

Call for Combined Asthma and Rhinitis Treatment Offers Opportunities for Drug Delivery Innovators



By Dr Troels Keldmann, Co-founder and Managing Director of Direct-Haler A/S

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Historically, asthma has been diagnosed, treated and monitored separately from allergic rhinitis. It has now been documented that 70-90 per cent of patients with asthma have co-existing allergic rhinitis, and that the two diseases are to be regarded as one syndrome: one airway, one disease. This insight has prompted specialists to state new treatment recommendations: to provide combined and simultaneous treatment of both asthma and allergic rhinitis (1,2,3).

Drug delivery devices have always played an important role in respiratory therapy. Pulmonary and nasal cortico-steroids are the most important drug class in treatment of the underlying inflammation in asthma and rhinitis. The effective cortico-steroid doses have a minimum risk of side effects, and best efficacy when delivered directly to the airways. This means that inhaled delivery (both nasal and pulmonary) of steroids will continue to be needed in the future.

Currently available asthma and rhinitis drug delivery systems are not optimised for combined and simultaneous use. This represents an opportunity for drug delivery innovators to create new medication management/delivery systems for:

1. Combined/simultaneous treatment of rhinitis/asthma
2. Multiple-route delivery combinations: pulmonary, nasal and oral – for optimal dosing efficacy and safety
3. Easy and convenient drug delivery to promote compliance

PRACTICE TODAY

Traditionally, physicians are specialised in either the upper or lower part of the respiratory system. Ear-nose-throat specialists focus on the airway system from the nostrils to the vocal cords; the pulmonologists specialise below the vocal cords. Disease specialisations including drug development has therefore also been separated (see Figure 1). The result is that asthma and rhinitis today are separately diagnosed, treated and monitored.

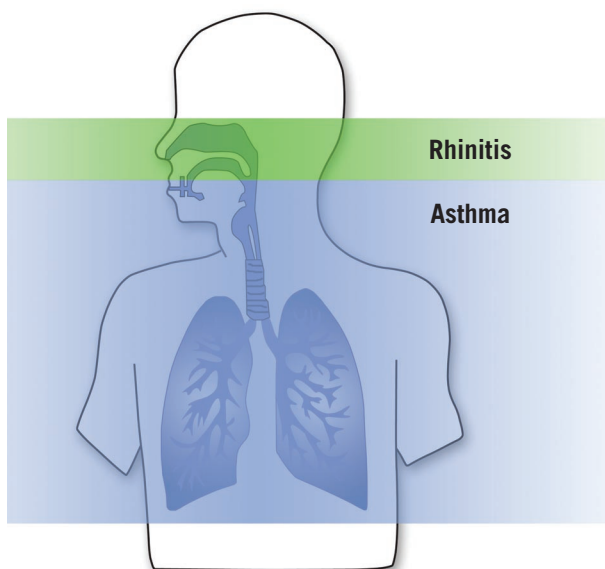
Observations and studies across specialisations have also been made by practitioners. And thanks to these studies, we now have an improved understanding of the close relation of these two diseases: the relationship between rhinitis and asthma can be viewed under the concept that the two conditions are manifestations of one syndrome, the chronic allergic respiratory syndrome, in two parts of the respiratory tract (4).

SIZE AND SEVERITY OF CO-EXISTING ASTHMA AND RHINITIS

The size of the asthma and rhinitis problem is illustrated by the data in Figure 2. In addition, it also captures the size of the combined problem of co-existing asthma and allergic rhinitis:

- ◆ 70-90 per cent of patients with asthma also have allergic rhinitis (5)
- ◆ The cost is around 46 per cent higher for patients with co-existing asthma and rhinitis than for patients with asthma only (8)

Figure 1: Historical Separation of Asthma and Rhinitis



- ◆ There is a direct correlation of disease severity: those with severe or poorly controlled rhinitis have worse asthma control or persistent asthma than those with mild or controlled rhinitis (9)

