Treating the ocular component of allergic rhinoconjunctivitis

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Conflict of interests

• All what I shall say in favor of ocular allergy is deeply biased by the fact that it represents a major area of interest for my research and clinical practice

• No other disclosure of interests with reference to this talk
ALLERGIES DON’T STOP AT THE NOSE.

Ocular allergy is the Cinderella among allergic diseases
Aim of the presentation

- Ocular allergy is a distinct entity, with the same dignity of lung, nose and skin allergy
- The red eye is a frequent condition
- Not all red eyes are allergic
- Allergic conjunctivitis is a heterogeneous disease which includes:
  - mild forms which affect anyway QoL
  - severe forms which may cause blindness
  (Severe Chronic Under-diagnosed Ocular Allergic Disease, SCUOD)
Prevalence of ocular symptoms in allergic rhinitis

Europe

USA

Canonica GW et al. *Allergy* 2007; 62: S85, 17-25

Schatz M. *Allergy* 2007; 62: S85, 9-16
Prevalence of nasal symptoms in allergic conjunctivitis

In a study of 898 consecutive allergic patients (Bonini St and Bonini Se Chibret Int J Ophthalmol. 1987; 5: 12-22) 359 (40%) had ocular symptoms

- Isolated (n=55)
  - 18%
- Associated with other allergic diseases (n=294)
  - 82%

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**Pollenosis conjunctivitis**
- (95.2%) Association with other allergic diseases
- (69.1%) Rhinitis alone
- (29.7%) Associated with rhinitis and asthma
- (1.2%) Asthma alone

**Vernal conjunctivitis**
- (41.5%) Association with other allergic diseases
- (6.2%) Rhinitis alone
- (81.5%) Associated with rhinitis and asthma
- (12.3%) Asthma alone
The Prevalence of Rhinoconjunctivitis Is Often Underestimated
Look beyond the nose!
The Italian TOSCA Study

752 consecutive patients with allergic diseases were diagnosed by 30 excellence specialist centres (Allergists, ENT, Dermatologists, Ophthalmologists, Pneumologists)

<table>
<thead>
<tr>
<th></th>
<th>2206 according to the current diagnostic approach of centres (specialty-oriented)</th>
<th>1546 according to a holistic diagnostic approach (patient-oriented)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis of Conjunctivitis</td>
<td>37.1%</td>
<td>53.0%</td>
</tr>
<tr>
<td>Diagnosis of Rhinitis</td>
<td>54.2%</td>
<td>69.9%</td>
</tr>
</tbody>
</table>

Diagnosis of Allergic Conjunctivitis in different specialistic settings

- 2206 allergic patients studied according to routine procedures
- 1546 allergic patients studied according to a standard questionnaire
The heterogeneity of the red eye syndrome

Red Eye

History

Symptoms

Bilateral

Recurrent

Allergic Conjunctivitis

Infectious conjunctivitis

Chlamydial

Viral

Bacterial

Parasitic

Fungal

Watery

Sticky

Burning

Autoimmune

Pemphigoid

Episcleritis

Uveitis

Vasculitis

Non-specific

Dry Eye

Foreign body

Chemical induced

Acne rosacea

Foreign body sensation
Clinical forms of Allergic Conjunctivitis

- Acute allergic conjunctivitis (AAC)
- Seasonal allergic conjunctivitis (SAC)
- Perennial allergic conjunctivitis (PAC)
- Vernal keratoconjunctivitis (VKC)
- Atopic keratoconjunctivitis (AKC)
- Giant-papillary conjunctivitis (GPC)
ALLERGIC CONJUNCTIVITIS

Seasonal or perennial

Vernal

Atopic

Giant papillary
IgE-FcR-Mast cell

Allergen Effects

Vasodilation
Exudation
Hypersecretion
Hyperreactivity of nerve endings

Red Eye

Symptoms

Redness
Oedema, Chemosis
Tearing, Excess Mucus
Itching, Burning

Red Eye Symptoms

Redness
Oedema, Chemosis
Tearing, Excess Mucus
Itching, Burning
Late-phase allergic reaction in the eye

- **PRE**
- **20 mn**
- **6h**

**Cells**
- Neutrophils
- Eosinophils
- Lymphocytes
- Monocytes

**Mediators**
- Histamine
- Histamine Tryptase
- Histamine LTs
- ECP
Prevalence of positive skin tests/RAST in different forms of allergic conjunctivitis

Bonini S et al, 1987; 2002
Non-specific conjunctival hyperreactivity in allergic and non-allergic subjects with a red eye

Hyperosmolar conjunctival provocation for the evaluation of nonspecific hyperreactivity in healthy patients and patients with allergy

Marta Sacchetti, Alessandro Lambiase, Silvia Aronni, Tamara Griggi, Valentina Ribatti, Stefano Bonini, Sergio Bonini

J Allergy Clin Immunol 2006; 118: 872-877
Heterogeneity of allergic inflammation and allergic eye diseases

Seasonal and perennial allergic conjunctivitis

Late-phase reaction

Type 1 hypersensitivity

Conjunctival hyperreactivity

Vernal and atopic keratoconjunctivitis

Th2 type allergic inflammation
THE SPECTRUM OF ALLERGIC DISEASE

HLA genes and allergen exposure

Genetic and environmental influences causing 5q cluster-cytokine genes overexpression

Neural and tissue factor (?)

