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FACULTY OF PHARMACY IN HRADEC KRÁLOVÉ

THESIS

2008 Mgr.Jitka Pokladníková

CHARLES UNIVERSITY IN PRAGUE
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PHARMACOECONOMIC AND PHARMACOEPIDEMIOLOGY ASPECTS OF ALLERGY RHINITIS TREATMENT AND PREVENTION

-thesis-

Mgr.Jitka Pokladníková

Promoters: Doc. RNDr. Jiří Vlček,CSc.

Co-promoters: MUDr.Irena Krčmová,CSc.

Research projects were conducted at the Department of Social and Clinical Pharmacy at Faculty of Pharmacy at the Charles University in Prague in Hradec Králové, the Czech Republic in cooperation with the Department of Allergology and Clinical Immunology, University Hospital and Faculty of Medicine, Charles University in Prague, Hradec Králové, Czech Republic; the Division of Pharmacoepidemiology and Pharmacotherapy of the Utrecht Institute for Pharmaceutical Science, Utrecht, the Netherlands; and at the WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, Uppsala, Sweden. The research was supported in part by the European Union Grant Leonardo da Vinci (CZ/05/A/PL/134243), in part by the Ministry of Health of the Czech Republic (MZ CR NI/7470-3) and the Ministry of Education of the Czech Republic (MSM 111600004). MSc Pharm Jitka Pokladníková received a Leonardo da Vinci fellowship for a practical training at the Uppsala Monitoring Centre. There was no conflict of interest at any stage of the research work: design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscripts.

Contributions

The work described in this thesis is my own original research done under the supervision of Doc. RNDr. Jiří Vlček,CSc. Unless otherwise stated, it is the work of the author.

MSc Pharm Jitka Pokladníková participated in the following stages of preparation of all manuscripts:

1) Study conception and design

2) Collection/extraction and management of data

3) Analysis and interpretation of data

4) Preparation of manuscript

5) Critical revisions and approval of final version of manuscript

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Contents

Abbreviations

AR	Allergic rhinitis
DM	Deutchmark
INC(s)	Intranasal corticosteroid(s)
NP	Neuropsychiatric events
SIT	Specific allergen immunotherapy
SLIT	Sublingual allergen immunotherapy
SCIT	Subcutaneous allergen immunotherapy
UMC	Uppsala Monitoring Centre
WHO	World Health Organization

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Introduction

1 INTRODUCTION

1.1 Allergic rhinitis

Allergic rhinitis (AR) is a chronic condition affecting 20 % of general population in Europe and the United States, and can reach up to 40 % in selected pediatric populations (1). Allergic rhinitis is characterized by the presence of seasonal or perennial nasal pruritus, sneezing, rhinorhea and nasal congestion that develop as a result of Ig-E mediated reaction to causal allergen (2). Indoor or outdoor aeroallergens such as pollen, mold, animals or house dust mites are mainly of plant or animal origin. A positive family history of atopy as well as environmental factors such as infection or pollutants can contribute to the development of AR (2).

The socioeconomic burden of AR on patients and society is immense. It has been estimated that the annual cost of AR in the United States (2002) was $7.3 billions with $4.6 billions accounting for physicians' visits (3). The prevalence of comorbidities such as asthma bronchiale, sinusitis, otitis media and polyposis in patients suffering from AR is relatively high and contribute to the overall burden of AR (2, 4). It is well known that a patient suffering from AR has a three to four times risk of developing asthma. On the other hand, more than 75 % of patients with asthma suffer from AR (4). The association between upper and lower respiratory airways diseases known as "one-airway respiratory disease" is well recognized and implemented into the therapeutic guidelines and recommendations (2).

The management of allergic rhinitis requires a long-term and complex therapy involving both symptomatic and causative pharmacologic and non-pharmacologic approaches, including surgery intervention. The strategy of AR management is based on a stepped-down or stepped-up pharmacotherapeutic algorithm and the main goal is to relieve symptoms, prevent exacerbations and development of complications (Figure 1) (2).