THEORIES EXPLAINING THE LINK BETWEEN ASTHMA AND RHINITIS

There are four theories, each expanding on the reasons for the close link between the two diseases (11), three of which are straightforward anatomical explanations. The first theory is that nerve fibres connect the upper airway and lower airways, meaning that nasal irritation provokes a bronchial reflex. The second theory concerns the breathing pattern, where nasal breathing is normal. It changes to mouth breathing when the nasal passage is blocked, whereby irritants will reach the lungs immediately. The third theory is that during sleep, the substance is dripping from the nasal passage to the lower airways, which triggers episodes of coughing or wheezing. The fourth theory states that there is a systemic propagation of the nasal inflammation to the lower airways.

IMPACT ON GUIDELINES

These new insights have already affected guidelines for rhinitis. The Allergic Rhinitis and its Impact on Asthma (ARIA) guideline (1) is the first guideline to incorporate this new knowledge. The ARIA guideline has replaced the International Consensus on Rhinitis (IRC) guidelines of 1994 and it is important to note that the ARIA guidelines offer the advantage of being evidence based.

The ARIA initiative has collected more than 2,500 scientific references and thereby created the formal fundament for translating the ‘one airway – one disease’ concept into the diagnosis and treatment of patients. This work has been sponsored by the major companies working in the field of respiratory diseases and is supported by WHO.

The ARIA guideline states a set of key recommendations (see Figure 3), ranging from how to consider allergic rhinitis as a risk factor in development of asthma, to a new categorisation: instead of perennial and seasonal, it should be labelled persistent and intermittent. This aligns the labelling with asthma. With regard to diagnosis, the co-existence leads to a recommended ‘double check’ when a patient is examined: physicians should check for both asthma and allergic rhinitis when a patient appears to have one of them.

Finally, in terms of treatment, the ARIA guideline recommends that a combined strategy should ideally be used to treat upper and lower airway diseases in terms of efficacy and safety (1). These recommendations have been restated by other references: the recommended clinical approach is to manage the two disorders discretely, but in tandem (2). Each should be treated separately even though they constitute the same disease (3). This explains the current belief that patients should be treated for each condition with the current treatments options – but in a combined and simultaneous way.

Figure 2: Facts and Figures on Co-Existing Asthma and Rhinitis

Allergic Rhinitis	Asthma	Allergic Rhinitis and Asthma
Prevalence Allergic rhinitis: 15-20% of population in developed countries	Asthma: 5% of adults, 8% of children in developed countries Mortality (US) 5,000 annual asthma deaths	70-90% of asthma patients also have allergic rhinitis (5) 38% of allergic rhinitis patients also have asthma (6)
Average annual cost per patient For medicine, hospital and rehabilitation: 1,543 Euro	For medicine, hospital and rehabilitation: 6,881 USD	For medicine, hospital and rehabilitation: 7,928 Euro (7) 46% higher costs than patients with only asthma (8)
Types and distribution 20% seasonal allergic 40% perennial allergic 40% mixed (increased symptoms at specific season).	40% non-allergic asthma 60% non-allergic asthma; hereof: Severe persistent 20% (60% of costs) Moderate persistent 20% (25% of costs) Mild persistent 20% Mild intermittent 40%	Patients with severe or poorly controlled rhinitis had worse asthma control or more persistent asthma than those with mild or controlled rhinitis (9)
Market value worldwide 10.6 billion USD (10) US market value: 70% Japan: 20%, Europe: 10%	10.3 billion USD (10) Growing 7% per year	

INVESTIGATING CROSS-IMPACT OF MEDICATIONS

The scientific knowledge base in this field is constantly expanding. It is very interesting to see that new studies are being run in order to understand what is achieved therapeutically when the known treatment options are combined. Studies of cross-impact of treatments show how rhinitis treatment can positively affect the asthma condition in patients with both diseases. The World Allergy Organisation (5,12) stated in 2003 that prompt and effective treatment of nasal disease can have a marked effect on preventing the development of asthma and on existing asthma symptoms.

