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There's something new in the AIR

Before considering the role of a new agent to treat and improve care of allergic rhinitis (AR), it seems wise to follow the immunological journey from exposure to an antigen to the final overwhelming inflammatory cascade it creates. But first, let's consider why some of us become allergic.

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New thoughts on the origin of allergy: Foetal origins

A TH2-like cytokine profile maintains the pregnant state. In fact, atopic compared to nonatopic mothers are more likely to have several children. The newborn destined to become atopic has low levels of interferon gamma and this continues to occur over the first two years of life. The cause of this defect remains to be discovered.

In addition, the foetus is capable of mounting allergen–specific responses from 23 weeks of gestation. Why we all do not become atopic is probably due to deletion of allergen–reactive T-cells from the host by anergy or apoptosis as a consequence of high-dose antigen exposure in the gut and the development of oral tolerance.

The gastrointestinal flora at birth

An important part of postnatal regulation of immunoglobulin E (IgE) reactivity seen at birth, may be the acquisition of the appropriate commensal gut flora (also known as the microbiome). There is evidence for this in both mouse and man.

Studies comparing the gut commensal flora of neonates from Sweden (with its high prevalence of allergic disease) to those from Estonia (low prevalence of disease) found less intensive colonisation with *lactobacilli* in Swedish children and more frequent clostridia.

In addition or alternatively, there may be impaired recognition and response to bacterial products derived from the microbiome in children who develop atopic disease. The gut flora is required for successful oral tolerance as gram-negative products such as lipopolysaccharides stimulate tissue macrophages to produce anti-TH2 cytokines, IL-1 and TNF-alpha.

The 'hygiene hypothesis'

Since atopic children have lower circulating levels of interferon gamma, greater exposure to bacteria or their products during early life may increase interferon gamma. Factors that have damped down this mechanism include:

- Improvements in public health and hygiene
- Changes in infant diets
- Early use of antibiotics
- Elective caesarean section
- Reduced exposure to bacteria with smaller family sizes (less siblings).

Several studies have demonstrated an inverse relationship between atopy, seasonal AR (and asthma) and size of family. A possible explanation for this phenomenon may be the TH1/TH2 paradigm.

In children living in small families where infections are less common, TH2 cells may develop instead of TH1 cells. As a consequence, IgE responses are produced.

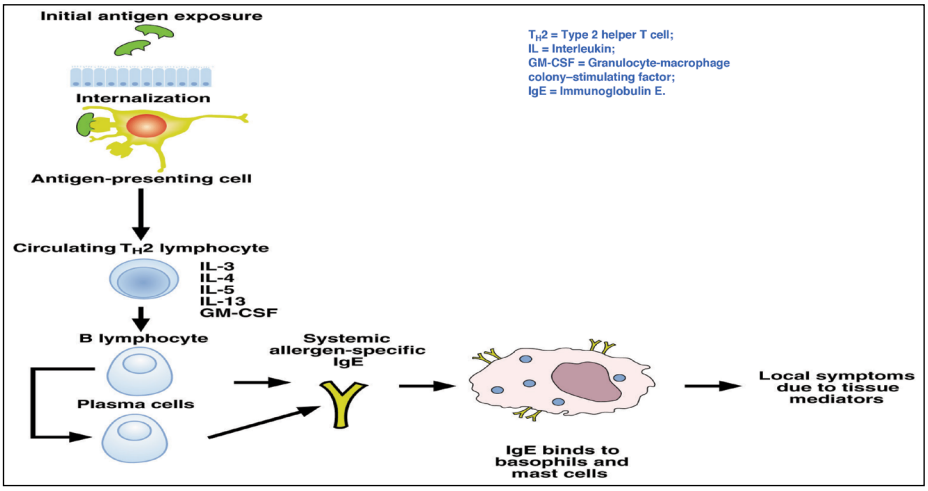
In children of large families, where infections are common, the immune system may be TH1 cell orientated. Atopy is also less common in individuals who grow up in a farming environment and here exposure to a less sterile environment is the postulated explanation.

Allergens and IgE

For antigens/allergens to trigger an immunological event they are required to be presented to T lymphocytes. In the airway such antigen-presenting cells (APC) are known as dendritic cells. Dendritic cells are formed from blood monocytes and move to the epithelium of the airway under the influence of chemokines.