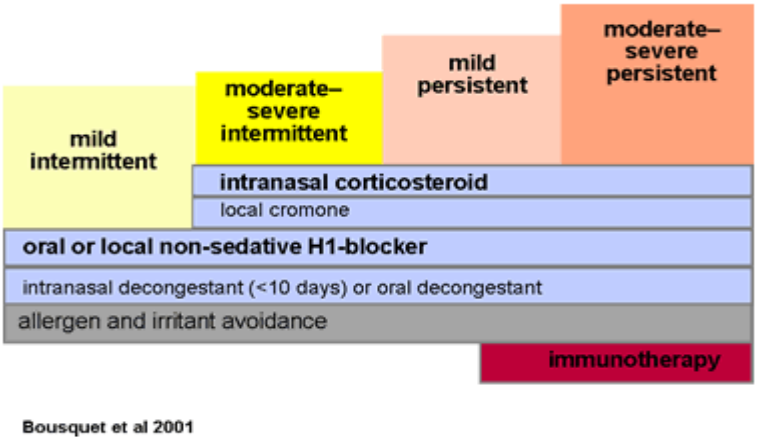

Figure 1: Treatment of allergic rhinitis[2]

Non-pharmacological interventions include patients' education and allergen avoidance. Available pharmacologic agents that are used in the treatment of AR are intranasal corticosteroids, H1-antihistamines, decongestants, cromolyn sodium, antileukotrienes, anticholinergics, intranasal saline, and anti-IgE.

Allergen specific immunotherapy (SIT) is offered to patients with poor response to conventional pharmacotherapy without severe organic changes. It is defined as the repeated administration of a specific allergen(s) to patients with Ig-E mediated conditions for the purpose of providing protection against the allergic symptoms and inflammatory reactions associated with natural exposure to the allergen(s) (5). From both an economic and a patient well-being perspective, allergen immunotherapy offers a real alternative because of its ability to reduce symptom-medication scores in the long term and improve the quality of life (6).

Furthermore, SIT is the only treatment that addresses the cause of IgE-mediated immunopathology and modulates the natural course of the disease (7). SIT has been shown to prevent further progress of the disease and the onset of new sensitizations and asthma long after it was discontinued (8, 9, 10). Subcutaneous allergen immunotherapy (SCIT) is a well-established standard of care in patients with allergic rhinitis, rhinoconjunctivitis, atopic asthma, and Hymenoptera anaphylaxis for whom symptomatic treatment and allergen avoidance are not a sufficient way to control the disease (7). Sublingual allergen immunotherapy (SLIT) is an alternative administration route recently proven to be effective and safe, with less serious systemic adverse effects than SCIT (11).

Rational pharmacotherapy in the treatment of AR based on evidence-based medicine is needed in order to provide patients with effective and safe medicines while assuring cost-effectiveness from

society perspective. Therapeutic value of individual pharmacotherapy approaches is constantly evolving and is determined by the latest available knowledge there is on efficacy, risks, and economic aspects of therapeutic options for a given condition across different populations. For example, subcutaneous allergen immunotherapy remains the gold standard administration form of specific allergen immunotherapy. At the same time, sublingual allergen immunotherapy has been widely used in clinical practice mainly in European countries and has just recently been validated as a viable alternative route to SCIT (11). Nevertheless, no data exists on the comparative benefits and costs of both administration forms in patients suffering from allergic rhinitis that would provide us with a solid rationale for their use from the perspective of a patient as well as drug policy-makers.

Another example concerning the therapeutic value of drugs used prophylactically for AR treatment is that of intranasal corticosteroids. Intranasal corticosteroids (INCs) are the most effective treatment alternative for moderate to severe form of AR as compared to other therapeutic groups and is recommended as the first line therapy (2). The risk-benefit ratio has been proven to be very good with the occurrence of some local side effects and a minimum of systemic effects (12, 13, 14). International drug-safety monitoring by the World Health Organization (WHO) has revealed some new information concerning systemic adverse events in connection with INC use that need to be communicated in order to ensure patients' safety.

Therefore, two main aspects of AR treatment are addressed in this thesis: (1) new data on costs and benefits of SIT, the only causative treatment of AR, and (2) new systemic adverse events during INC use, notably neuropsychiatric and some hormonal disorders, specifically, gyneacomastia. Those new findings are valuable for health care professionals and health-care policy makers and put SLIT and INCs treatment in a new light.