GM-CSF

Enhanced specific IgE response

High total IgE

Upregulation of inflammatory cells

Increased number Eosinophilic and releasability of inflammation MC and basophils

I II III IV V

Clinical phenotypes

Tissue hyperreactivity

Il-4 IL-3 IL-5
## Dry eye

<table>
<thead>
<tr>
<th></th>
<th>Aqueous tear deficiency</th>
<th>Melbonian gland disease</th>
<th>Itchy-Dry Eye association (IDEA)</th>
<th>Allergic conjunctivitis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinics</strong></td>
<td>Autoimmune diseases</td>
<td>No systemic disease</td>
<td>Polycistic ovaries with hyperandrogenism</td>
<td>Allergy</td>
</tr>
<tr>
<td><strong>Treatment</strong></td>
<td>Immunosoppressive agents</td>
<td>Tear substitutes</td>
<td>Anti-androgenic drugs</td>
<td>Anti-allergic drugs</td>
</tr>
<tr>
<td><strong>Skin tests</strong></td>
<td>---</td>
<td>---</td>
<td>+/- (25% + ve)</td>
<td>+++ (50-90% + ve)</td>
</tr>
<tr>
<td><strong>Schirmer test</strong></td>
<td>↓</td>
<td>→ /↓</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Break-up time</strong></td>
<td>→ /↓</td>
<td>↓</td>
<td>↓</td>
<td></td>
</tr>
<tr>
<td><strong>Goblet cells density</strong></td>
<td>↓</td>
<td>→ /↓</td>
<td>↑</td>
<td>↑</td>
</tr>
</tbody>
</table>

*Bonini S et al., Am J Ophthalmol 2007*
Asthma

Rhinitis

Conjunctivitis

Type I Hypersensitivity
Late-phase IgE dependent inflammation
IgE Allergic inflammation without IgE
Target organ
Hyperreactivity

Pollinosis

Hyposensitisation
Antihistamines
Topical steroids
Antileukotrienes
β2 agonists
Anticolinergics
# Meta-Analysis of INS vs Oral Antihistamines: Ocular Symptoms

**Table:**

<table>
<thead>
<tr>
<th>Study</th>
<th>Favour INS</th>
<th>Favour AH</th>
<th>Standardised Mean Difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Robinson</td>
<td></td>
<td></td>
<td>2.1 (0.646, -1.438 – 0.146)</td>
</tr>
<tr>
<td>Brooks</td>
<td></td>
<td></td>
<td>3.3 (0.382, -1.008 – 0.244)</td>
</tr>
<tr>
<td>Bronsky</td>
<td></td>
<td></td>
<td>18.1 (-0.338, -0.608 – -0.069)</td>
</tr>
<tr>
<td>Bunnag</td>
<td></td>
<td></td>
<td>15.7 (-0.216, -0.696 – 0.265)</td>
</tr>
<tr>
<td>Schoenwetter</td>
<td></td>
<td></td>
<td>23.3 (-0.149, -0.386 – 0.088)</td>
</tr>
<tr>
<td>Bernstein</td>
<td></td>
<td></td>
<td>17.8 (0.000, -0.271 – 0.271)</td>
</tr>
<tr>
<td>Darnell</td>
<td></td>
<td></td>
<td>10.7 (0.022, -0.329 – 0.373)</td>
</tr>
<tr>
<td>Simpson</td>
<td></td>
<td></td>
<td>5.2 (0.030, -0.470 – 0.530)</td>
</tr>
<tr>
<td>Juniper</td>
<td></td>
<td></td>
<td>5.1 (0.224, -0.284 – 0.732)</td>
</tr>
<tr>
<td>Wood</td>
<td></td>
<td></td>
<td>5.6 (0.869, -0.387 – 1.351)</td>
</tr>
<tr>
<td>Beswick</td>
<td></td>
<td></td>
<td>3.0 (0.908, -0.251 – 1.566)</td>
</tr>
<tr>
<td><strong>Combined</strong></td>
<td></td>
<td></td>
<td>100.0 (-0.043, -0.157 – 0.072)</td>
</tr>
</tbody>
</table>

\[ x^2 = 32.4, \ df = 10, \ P < 0.0005 \]