The antigen-containing dendritic cells then move into regional lymph nodes where interaction with T cells occurs. Within the APC, peptide components of the antigen combine with HLA Class II molecules and are expressed on the surface of the cell. It is this complex which T cells recognise and bind to via the T cell receptor. This bonding is further augmented by cellular adhesion molecules of the immunoglobulin super-family class. (Figure 1).

Figure 1: Antigen presentation to T-cells and resultant activation of mast cells



CD4+ cells collaborate with neighbouring B cells to produce IgE through the process of immunoglobulin class switching. This process requires not only physical contact between T and B cells (cognate interaction) but also simulation of B cells by cytokines, especially interleukin (IL)-4 but also IL-5, IL-6 and IL-13.

Recently it has been shown that CD4+ T cells in fact comprise two groups of cells, the so-called TH1 and TH2 populations. These two sets of T helper cells secrete different cytokines.

The TH2 population produces the cytokines which augment IgE production, while TH1 cells suppress IgE production by B lymphocytes. Clearly, atopic individuals have a TH2 subset, and exciting possibilities may exist in this regard for prevention of atopy.

Cells in allergy

The mast cell is the primary cell active in allergy induced inflammation. Mast cell granules contain and subsequently release mediators such as histamine, prostaglandin D_2, leukotrienes C_4 and D_4, thromboxane A_2, and platelet activating factor. Mast cells also appear to be an important source of the cytokines which stimulate IgE synthesis viz IL-4, IL-5 and IL-6.

Eosinophils also play a pivotal role in allergic inflammation, probably controlling the late phase of these conditions. Their presence in the airway epithelium is a result of a complex interaction of adhesion molecules, chemokines, cytokines and other pro-inflammatory mediators.

The nett result of eosinophil activation is the release of a number of products which produce disease. Of all the products of the eosinophil, the granule proteins are most well-known. The T lymphocyte (especially TH2) also plays an important role in allergy, from the induction of IgE production to the elaboration of controlling cytokines.

Cytokines and chemokines

The various cells, which orchestrate allergy, communicate with one another through a group of molecules that allow this cell-to-cell communication and thereby facilitate immune and inflammatory responses. Initially thought to be produced only by the cells of the specific immune and haematological systems, they are now known to be produced by many cells.

Chemokines are cytokines with potent chemotactic function, attracting cells to the site of inflammation. Cytokines include the lymphokines, monokines, interleukins, interferons and haemopoietic growth factors, and are low molecular weight proteins with a short half-life.

IL-5, together with IL-3 and granulocyte macrophage colony stimulating factor (GM-GSF), enhance eosinophil activity. Other cytokines such as IL-2, IL-8, and RANTES have recently been shown to be eosinophil chemoattractants. Other cytokines, implicated in IgE synthesis, include IL-4, IL-5 and IL-6, whereas interferon γ (IFNγ), IL-8, and IL-12 are inhibitory.

A number of different cytokines are therefore involved in allergy, the important specific cytokines being IL-5 (with IL-3 and GM-CSF) in eosinophil activation, and IL-4 in IgE regulation in atopic disease.

Clearly other cytokines are implicated and, while targeting single mediators may be of value, an understanding of the cell/s of origin, and control of cytokine synthesis in allergic disease will be essential for future therapeutic intervention.

Table 1: AR: Major symptoms and responsible mediators

Pathological event	Symptoms elicited	Mediator(s) responsible
Pruritus	Tickling, palatal 'clicking'	Histamine (H_1), prostaglandins
Mucosal oedema	Nasal obstruction	Histamine (H_1), eicosanoids, kinins, prostaglandins
Sneezing	Sneezing or feeling of the need to sneeze	Histamine (H_1), eicosanoids
Mucus secretion	Runny nose, postnasal drip	Histamine ($H_1 \pm H_2$), eicosanoids, muscarinic discharge
Late-phase allergic reactions	Congestion, nasal hyperirritability	Inflammatory factors, eicosanoids, chemotactic factors

Pathogenesis of allergic rhinitis

Within the nasal mucosa a process occurs with allergen exposure, with a range of inflammatory cells present. Mast cells are found, bearing specific IgE directed against allergens. Contact by allergen leads to degranulation and the release of inflammatory mediators.

Basophils also migrate into nasal mucosa and nasal secretions and are activated in similar fashion to mast cells. Eosinophils also play a crucial role, with release of a large number of inflammatory mediators.