1.2 Pharmacoeconomics of allergen specific immunotherapy

1.2.1 Efficacy

Although SLIT has been recently validated as a viable alternative to SCIT, the benefits of SLIT compared to a standard SCIT have not yet been established on a large scale. In a study with 20 patients with grass allergy by Ongari, SLIT and SCIT were similar in efficacy when compared to pharmacological treatment (15). SLIT and SCIT were found equally effective after 12 months in other two small studies by Quirino and Mungan (16, 17). Yet another study by Bernardis showed clinical improvement with *Alternaria tenius* extract in 23 patients in both SLIT and SCIT groups after one year (18). While the quoted studies add compelling data to the discussion, the data lacks significance because of multiple methodology flaws -- including small study sizes, the absence of randomization

prior to study group allocation, the lack of placebo control, and the failure of the studies to encompass the recommended treatment duration.

The most methodologically valid study was performed by Khinchy (19). Khinchy conducted a double blind, double dummy and placebo-controlled study of 58 patients with birch allergy who were randomized into SLIT, SCIT and a placebo arm. In the first year of treatment (the only year evaluated), Khinchy did not find any significant difference in either symptoms or drug intake reduction between the SLIT and SCIT groups. There are additional studies of either SLIT or SCIT confirming improvement of quality of life after SIT administration (20, 21).

Compliance is an important factor that can influence effectiveness as well as cost of a disease. Published studies report SCIT non-compliance rates of up to 50 %, citing inconvenience and side effects as the primary reasons for SCIT discontinuation (22, 23). In contrast, SLIT compliance rates were shown to be relatively high (24, 25, 26).

1.2.2 Cost

Pharmacoeconomics analyzes the cost and impact of pharmaceutical products and services on individuals, healthcare systems and society. Pharmacoeconomic outcomes provide healthcare decision makers with knowledge on how to allocate limited resources when the number of alternatives available to treat disease, the cost of medicines and technologies and aging population increase (27).

The overall costs associated with allergic rhinitis and certain adverse effects of pharmacologic treatment, such as discomfort, somnolence, and cognitive impairment (impaired learning, memory, and performance), are substantial and create a significant economic burden to the society (28).

Costs of subcutaneous allergen immunotherapy were evaluated in a couple of studies coming mainly from the United States where SLIT is not yet approved by the US Food and Drug Administration. A study from (1996) showed that SIT- related physician's visits encountered for 50 % of all visits of approximately 1.8 millions of patients with allergic rhinitis (29). Allergen immunotherapy related costs reached 691 billions (20 % of total direct costs of AR). Annual direct costs of AR of patients undergoing allergen immunotherapy was 5.8 fold times higher compared to the rest of the patients with allergic rhinitis ($661 vs $114). Total costs for medication was 23 % higher in patients treated by SIT compared to the rest of the patients ($135 vs $70). Another study found that the average annual costs of AR in 2667 subjects of a total of 122 196 of patients registered at Harvard Pilgrim Health Maintenance Organization undergoing allergen immunotherapy was $416 and $496 in patients with AR and AR and comorbid asthma, respectively (30).

The cost-savings potential of SCIT and SLIT compared with standard pharmacologic therapy has only been described in a few studies. A modeling approach of the economic consequences of SIT lasting 3 years with those of continuous symptomatic treatment in patients with either pollen or mite allergy was used in a 10-year follow-up study in Germany (31). The evaluation was conducted from

the perspectives of society; healthcare system; and statutory health insurance provider. The break-even point was reached between year 6 and year 8 after the start of therapy, resulting in net savings of between 650 and 1190 deutschmarks (DM) per patient after 10 years. The incremental cost-effectiveness ratio of SIT were between -DM3640 and -DM7410, depending on study perspective and nature of the allergy (1990 values for symptomatic treatment and treatment of asthma, 1995 values for SIT; DM1 approximately $0.58). The authors concluded that SIT was more likely to result in net savings than in additional costs. Initial resource investments and subsequent resource savings associated with SCIT in the long term compared with standard care was also observed in other national environments across Europe such as Austria, Denmark, Finland, Germany, the Netherlands, Sweden and France (32, 33, 34, 35).

In case of SLIT, a modeling study as well as observational study from clinical practice demonstrated its cost-effectiveness compared to conventional pharmacotherapy from society and third party payer perspectives (36, 37).

Even though both administration forms are widely used across Europe including the Czech Republic, there are no data on the comparative benefits and costs of SLIT vs SCIT after the whole recommended treatment period.

