

## 7 SUMMARY

Rational pharmacotherapy should ensure a safe and cost-effective treatment of patients with allergic rhinitis (AR). Two main aspects of treatment of AR were addressed (1) comparative benefits and costs of subcutaneous and sublingual allergen immunotherapy in patients with allergic rhinitis, and (2) systemic adverse events – neuropsychiatric disorders and gynaecomastia - during intranasal corticosteroid use.

### (1) Allergen specific immunotherapy: benefits and costs

- Our pharmacoeconomic study on allergen specific immunotherapy showed that sublingual and subcutaneous immunotherapy reduced clinical symptoms and the need for symptomatic medication in adults with grass pollen induced rhinoconjunctivitis compared to standard pharmacological treatment. The clinical efficacy of the sublingual and subcutaneous immunotherapy was not significantly different in the third year of specific immunotherapy. Nevertheless, the SCIT group exhibited slightly better improvement in visual analogue scale and a greater reduction of systemic antihistamines versus SLIT in the third year compared to the baseline year.

Overall, SLIT showed a better cost profile from all three perspectives. SCIT was financially favorable from a patient perspective where no loss of income and travel costs were present.

Larger comparative studies examining the cost-effectiveness of sublingual and subcutaneous routes of administration including the durability and preventive effect of immunotherapy, as well as safety and compliance, must be conducted to confirm the advantage of sublingual route of administration of SIT and its cost saving potential.

### (2) Safety of intranasal corticosteroids

Intranasal corticosteroids are the first line treatment of moderate to severe persistent rhinitis and other inflammatory disorders. The majority of professional community perceives them as safe and with minimal occurrence of systemic effects. Our safety studies indicate there are new previously unrecognized systemic adverse effects such as neuropsychiatric disorders or gynaecomastia that may develop during the INC use. Since these reactions can be serious or embarrassing, further study is needed to clarify the mechanisms underlying these events, identify risk factors and further update the safety profile of intranasally administered corticosteroids. Those drug-related safety issues need to be also communicated to the professional community, health care providers as well as patients.

- **Neuropsychiatric disorders** - Taken together, the data – i.e. the numbers of reports, the pattern of reporting and its similarity with what is known as well as reported for systemic corticoids – are suggestive of an involvement of the INCs. In addition the general pattern of recovery after stopping the suspect drug and the presence of reoccurrence of the symptoms after readministration (a ‘positive rechallenge’) provide, we believe, additional support to this view. In the light of the large scale world-wide use of INCs the numbers or case reports are small and the frequency of such reactions is probably low. On the other hand underreporting is vast but unknown and the frequency remains uncertain and likely underestimated.

- **Migraine** - Although there is a known connection between allergic rhinitis and migraine, the reports in Vigibase suggest that, in addition, INCs might cause or worsen migraine or migraine-like headache. It is important to note that none of the studies investigating the connection between allergic rhinitis and migraine looked at the possible link between migraine and antiallergy drug use. Perhaps an INCs-related inflammatory process of the mucosa in the nose or paranasal sinuses may in turn lead to (unilateral) headache. In order to collect more information regarding the possible but ill-understood connection between INCs and migraine-like headache, health care practitioners are requested to report similar observations to the national pharmacovigilance programs in their countries. In addition, further studies are needed to determine whether the reported association between INCs and migraine or unilateral headache is real or not and, if so, what the possible mechanism might be.
- **Gynaecomastia** - Eight case reports in the WHO-UMC database coming from two countries, suggest that intranasal administration of corticosteroids can occasionally lead to the development of gynaecomastia. Although gynaecomastia has not been described in the literature in connection with inhaled corticosteroids, it is worth mentioning that a total of 15 such case reports, originating from five countries, have so far been stored in the Vigibase. Further study is needed to confirm the association between intranasal corticosteroids and the development of gynaecomastia.

In conclusion, the aim of allergic rhinitis management is to improve patient's quality of life and resume his/her everyday life activities. A therapeutic plan should be individualized and include patient education, allergen avoidance and symptomatic therapy. Allergen specific immunotherapy should be recommended to each patient according to the latest therapeutic guidelines. Based on our study outcomes, further considerations should be paid to the safety as well as cost-effectiveness of treatment options in patients with seasonal allergic rhinoconjunctivitis.

Firstly, an individualized treatment plan for SIT candidates should also focus on the economic advantages of different administration routes selecting the most cost-effective option for the patient. Health-care policy should support treatment alternatives that are convenient for both an individual and a society. In this respect, our study showed that sublingual administration route of SIT turned out to be the best alternative for all patients from all perspectives except for those who do not have travel and loss of income costs. When our results are confirmed in larger studies, health care decision-makers should set the guidelines for the drug reimbursement and cost so that sublingual route of SIT becomes more available for its superior safety and cost-effectiveness.

Secondly, all patients who are prescribed an INC should be monitored for possible systemic effects of corticosteroids including neuropsychiatric events until more information becomes available. An additive effect of corticosteroids with an increased risk for systemic adverse effects should be anticipated in patients using different administration routes of corticosteroids simultaneously.

Physicians and pharmacists should monitor the safety of medicines and select the most optimal cost-effective therapeutic choice for the greatest patient's benefit.