In rhinitis, as in asthma, pathophysiological responses can be divided into early/immediate and late-phase responses. The early-phase occurs immediately after degranulation of both mast cells and basophils, with many of the responses attributable to histamine, which acts through its H_1 receptor.

The late-phase occurs four to 24 hours after mast cell degranulation, and eosinophils are probably most important. Chronic, ongoing nasal hyperreactivity during allergen exposure is the result of accumulation of neutrophils in the nasal mucosa as part of the late-phase allergic reaction.

The late-phase response manifests mainly as nasal obstruction, and probably results from cellular infiltration.

Inflammation of the nasal mucosa is a function of epithelial cell damage, mucous production and cellular infiltration. The sources of nasal secretions (mucous) are vascular exudation, submucosal gland secretion and secretion from goblet cells (Table 1).

Phases of allergy

Following exposure to an allergen or physical trigger factor, allergic pathology, and consequent symptoms progress in an orderly fashion through a number of phases.

Within minutes of exposure, the early-phase begins. In the upper airway this is mainly a function of mast cell activity. The early-phase may last some hours and may resolve spontaneously.

The early-phase is usually followed some hours later by the late-phase, in which eosinophils and other cells produce the classic inflammation described before. Chronic rhinitis with unresolved inflammation is the usual scenario in an untreated or partially-treated patient.

Clinical significance

Rhinitis is defined as inflammation of the lining of the nose with the occurrence of nasal congestion, itching, sneezing and/or watery or mucoid rhinorrhoea.

There are many different stimuli, usually inflammatory, due to allergens, infections, chemicals, medications, or irritants. However, occasionally rhinitis is non-inflammatory, resulting from cold air, spicy foods, or strong odours.

Atopy is of paramount importance in allergic rhinitis, with both genetic and acquired components. The triggers are usually inhalant allergens. Aero-allergens are usually derived from natural organic sources such as house dust mite, pollens, mould spores, insect emanations and animals. Particle size is usually 2-60µm diameter, and allergens are usually proteins of MW 10 000-40 000 daltons.

Clearly the most important message from our understanding of the pathophysiology of allergic diseases such as AR is that this is an inflammatory disease, and only by treating

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References: **1.** Ryaltris® Professional Information. May 2020. **2.** Patel P, Salaptek AM, Tantry SK. Effect of olopatadine-mometasone combination nasal spray on seasonal rhinitis symptoms in an environmental exposure chamber study. *American College of Allergy, Asthma & Immunology*. 2019;122:630-638.

S3 RYALTRIS® (Nasal spray). Reg. no. 53/21.5.1/0457. Each spray delivers 600 µg olopatadine (as olopatadine hydrochloride) and 25 µg mometasone furoate (as mometasone furoate monohydrate). Contains the preservative benzalkonium chloride 0.02 % w/w. Sugar free. For full prescribing information refer to the professional information approved by the South African Health Products Regulatory Authority. Date of publication: 5 May 2020.

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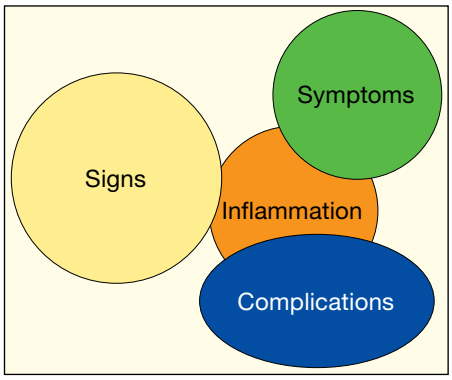
Figure 2: Inflammation is the central issue in AR



inflammation can any successful attempt be made to prevent morbidity (Figure 2).

Anti-inflammatory treatment will prevent inflammation to environmental factors and reduce both early and late reactions, whereas antihistamine therapy will alleviate early symptoms but have less effect on inflammation.

The evidence presented suggests that in South Africa we face an allergy explosion or epidemic. The effects of our man-made environment are responsible for much of this.