**Note:** Weiner et al. *BMJ*. 1998;317:1624. Courtesy of Prof. L. Bielory
Potential mechanisms for the efficacy of inhaled nasal steroids on ocular symptoms

- Systemic absorption
- Reduction or disappearance of the blockage of the nasolacrimal duct
- Nasal ocular reflex
- Combination of the above
Biodisponibilità degli steroidi topici

Bryson HM et al. Drugs 1992;43:760
Potential Mechanisms for the efficacy of inhaled nasal steroids on ocular symptoms

- Systemic absorption
- Reduction or disappearance of the blockage of the nasolacrimal duct
- Nasal ocular reflex
- Combination of the above
Naso-Nasal and Naso-Ocular Reflexes

Central Nervous System

- Right Eye
- Right Nostril
- Left Eye
- Left Nostril

Ag
Localization of NGF in the nasal mucosa of allergic rhinitis patients

Bresciani M et al. Allergy, 2008 in press
Intranasal Steroids: Mechanism of Improvement in Eye Symptoms

• Nasal inflammation causes priming, which increases the nasal ocular reflex

• Reducing nasal inflammation with intranasal steroids reduces the nasal-ocular reflex and is the mechanism by which this class of medications reduces ocular allergy symptoms
A Step-Wise Approach in the Treatment of Allergic Conjunctivitis

Grade 0 Quiescent
  Occasional antiallergic eye drops

Grade 1 Mild/intermittent
  Intranasal topical steroids

Grade 2 Moderate: A intermittent, B persistent
  No treatments

Grade 3 Severe
  Topical pulsed steroid
  Cyclosporine A eye drops
  Daily administration of antiallergic eye drops (mast cell stabilisers/antihistamine/dual action)

Grade 4 Very severe
  Topical pulsed steroid (high dose)

Grade 5 Evolution
  Occasional antiallergic eye drops
  Lubricant eye drops/vasoconstrictor eye drops when necessary

Patient with allergic rhinitis

Always ask for ocular symptoms

Ocular symptoms
70%

No ocular symptoms
30%

Ophthalmologist

Treat the nose with nasal topical steroids

- Association with asthma or eczema
- Contact lenses
- Severe symptoms (giant papillae, intense photophobia, eye pain)
- High total IgE, polysensitization
- Eosinophils in tears or conjunctival scrapings

No effect on ocular symptoms

Efficacy on ocular symptoms
New potential approaches in the treatment of ocular allergy

• Modulation of inflammation through TLR ligands

• Inhibition of neurotrophins
Toll-Like receptors expression in VKC

Micera A et al, 2006
NCT 00445120
Lactobacillus Rhamnosus GG oral treatment. Efficacy in VKC

Randomized, placebo-controlled, double-masked, cross-over, multicentric study
NGF levels in plasma and tears of VKC patients

Controls
VKC patients
NGF and NGF receptors in allergic inflammation and tissue remodelling

- **Multipotent progenitors**
- **CD34+**
- **Epithelial cells**
- **APC**
- **Th**
- **B**
- **MC**
- **Eos**

References:

- Micera A et al. PNAS 2001; 98: 6162
- Bonini S et al. PNAS 1996; 93: 10955
- Lambiase A et al. JACI 1997; 100: 408
- Solomon A et al. JACI 1998; 102: 454
# NGF and dry eye

## A pilot open study in humans

<table>
<thead>
<tr>
<th>Patients: 5 severe dry eye</th>
<th>Improvement of subjective symptoms (photophobia, redness and dryness)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dose of NGF: 1 eye-drop</td>
<td>Improvement of clinical signs</td>
</tr>
<tr>
<td>(100μg/ml) 3 times daily</td>
<td>Corneal staining 5/5 (6 ±2 vs 0)</td>
</tr>
<tr>
<td>Duration: 1 month to 3</td>
<td>Schirmer test 5/5 (from 1mm/5’ to 9mm/5’)</td>
</tr>
<tr>
<td>years</td>
<td>Break-up time 4/5 (2±2 vs 8±2)</td>
</tr>
<tr>
<td>No ocular or systemic</td>
<td>Corneal sensitivity 4/5 (3±2 vs 4±1)</td>
</tr>
<tr>
<td>side effects</td>
<td>BVA 3/5 (from 1 to 3 Snellen line)</td>
</tr>
</tbody>
</table>
We are now investigating whether inhibition of NGF through specific TrkA antibodies may modulate conjunctival hyperreacivity and mucus production.