1.3 Pharmacovigilance of intranasal corticosteroids

1.3.1 The role of pharmacovigilance

The main role of pharmacovigilance is to detect, evaluate, understand and prevent any drug-related problem such as an unexpected adverse reaction (ADR), dependence, long-term efficacy, resistance, risk factors, quality and cost-assessment. Pharmacovigilance is an essential part of each nation's drug policy. Drug regulatory bodies such as the European Commission for Europe or the Food and Drug Administration for the United States set the legal framework for drug use and issue drug regulation requirements (e.g.: pre-registration toxicology and clinical studies, registrations and post-marketing surveillance).

Drug regulation initiatives have developed over time in different countries. After the thalidomide tragedy in the 60s´ that caused skeleton malformations to thousands of babies of mothers who were exposed to thalidomide during pregnancy, national as well as international initiatives led to the setting of spontaneous reporting systems in different countries. In most countries, the reporting of ADRs is done by health care professionals on either volunteer or mandatory basis. In some countries, consumer reports are also accepted. In Europe, pharmacovigilance centers further collaborate internationally within the WHO Drug Safety Monitoring System and Eudravigilance. Eudravigilance is a common data processing network and database management system for direct electronic

exchange, processing and evaluation of ADR reports related to medicinal products authorized in the European Economic Area.

Drug safety data collected by national pharmacovigilance centers throughout the post-marketing period provides physicians, pharmacists, patients, drug regulators and pharmaceutical companies with valuable information on the risk-benefit ratio of medicines. An informed therapeutic choice can then be made for the greatest benefit of the patient. Despite of all the progress that has been made in the field of pharmacovigilance over the past decades, drug safety issues still persist and need to be effectively addressed. For example, in the United States, ADRs belong to the 4-6th largest cause of mortality (38). In some countries like the United Kingdom, the incidence of drug related hospital admissions was estimated at 10 % (39). Moreover, the costs associated with drug related mortality and morbidity can be high and reach as much as $177.4 billions (2000) as in the case of the United States (40).

The World Health Organization pharmacovigilance programme

The WHO international pharmacovigilance programme monitors the safety of medicines on a global scale since 1968 (41). A primary aim of the international pharmacovigilance programme is to detect new signals early in the post-marketing phase after the medicine has been released. The World Health Organization defines a signal as any reported information on a possible causal relationship between an adverse event and a drug that has been not previously known or completely documented (42). An adverse event is further defined as any untoward medical occurrence that may present during treatment with a pharmaceutical product but which does not necessarily have a causal relationship with this treatment (42). On the other hand, an adverse drug reaction is a response to a drug which is noxious and unintended, and which occurs at doses normally used in humans for the prophylaxis, diagnosis or therapy of disease, or for the modification of physiological function (42). All adverse effects are categorized into three major groups and are referred to as types A, B, C and D (43). A signal must be first detected and evaluated before an adverse event becomes an established adverse drug reaction.

Signal detection

Case reports (case series) as well as spontaneous reporting plays a major role in the detection of adverse events (44). Other sources of generation of new signals are shown in table 1. They all provide us with valuable information for signal detection. A minimal number of 3 to 9 case-reports is needed for signal generation in spontaneous reporting (43). The number of users of a drug, the frequency of the adverse effect and reporting rate will determine how fast we detect a signal e.g.: in order to discover an adverse effect with a frequency of 1 in 2000 users and a low background frequency of 1 in 100 000, a

study population of about 16 000 drug users would be needed (45). Suitable methods for signal detection based on the frequency of a reaction are shown in table 2 (44).

In the WHO spontaneous reporting system, both qualitative (reaction severity such as agranulocytosis) and/or quantitative tools are used for the detection of important signals (46). The unexpected adverse drug reactions to drugs are quantitatively analysed using the Bayesian Confidence Propagation Neural Network methodology (BCPNN), a data-mining technique used for the detection of new signals in spontaneous reporting of adverse drug reactions (47, 48). The measure of disproportionality expressed as the Information Component (IC) is used to indicate the frequency of specific drug-ADR combination that occurs more frequently in the database than expected in relation to the number of all reports with the particular drug and ADR and the total number of reports in the database (48).