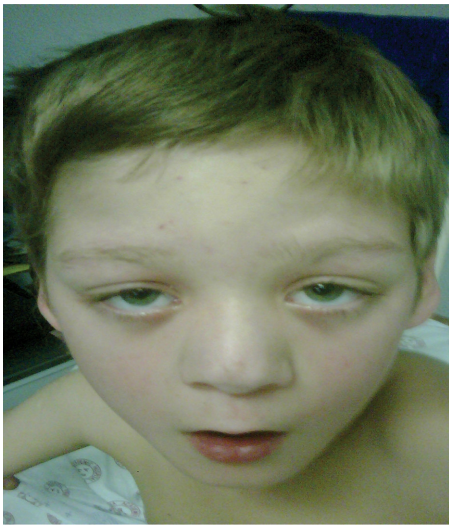
History and examination

A thorough history is the cornerstone of assessment, particularly in young children some other tests are not possible. Children with AR can be either 'runners' or 'blockers'. Presenting symptoms of hay fever are:

1. ***Blockers:*** Blocked nose, post-nasal drip, always clearing throat, rings under eyes (allergic shiners), always rubs nose (allergic salute), snores, restless sleeper, tired and irritable during the day, learning problems, sore throat, halitosis, mouth breathing, sore stomach (mucous gastritis), occasional diarrhoea.
2. ***Runners:*** Runny nose, sneezing, itchy and red eyes, frequent colds.

Associated features are frequent tonsillitis, history of tympanostomy, tonsillectomy, adenoidectomy, or sinus operations. Frequent previous diagnoses are post-nasal drip, sinusitis, and catarrh.

Figure 3: A typical allergic face



Clinical features of hay fever are allergic facies characterised by pallor, allergic shiners, mouth breathing and a nasal crease (Figure 3). The eardrums can be dull and retracted, the nasal mucosa pale (or hyperaemic) and swollen with mucous, and the throat may have a granular pharyngitis with post-nasal drip. This pharyngitis is characterised by hyperaemic mucosa with raised blebs of shiny mucosa.

Confirmation of the presence of atopy

Tests available to investigate the presence of atopy are:

- Total IgE
  This is often used as a screening test, but its use is limited because:
  - » Normal reference values are not available for all populations, it has poor sensitivity and specificity
  - » Non-allergic conditions (eg parasitic infestations) can produce elevations. (The same limitations apply to the absolute eosinophil count).
- Phadiatop®
  This is the most reliable *in vitro* test for screening of patients for sensitivity to inhaled allergens. The sensitivity in South African children is 100% and specificity is 90%. It does not detect and is therefore not influenced by parasitic IgE. Disadvantages are:
  - » Only a positive or negative result is obtained, without identification of the specific aero-allergens
  - » Cost!

Identification of the specific allergen

Tests available to investigate allergy are either *in vitro* (RAST®) or *in vivo* SPT (skin prick test).

- Radio-allergo-sorbent test (RAST®)
  The RAST®, which tests for allergen-specific IgE, can be used either for single individual allergens or for mixes of similar related allergens. In practice, patients may react to groups of allergens, to cross-reacting allergens, or only to individual allergens within a specific group. For this reason, mixed-allergen tests have been developed. Four hundred and sixty individual allergen and 66 mixed-allergen RASTs are available. A thorough history will guide one to careful selection of the correct tests to perform.
- Skin prick test
  The skin prick test (SPT) is regarded as the gold standard for the diagnosis of allergy. It has many advantages over the *in vitro* tests:
  - » Reliability, particularly for aero-allergens
  - » Easy to perform in the doctor's consulting rooms
  - » Rapid results (within 10-15 minutes)
  - » Low cost.

Evaluation of the patient's environment

When taking an allergy history, specific questions about the environment should include:

- Cigarette smoking (active or passive)
- Animal contact (especially cats) in the home, neighbour, school etc
- Feathers in the patient's bed (pillows or duvet)
- Abundant fluffy toys
- Proximity of home to water (in drier regions of South Africa, living near water may be associated with higher house-dust mite (HDM) counts, and consequent greater sensitivity).

