
<td><strong>Initial therapy</strong></td>
<td><strong>Mild</strong></td>
<td><strong>Moderate</strong></td>
<td><strong>Severe/severest</strong></td>
</tr>
<tr>
<td><strong>Disease type</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>(1) Second generation antihistamines</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2) Release suppressors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(3) Anti-LT agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(4) Anti-PGD2/TXA2 agents</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(5) Th2 cytokine inhibitors</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>(6) Steroid for nasal spraying</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>One of (1) through (6) for the sneezing/rhinorrhea type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>One of (3), (4), (5) and (6) for nasal congestion type or complete type primarily involving nasal congestion</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Second generation antihistamines
- Anti-LT agents or anti-PGD2/TXA2 agents
- Th2 cytokine inhibitors
- Steroid for nasal spraying

- Second generation antihistamines + Steroid for nasal spraying
- Anti-LT agents or anti-PGD2/TXA2 agents + Steroid for nasal spraying + Second generation antihistamines

- Second generation antihistamines + vasoconstrictor combinations + Steroid for nasal spraying

- Steroid for nasal spraying + Second generation antihistamines
- Anti-LT agents or anti-PGD2/TXA2 agents + Second generation antihistamines

- Second generation antihistamines + vasoconstrictor combinations + Steroid for nasal spraying

- As needed, nasal constrictor for nasal application is used for 1-2 weeks before the start of treatment.

- In cases where symptoms are particularly severe, oral steroid is prescribed for 4-7 days.

- Ophthalmic antihistamine solution or release suppressors
- Steroid for nasal spraying
- Second generation antihistamines
- Anti-LT agents or anti-PGD2/TXA2 agents

- Second generation antihistamine + vasoconstrictor combinations + Steroid for nasal spraying

- Ophthalmic antihistamine solution, release suppressors or steroid
- Steroid for nasal spraying

- Allergen immunotherapy
- Antigen removal/avoidance

- Surgery in cases of nasal congestion type accompanied by morphological abnormalities of nasal cavity
Phenotyping of Japanese cedar/cypress pollinosis based on ARIA classification

<table>
<thead>
<tr>
<th>Severity Assessment by PG-MARU &amp; ARIA</th>
<th>Severity Assessment by PG-MARU &amp; ARIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 3382)</td>
<td>Total (n = 3382)</td>
</tr>
<tr>
<td>41.9 33.5 24.6</td>
<td>41.9 33.5 24.6</td>
</tr>
<tr>
<td>Severest (n = 795)</td>
<td>Severest (n = 795)</td>
</tr>
<tr>
<td>42.9 37.1 20.0</td>
<td>42.9 37.1 20.0</td>
</tr>
<tr>
<td>Severe (n = 995)</td>
<td>Severe (n = 995)</td>
</tr>
<tr>
<td>43.8 35.2 21.0</td>
<td>43.8 35.2 21.0</td>
</tr>
<tr>
<td>Moderate (n = 1057)</td>
<td>Moderate (n = 1057)</td>
</tr>
<tr>
<td>41.4 31.0 27.5</td>
<td>41.4 31.0 27.5</td>
</tr>
<tr>
<td>Mild (n = 468)</td>
<td>Mild (n = 468)</td>
</tr>
<tr>
<td>37.8 30.8 31.4</td>
<td>37.8 30.8 31.4</td>
</tr>
<tr>
<td>No symptoms (n = 67)</td>
<td>No symptoms (n = 67)</td>
</tr>
<tr>
<td>37.3 23.9 38.8</td>
<td>37.3 23.9 38.8</td>
</tr>
</tbody>
</table>

Fig. 5 Proportion of respondents visiting a medical institution by severity according to PG-MARU.

<table>
<thead>
<tr>
<th>Severity Assessment by PG-MARU &amp; ARIA</th>
<th>Severity Assessment by PG-MARU &amp; ARIA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total (n = 3382)</td>
<td>Total (n = 3382)</td>
</tr>
<tr>
<td>41.9 33.5 24.6</td>
<td>41.9 33.5 24.6</td>
</tr>
<tr>
<td>Moderate/severe persistent (n = 2274)</td>
<td>Moderate/severe persistent (n = 2274)</td>
</tr>
<tr>
<td>46.9 32.8 20.3</td>
<td>46.9 32.8 20.3</td>
</tr>
<tr>
<td>Moderate/severe intermittent (n = 805)</td>
<td>Moderate/severe intermittent (n = 805)</td>
</tr>
<tr>
<td>29.9 38.6 31.4</td>
<td>29.9 38.6 31.4</td>
</tr>
<tr>
<td>Mild persistent (n = 149)</td>
<td>Mild persistent (n = 149)</td>
</tr>
<tr>
<td>45.6 23.5 30.9</td>
<td>45.6 23.5 30.9</td>
</tr>
<tr>
<td>Mild intermittent (n = 154)</td>
<td>Mild intermittent (n = 154)</td>
</tr>
<tr>
<td>26.6 27.3 46.1</td>
<td>26.6 27.3 46.1</td>
</tr>
</tbody>
</table>

Fig. 6 Proportion of respondents visiting a medical institution by severity according to ARIA.