Table 1: Information sources for signals[44]

Sources for Signals
Qualitative signals: Observations in patients
Spontaneous-reporting systems
Anecdotal literature reporting
Intensive hospital monitoring
Prescription event monitoring
Follow-up studies
Monitored release programmes
Quantitative signals: Observations in populations
Large data resources on morbidity and drug use (including record linkage)
Case-control studies
Follow-up studies
Prescription event monitoring
Intensive hospital monitoring
Large spontaneous-reporting systems (WHO Uppsala Monitoring Centre, Food and Drug Administration)
Experimental findings
Clinical trials
In vitro experiments
Animal toxicology

Table is published with author's approval.

Table 2: Selection of analytical studies according to frequency of adverse effect[44]

Detection method	**Frequency of adverse effect**						
	>1/10	1/10 – 1/100	1/100 – 1/1000	1/1000 – 1/5000	1/5000 – 1/10000	1/10000 – 1/50000	<1/50000
Spontaneous reporting	-	+	++	++	++	++	+
International reporting	-	-	+	++	++	++	++
Intensive monitoring	-	+	++	++	+	-	-
Prescription event monitoring	-	+	++	++	+	-	-
Case-control surveillance	-	-	+	++	++	-	-
Large data resources (record-linkage)	-	-	++	++	+	+	-
Follow-up studies	-	+	++	+	-	-	-
Monitored release	-	+	+	-	-	-	-
Clinical trials	++	++	+	-	-	-	-

- (of little or no use), + (may be helpful), ++ (preferable)

Table is published with author's approval.

Signal evaluation

An adverse reaction can be attributed to a drug treatment when causality between the drug and the reaction is established (49). Other factors such as concomitant therapy or disease may itself contribute to the development of an adverse reaction. Therefore, analytical studies need to be conducted to test the association between the drug and an adverse event and further determine risk factors that are associated with the development of an adverse drug reaction. The most commonly used analytical studies are case-control studies, cohort studies or randomized clinical trials. Statistically sound associations must be further tested for its causality. Bradford and Hill described several causality criteria that need to be considered before causality between a drug and a reaction is established such as the time and dose-response relationships, the specifity of the disorder, and the consistency and biological plausibility of the data (45). Causality is strengthened when an adverse drug reaction disappear after the drug is discontinued and reappear after the drug is reintroduced.

A number of case-causality assessment scales have been developed (49). WHO causality categories and the Naranjo method are the most commonly used approaches. The WHO-UMC Causality assessment system has been developed in cooperation with the National Centres participating in the Programme for International Drug Monitoring and is meant as a practical tool for the assessment

of case-reports based on the case history clinical-pharmacological aspects and the quality of the documentation of the observation (table 3) (50).

Table 3: WHO scale of causality assessment[49]

WHO Causality assessment scale	
1.CERTAIN	A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
2.PROBABLE/ LIKELY	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition. Event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
3.POSSIBLE	A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
4.UNLIKELY	A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
5.CONDITIONAL/ UNCLASSIFIED	A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.
6.UNASSESSIBLE/ UNCLASSIFIABLE	A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

Table is published with author's approval.

Frequency of an adverse event

Estimation of the frequency of an adverse event or risk of such reaction needs to be addressed. Risk is defined as a probability of an adverse reaction to occur in an individual (45). The frequency of an adverse reaction needs to be related to the overall number of exposed individuals to a drug treatment. Sales data expressed as the number of defined daily doses (DDDs – an average daily dose prescribed for the main indication in adults) or number of packages sold throughout the study period can be used. It is well known that underreporting is vast but unknown and the frequency of adverse events thus remains uncertain (51). The frequency of an adverse reaction may thus be underestimated.

1.3.2 Safety of intranasal corticosteroids

The systemic use of corticosteroids is limited by the occurrence of frequent and serious adverse effects. The introduction of corticosteroids for intranasal administration, such as beclometasone and fluticasone, has been a breakthrough and today INCs are the first line treatment of moderate to severe persistent rhinitis and other inflammatory disorders (non-allergic rhinitis, rhinosinusitis and chronic sinusitis) (2). INCs act predominantly locally and are considered to exert minimal systemic effects (12, 13, 14). Nevertheless, in rare cases symptoms of hypercorticism have occurred, including menstrual irregularities, acneiform lesions, cataract and cushingoid features, mainly when the recommended doses were exceeded or in individuals who were particularly sensitive or predisposed by virtue of recent systemic steroid therapy (52, 53, 54, 55).