Rhinitis management

As stated previously, market research recently conducted in the metropolitan areas of South Africa on a sample of two thousand respondents has indicated that only 49% of

Figure 4. Combining two treatments to maximise the treatment of all phases of allergic rhinitis inflammation

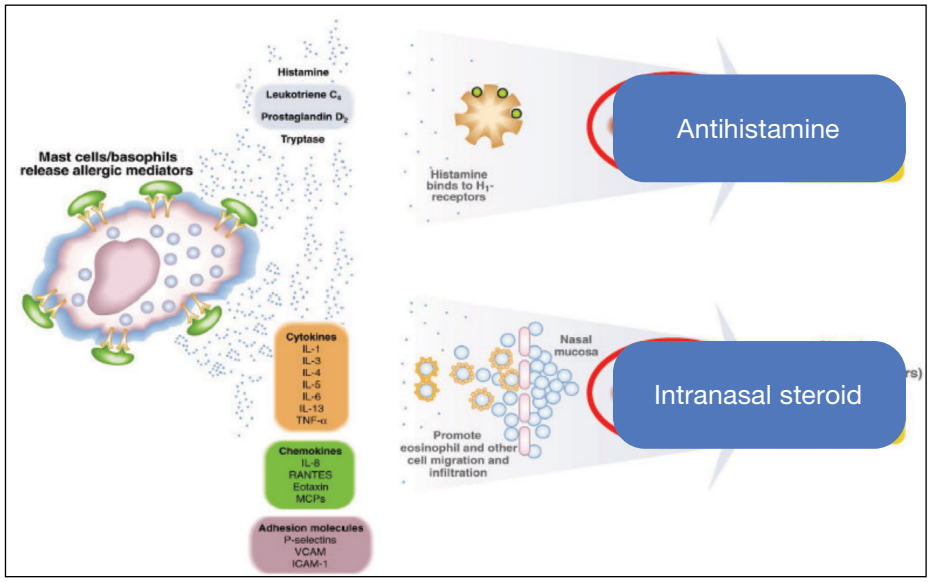
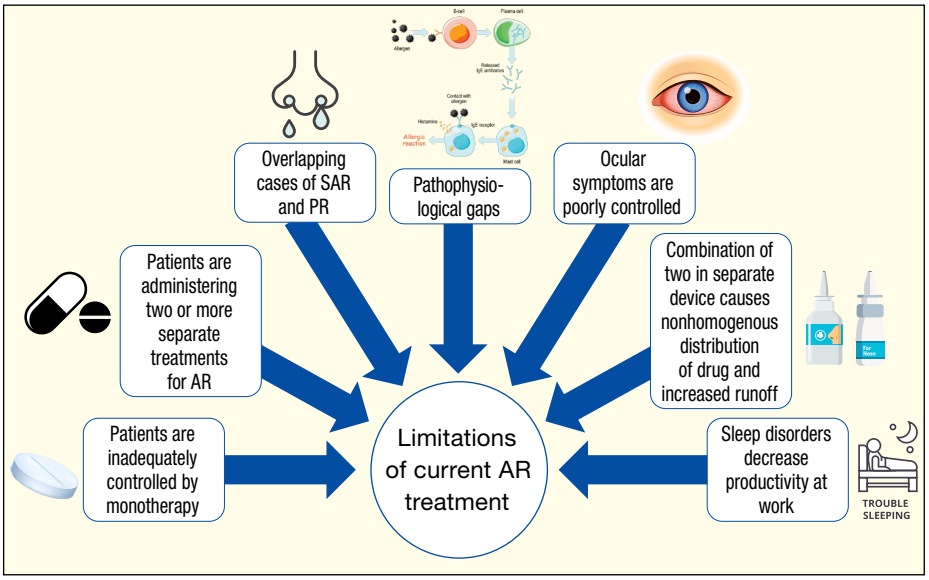


Figure 5. Limitations of current allergic rhinitis treatment



allergic (chronic) rhinitis sufferers consulted a medical practitioner. Of the remainder, 12% consulted a pharmacist, 24% self-medicated, and 15% did not treat their condition at all.

The remedies used to treat allergic rhinitis were many, varied and differed between the different race groups. The research showed the need for education on the use of the more sophisticated and appropriate medications.

From the market research conducted, it was clear that 50% of AR sufferers did not seek medical advice, but an appropriate educational programme could see better-educated pharmacists being directed or 'governed' by the guidelines of the SA Allergic Rhinitis Working Group and referring those sufferers who do not respond to over-the-counter treatments to a medical practitioner.

Pharmaceutical companies should ensure that products are correctly marketed for the correct indication, and that some sort of consumer education is undertaken to assist doctors and pharmacists.

New therapy

But now for a new therapy that makes AR care easier to achieve, combining the two major impacts of two therapies (Figure 4).