There are studies that seek to express this benefit in numbers. In a cohort study (13) of patients with both asthma and rhinitis, it was found that the risk of asthma-related events was reduced by one-third to one-half by adding rhinitis treatment – compared with patients who did not receive added rhinitis treatment.

Another recent study goes into further detail (14). It shows that adding oral antihistamines to the asthma therapy gives good results, but adding nasal corticosteroids give better results. However, the very best result is achieved when adding a combination of both nasal steroid and oral antihistamine to the asthma treatment.

Figure 3: New Recommendations for Diagnosis and Treatment

Diagnosis of co-existing asthma and rhinitis

- Allergic rhinitis should be considered a risk factor for asthma along with other known risk factors (1)
- Patients with persistent allergic rhinitis should be evaluated for asthma by history, chest examination and, if possible and when necessary, the assessment of airflow obstruction before and after bronchodilator (1)
- Patients with asthma should be appropriately evaluated (history and physical examination) for rhinitis (1)

Treatment of co-existing asthma and rhinitis

- A combined strategy should ideally be used to treat upper and lower airway diseases in terms of efficacy and safety (1)
- The recommended clinical approach is to manage the two disorders discretely but simultaneously (2)
- You should treat each disease separately; that even though it's one disease, you can't just treat the nose and take care of the asthma, or treat the asthma and take care of the nose. Each one has to be treated appropriately (3)

Figure 4: Big Respiratory Pharma R&D Initiatives and External Communications – Response to the Close Link between Asthma and Allergic Rhinitis

1997

Glaxo Wellcome (now GSK) stated at an investor meeting that the company 'particularly wishes to target the 80% of asthmatics who have rhinitis, as the severity of their asthma symptoms declines with successful treatment of their rhinitis'.

2000

Merck and Schering-Plough establish partnership to pursue a fixed oral combination of Schering-Plough's oral antihistamine Loratidine and Merck's Singulair – an oral anti-leukotriene. Loratidine is a strong commercial success in rhinitis treatment and Singulair is a successful oral asthma treatment.

2002

Aventis (now Sanofi-Aventis) stated in a press release that 'a key focus for Aventis is the link between asthma and allergic rhinitis'. The successful oral antihistamine Allegra was available at the time studied for its potential application in asthma treatment.

2003

Merck's Singulair has for a long time been a successful oral drug for asthma treatment. But with additional clinical studies in rhinitis treatment has led to approval for Singulair's use for rhinitis indication.

2005

AstraZeneca's Internet site AZ-air.com is designed for respiratory specialists. Here is given the advice 'optimisation of the rhinitis treatment will help improve control of the asthma, but asthma must also be appropriately treated'.

2005

Merck is sponsoring a media think-tank organised by Allergy UK and Merck together. The think-tank addresses the need for creating public awareness of co-existing asthma and allergic rhinitis.

The latest addition to impact on treatment guidelines is the IPAG guideline of the International Primary Care Respiratory Group (15). The IPAG guideline has two aims: to become an integrated treatment guideline for respiratory diseases based on GINA, GOLD and ARIA guidelines; and to make the new guideline in a format which is useful to the GPs. There is no doubt that such an initiative is very important.

ACTION BY BIG RESPIRATORY PHARMA

Often drug delivery companies develop enabling technology designed to be ready for implementation when the pharma industry is ready to apply and exploit it. The big respiratory pharma companies are already very much aware of the new respiratory logic concerning asthma and allergic rhinitis. Figure 4 presents public statements and communications on the asthma and rhinitis link from the following companies: GlaxoWellcome (now GSK), Merck, Schering-Plough, Aventis (now Sanofi-Aventis) and AstraZeneca.

CURRENTLY AVAILABLE MEDICATION SYSTEMS

The active substances needed for treating the combined asthma and rhinitis disorder already exist (see Figure 5): pulmonary corticosteroid or combination with long acting beta-2-agonist; the nasal steroid in nasal spray form, oral antihistamines or oral antileukotrienes, and finally, the pulmonary rescue medication.