Pharmacological characteristics of INCs

Taken together, the nasal cavities have a substantial mucosal surface of about 180 cm^2. After nasal administration about 30% is absorbed by the mucosa and, since there is no first-pass through the liver, the unchanged drug enters directly into the systematic circulation. The remaining 70% is rapidly nasociliary cleared into the throat and gastroinestestinal tract (56). Different corticosteroids are absorbed in varying proportions, however, and the systemic bioavailability ranges from <1 to up 40-50% (57, 58, 59, 60, 61). Pharmacological properties such as glucocorticoid receptor potency, affinity and residency time will in part determine the systemic pharmacodynamic response. In addition, pharmacokinetic factors including plasma elimination half life and volume of distribution (due to lipophilicity) will contribute to the effects at steady state in terms of drug accumulation in the blood and retention in systemic tissue (56). The amounts delivered are small and in licensed doses the effects of INCs on cortisol homeostasis and the pituitary-adrenocortical axis are considered to be small and of little significance. Between the various drugs used for intranasal administration there are substantial differences in the pharmacokinetic and pharmacodynamic properties.

Recent evidence shows that some drugs may after absorption by the olfactory epithelium by-pass the blood-brain barrier and be transported through the olfactory and trigeminal nerves directly into the central nervous system; there are intraneuronal and extraneuronal pathways (62, 63). In this way small amounts of a drug can in the brain reach comparatively high levels. No information is available, however, whether or not INCs reach the central nervous system through this pathway.

1.3.2.1 Neuropsychiatric disorders

As early as 1989, two case reports were published describing the occurrence of mania in suspected connection with the intranasal administration of beclometasone. In the one report mania occurred in a patient with a pre-existent bipolar disorder in remission, however, while erythromycin - known to affect the central nervous system - had been taken simultaneously (64). In the other patient mania was associated with vivid visual and auditory hallucinations, disorientation and impaired memory (65). This patient had a history of a previous manic episode during the systemic use of prednisolone. Iatrogenic Cushing's syndrome was also reported with dexamethasone nasal drops in several literature reports (66, 67, 68, 69, 70).

Most of information on neuropsychiatric disorders during INC use comes from literature case-reports and no such information is listed in so far published placebo controlled trials where the number of subjects (up to 3000-4000) could be to small to detect less frequent adverse effects (44).

In 1999 Cave and co-workers at the UK Medicines Control Agency reviewed the spontaneous reports of suspected adverse reactions to intranasal and inhaled corticosteroids received at the agency of the years, in the light of the information published in the literature (52). Five areas of concern were covered: hypothalamic-pituitary-adrenal axis suppression, osteoporosis and changes in bone mineral density, growth retardation in children, and cataract and glaucoma. The authors concluded with regard to intranasal administration that at licensed doses 1. adrenal suppression occurs but the clinical relevance is uncertain, 2. growth retardation occurs but the final stature may not be affected, and 3. there is insufficient evidence that cataract, glaucoma or osteoporosis may happen. The study did not address the possible occurrence of central nervous system or other systemic effects. It is noteworthy, though; that there had been 9 reports of patients with adrenocortical suppression, of whom all but one had also had Cushingoid symptoms (such as weight gain, facial swelling and striae). Interestingly all of these patients had been taking corticosteroids for a relatively short period of time, suggesting that in susceptible individuals adrenal suppression may occur rapidly. All but one of these patients had used doses within the licensed range. On the bases of these findings, the Committee on Safety of Medicines advised in 1998 with regard to intranasal corticosteroids the following: *Systemic effects may occur, particular at high doses prescribed for prolonged periods. In children growth retardation has been reported at licensed doses. Prolonged treatment with higher than recommended doses may result in*

clinically significant adrenal suppression. Additional systemic corticosteroid cover should be considered during periods of stress or elective surgery (52).

In a more recent position statement (2006), the Joint Task Force for the American Academy of Allergy, Asthma and Immunology nevertheless concluded that intranasal corticosteroids because of their potential to cause systemic effects should remain prescription only drugs (71).