Recalling that the early-phase of an allergic response is driven by histamine and the late-phase by eosinophils, it makes perfect sense to combine treatments to both phases in one therapy (Figure 4).

This two-pronged approach should lend value to ensuring nasal symptoms, complications, and interventions, are minimised on a duplicate process.

So, to the current problem with allergic rhinitis treatment is that we have had all these treatments and interventions for years and yet AR is still badly managed. There are many reasons for the poor outcomes for AR treatment (Figure 5).

We are left with SA patients with AR who continue to suffer.

Now it is time to stand up and demand better care. And we have. A new care combining the two principal ingredients for AR care.

They are a safe and effective topical corticosteroid and an effective multiple action molecule that has antihistamine effects that will take care of break-through symptoms. This product is RYALTRIS® (Figure 6).

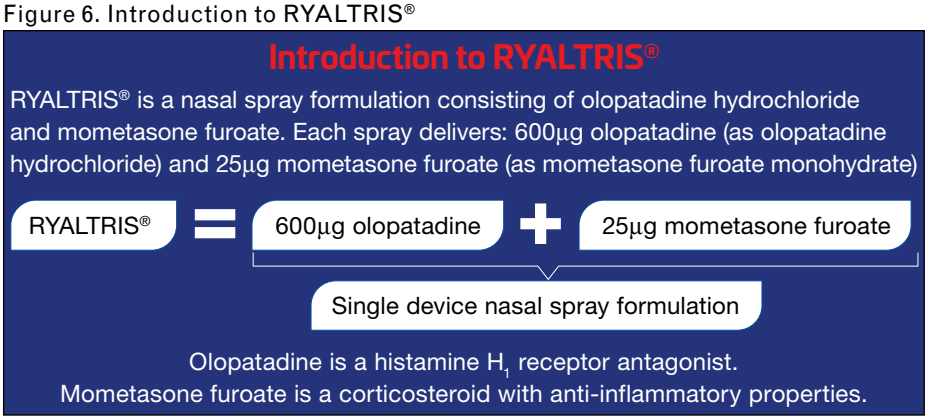
The antihistamine in RYALTRIS® is a multiple action molecule, olopatadine, with additional actions that suppport AR care (Table 2).

There is no doubt that many sufferers of AR need a combination therapy for many reasons (Table 3).

Table 2. Multiple action olopatadine
Olopatadine supresses the migration of THP-1 monocytes induced by SN100A12 protein
Olopatadine inhibits anti-IgE stimulated conjunctival mast cell upregulation of ICAM-1 expression on conjunctival epithelial cells
Type 1 allergy-induced endolymphatic hydrops and the suppressive effect of H1-receptor antagonist (olopatadine hydrochloride)
Mast cell stabilisation and anti-histamine effects of olopatadine ophthalmic solution: A review of pre-clinical and clinical research.

Table 3. The need for combination allergic rhinitis treatment
Need for combination treatment
» Evidence suggests that combination of an antihistamine and corticosteroid nasal spray might be more effective in reducing AR symptoms and have additional benefits than monotherapy alone
» Intranasal formulations of antihistamines and corticosteroid are efficacious monotherapies, which have different onset of action. Antihistamines provide immediate (15-30 minutes) but short-term symptom relief lasting up to 12 hours, and corticosteroids provide sustained symptom relief with a longer onset of action (3-36 hours)
» Furthermore, combined [fixed dose combination (FDC)] treatment in single device may reduce medical and pharmacy costs (depending on local pricing) compared to using multiple monotherapies
» Single device use also improves the patient compliance and adherence to the treatment
» Single medication device offers homogenous uniform distribution as well as no runoff posteriorly and anteriorly It offers broader disease coverage and faster symptom control
» Intranasal antihistamines are more effective at reducing symptoms of itching, rhinorrhoea and sneezing compared to oral antihistamines, but are less effective at reducing concurrent ocular symptoms. INCS are particularly useful for improving ocular symptoms

Figure 6. Introduction to RYALTRIS®



Conclusion

We have always known that AR nasal inflammation and its associated symptoms and complications have two major sources, release of histamine from mast cells and basic proteins released from eosinophils. The degree to which individual patients suffer symptoms, although it is partly due to lack of medication adherence, is often from failing to target both inflammatory processes. RYALTRIS® is a new combination product that has been shown in clinical trials, to add value to control of AR.

References available on request. SF