Pulmonary and nasal cortico-steroids are the most important drug class in treatment of the underlying inflammation in asthma and rhinitis. The effective steroid doses pose the least risk of side effects when delivered directly to the airways. This means that inhaled delivery (both nasal and pulmonary) of steroids will continue to be needed in the future.

DEFINING FUTURE NEED

What is needed today must look beyond the call for combined/simultaneous asthma and rhinitis therapy. The current delivery systems are not optimised for the new 'one-airway, one disease'

concept. Anyone seeking to apply the shown delivery formats in combination will find that dosing schedules are not co-ordinated and it will be difficult to comply with the regimens. Therefore, we should seek to create flexible medication management systems for combined/simultaneous treatment of rhinitis/asthma.

It is important to note that the pulmonary route is essential in asthma treatment, and the nasal and oral routes are essential in rhinitis treatment. As a result, the need for flexibility to accommodate multiple route delivery combinations is paramount. Here are a few examples of how such new combinations could be applied in respiratory treatment:

- ◆ In the treatment of allergic rhinitis, it could be an idea to combine a once daily dose of non-sedating oral antihistamine with one daily dose of nasal cortico-steroid. The antihistamine is for symptom control and reducing airway sensitivity, and the nasal steroid is for controlling and reducing the local inflammation.
- ◆ In a disease stage, when both the asthma and allergic rhinitis are moderate to severe, it could be an idea to add the pulmonary dose. This would mean combined dosing of for instance nasal cortico-steroid, pulmonary steroid/beta-2-agonist, and an oral antihistamine.

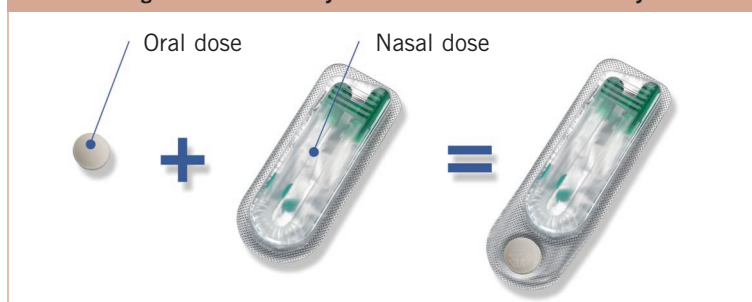
THE KEY CHARACTERISTICS OF A NEW GENERATION OF DEVICE TECHNOLOGY

Accommodation of such novel types of combinations will require new types of medication and delivery systems. The characteristics for such a new generation of device technologies would, as already mentioned, include flexibility (pulmonary, nasal and oral delivery combinations), suitability

Figure 5: The Challenge of Combining Current Medication Systems



Figure 6: Unit-Dose System with Combination Flexibility



to once-daily dosing for compliance enhancement and an easy to use, convenient drug delivery device system. Many different types of device concepts can be developed to meet such criteria. Each technology platform, be it pMDIs, nebulisers or DPIs, will have a basis for creating different 'combination device' concepts.

Historically, pMDIs and DPI (Turbohaler) have been used for both pulmonary and nasal delivery of cortico-steroids. For nasal delivery, the mouthpiece has been changed to a nostril piece, for improved access to the nasal cavity. In future searches for new concepts, an alternative approach to consider could be modular device systems, allowing unit-dose combinations for different delivery routes (see Figure 6).

CONCLUSION

It is an exciting time to work in respiratory therapy. The new understanding of the links between asthma and rhinitis is documented. It represents both a challenge and an opportunity for all of us involved in respiratory drug development and delivery to transform the new insight into patient benefits.

A continued drive toward innovation is needed. The scientific minds that work in the fields related to respiratory diseases should step closer to each other to combine the strengths of each specialisation. A combined approach is required if we sincerely wish to improve the treatment of co-existing asthma and allergic rhinitis. ♦

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