The potential risk factors for the development of neuropsychiatric disorders were not yet determined. Nevertheless, fluticasone and beclometasone have a comparatively high potency for systemic adverse effects systemic adverse effects based on their pharmacokinetic and pharmacodynamic determinants (56). In case of systemic administration of corticosteroids, severe psychiatric symptoms generally increased in doses exceeding the equivalent of 40 mg of prednisone (72). Neuropsychiatric disorders occurred also with small doses of prednisone and the minimum of corticosteroid dose that may in an individual patient trigger a neuropsychiatric disorder is not known.

Although only small amounts of corticosteroids are administered and systemic blood levels are likely to be low, i.e. below or perhaps slightly above physiological levels, such amounts may nevertheless interfere with normal cortisol homeostasis, suppress the circadian cycle and impair the physiological responses to stress. This may in turn lead to periods of non-physiological corticoid levels and to mild but clinically relevant states of hypo- or hypercorticism. More study is needed to clarify the consequences of the exposure to external corticoids in roughly physiological amounts.

The glucocorticoid receptor is member of a family of nuclear steroid receptors, which also includes mineralocorticoid, oestrogen, progesterone and androgen receptors. In the past 10 or 15 years much experimental work has improved the understanding of these receptors and their actions and interactions. They are closely related in structure and many synthetic drugs can bind to more than one receptor. The brain contains both gluco- and mineralocorticoid receptors. Natural corticosteroids play important roles in fear and anxiety and in the response of the body to stress of any kind. Essential to the stress response is the paraventricular nucleus of the hypothalamus, which expresses corticotrophin-releasing hormone, vasopressin and other neuropeptides that drive the activity of the sympathico-adrenomedullary and the hypothalamic-pituitary-adrenal systems. These systems influence each other. The hypothalamic-pituitary-adrenal system involves corticosteroid hormone secretion by the adrenal cortex and is slower and more persistent in its actions. Disturbances in mood, cognition or behaviour often coincide with abnormal levels of corticosteroids. Some 50 % of patients with depression have a hyperactive hypothalamic-pituitary-adrenal system and hypercortisolism, whereas on the other hand about 50% of patients with Cushing's disease suffer from depression. In the rat, chronically too high but also too low levels of corticosteroid hormones during stress and the resultant mineralo-glucocorticosteroid imbalance, impair information processing, and enhance the vulnerability of specific hypocampal neurons. Corticosteroids control the expression of "candidate vulnerability genes" in individuals that are genetically predisposed for stress-related diseases such as depression (73, 74, 75, 76, 77).

It is important to note that neuropsychiatric adverse effects have been also documented with low dose glucocorticosteroids via inhalation route of administration supporting the connection between low dose glucocorticosteroids and development of neuropsychiatric disorders in susceptible individuals. In the eighties a few cases have been described of patients with psychiatric disturbances in association with the use of budesonide for inhalation (78,79). In a subsequent prospective general practice study in Sweden involving 60 pre-school children treated with budesonide such effects were observed in as many as 15% of patients, occurring after increasing the dose because of an upper respiratory tract infection (80). Another randomized prospective study reported psychiatric symptoms at a similar rate in both children and adults with a low dose inhaled budesonide for three years compared to placebo group (81). A recent case control study, in which children were found to have an increased risk of experiencing psychiatric events during the use of inhaled corticosteroids, is in support of this view (82). Global Strategy for Asthma Management and Prevention published by the Global Initiative for Asthma (2006) cite hyperactive behaviour, aggressiveness, insomnia, uninhibited behaviour and impaired concentration in children under five years of age as possible side effects associated with inhaled corticosteroid therapy (83).

1.3.2.2 Migraine-like headache

Headache is commonly observed in clinical trials and mentioned as adverse reaction in the product information of all approved INCs, but migraine is not. In clinical trials with intranasal fluticasone, mometasone and triamcinolone, however, the occurrence of headache was found to be comparable to that observed with placebo (84, 85, 86, 87, 88, 89, 90, 91). Headache can also occur as a sign of corticosteroid-induced benign intracranial hypertension. Also, chronic rhinosinusitis is a known cause migraine-like headache (92).

As has been shown by Ku and co-workers, there is a strong connection between allergic rhinitis and the occurrence of migraine (93). According to this study more than 34 % of patients with allergic rhinitis experienced migraine headaches, compared with only 4 % of people without allergic rhinitis. Another study by Aamodt et al found migraine and non-migrainous headache to occur approximately 1.5 times more likely among patients with current asthma, hey fever and chronic bronchitis (94). Both studies did not address a possible additional link with the treatment of rhinitis.