Mechanism for Hypersensitivity Enhancement Associated with Allergic Rhinitis

Minimal Persistent Inflammation (MPI)

Even exposure to antigen to an extent not causing symptoms leads to mucosal infiltration by inflammatory cells (eosinophils, neutrophils, etc.) and expression of adhesion molecules.

Priming Effect

Once the disease has developed, the antigen level required for expression of similar symptoms decreases to 1/10-1/100. Infiltration by inflammatory cells (primarily eosinophils and mast cells) and release of mediators from inflammatory cells are involved.

(Canonica GW, et al. CEI 158: 260, 2009)
Minimal Persistent Inflammation

Minimal persistent inflammation (MPI)

Hypersensitivity

Onset threshold

Antigen exposure

Minimal persistent inflammation: MPI

Immediate type reaction

Delayed type reaction

Minimal persistent inflammation: MPI

Inflammation

Course over time

Action Mechanism of Steroid (Glucocorticoid) on Airway Mucosa

Infiltrating cells

- Eosinophil: Count ↓ (Apoptosis ↑)
- Th2 cell: Cytokine ↓
- Mast cell: Count ↓
- Macrophage: Cytokine ↓
- Dendrocyte: Count ↓

Structural cells

- Epithelial cell: Cytokine ↓, Mediator ↓
- Vascular endothelial cell: Permeability ↓
- Airway smooth muscle cell: b2 receptor ↑, Cytokine ↓
- Secretory gland/goblet cell: Mucus formation ↓

Steroid

Immune regulation

Suggested approach to precision medicine in asthma

1. Diagnosis
2. Characterize phenotype
   - Gender
   - Age
   - Race/Ethnicity
   - Obesity
   - Smoking status
   - Early vs. late onset
   - Atopic status
   - Lung function/AHR
3. Characterize endotype
   - Biomarkers: blood, sputum, exhaled breath
4. Type 2 immune response
5. Non-Type 2 immune response
6. Prognostic BM

TAILORED THERAPY

PRIMARY AND SECONDARY PREVENTION

FIG 3. Suggested approach to precision medicine in asthmatic patients. First, the correct diagnosis of asthma should be verified, and comorbidities should be treated properly. In a second step phenotype is established based on visible properties. Further characterization of the patient’s endotype is crucial to ensure the optimum response to treatment and risk prediction, especially for those with severe and uncontrolled disease. Validation of prognostic biomarkers related to disease severity and risk prediction (including risk to develop asthma) open new pathways for primary and secondary asthma prevention. AHR, Airway hyperresponsiveness; BM, biomarkers.
Take Home Messages

• There are cases of local allergic rhinitis (LAR) free of systemic sensitization.

• Addition of bepotastine is effective in patients not responding to nasal spraying steroid.

• In Japan, sublingual immunotherapy is now available for use for Japanese cesar pollinosis and house dust mite allergic rhinitis.
副鼻腔炎の分類: フェノタイプとエンドタイプ

フェノタイプ (Phenotype):
臨床的な特徴を基にした分類
- 急性、慢性
- 軽症、重症
- 小児、成人
- 鼻茸あり、鼻茸なしなど

エンドタイプ (Endotype):
分子病態や治療反応性を基にした分類（真の原因に基づいた分類）
- 好酸球性、好中球性（エンドフェノタイプ？）
- アレルギー性真菌性副鼻腔炎
- AERD（アスピリン過敏）
- 抗IgE抗体反応性
- 抗IL-5抗体反応性など

個別化治療 (Personalized Medicine)

Correlation between the naso-ocular symptoms and QOL during the peak season of cypress pollen dispersion and the amounts of Cry j 1-induced cytokine production by PBMCs

<table>
<thead>
<tr>
<th></th>
<th>IL-5</th>
<th>IL-13</th>
<th>IL-31</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naso-ocular</td>
<td>ρ</td>
<td>-0.057</td>
<td>-0.104</td>
</tr>
<tr>
<td>Symptom score</td>
<td>ρ</td>
<td>0.744</td>
<td>0.565</td>
</tr>
<tr>
<td>QOL score</td>
<td>ρ</td>
<td>0.260</td>
<td>0.221</td>
</tr>
<tr>
<td></td>
<td>ρ</td>
<td>0.170</td>
<td>0.244</td>
</tr>
</tbody>
</table>

(n=29)

by Spearman’s correlation coefficient by rank