One of several mechanisms that have been proposed to act in the development of migraine in patients with comorbid atopic disorders suggests an involvement of the immune system with histamine release playing an important role. An elevated plasma Ig-E, histamine, decreased lymphocyte phagocytotic function and increased plasma tumor necrosis factor alpha were found in subjects with migraine. It has been hypothesized that stress relief enhances immune activity and triggers a burst of circulating vasoactive compounds that function as mediators of inflammation and potential precipitators of a migraine attack in vulnerable subjects (95).

According to the review article by Trangsrud and colleagues, INCs commonly cause some form of irritation of the nasal mucosa (84). Nasal dryness, burning, stinging and sneezing together with headache and epistaxis occur in 5-10 % of patients, regardless of the INC product used.

There is a possible link between platelet function and migraine, and corticosteroids may have a prothrombotic action (96, 97). The systemic levels of corticosteroids after intranasal administration are low, however, and unlikely to lead to significant effects on the clotting and fibrinolytic cascades. A few case reports have been described of cerebral venous sinus thrombosis in connection with oral corticosteroid use, presenting as migraine-like headache (98). The occurrence of transient migraine is most unlikely to be to have been linked, however, with cerebral thrombosis.

1.3.2.3 Gynaecomastia

Mild forms of gynaecomastia are frequently encountered in the male population. Gynaecomastia is the most common disorder of the male breast in adolescents and adults, and reflects an underlying hormonal imbalance with an increase in oestrogen action relative to androgen action. Transient gynaecomastia occurs frequently in neonates and boys in the middle to late puberty (99, 100, 101). Other causes, apart from congenital and acquired disorders of androgen and oestrogen production, include various tumours, renal failure, cirrhosis of the liver, thyrotoxicosis and Cushing's disease (102). Iatrogenic gynaecomastia is reported with a variety of drugs used in the treatment of mental, cardiovascular, gastrointestinal, hormonal and immune system related disorders and can occur during the systemic use of corticosteroids (102, 103). Several cases of gynaecomastia in connection with INC use was reported by the international spontaneous reporting system and further analyzed in this dissertation.

2

Scope and outline of the thesis

2 SCOPE AND OUTLINE OF THE THESIS

The overall aim of this thesis is to examine two aspects of allergic rhinitis treatment: the pharmacoeconomics of sublingual and subcutaneous administration form of specific allergen immunotherapy, the only causative treatment of allergic rhinitis (Chapter 4) and the safety of intranasal corticosteroids, specifically, signal detection of neuropsychiatric disorders, migraine-like headache, and gynaecomastia - in connection with intranasal corticosteroid use, currently the most effective conventional treatment of moderate/severe form of allergic rhinitis (Chapters 5).

- Chapter 4.1 – the purpose of this study was to evaluate the benefits and cost of SCIT and SLIT in patients with seasonal allergic rhinoconjunctivitis after 3 years of SIT administration from third-party payer's, patient's, and society perspectives.

- Chapter 5.1 – the aim of this study was to characterize an unexpected accumulation of case reports of a variety of neuropsychiatric disorders in patients using INCs with respect to: (1) general information (country of origin, type of reporter), (2) patient-related information (age, sex, and comorbidity), (3) adverse reaction-related information (time of onset, dechallenge, rechallenge, outcome and causality assessment), and (4) drug-related information (type of suspect drug and dose, concomitant medication, duration of treatment).

- Chapter 5.2 – the focus of this study was to evaluate a signal „migraine-like headache" in connection with intranasal corticosteroid use with regards to: (1) general information (country of origin, type of reporter), (2) patient-related information (age, sex, and comorbidity), (3) adverse reaction-related information (time of onset, dechallenge, rechallenge, outcome and causality assessment), and (4) drug-related information (type of suspect drug and dose, concomitant medication, duration of treatment).

- Chapter 5.3 – the aim of this study was to assess a signal „gynaecomastia" in connection with intranasal corticosteroid use with regards to: (1) general information (country of origin, type of reporter), (2) patient-related information (age, sex, and comorbidity), (3) adverse reaction-related information (time of onset, dechallenge, rechallenge, outcome and causality assessment), and (4) drug-related information (type of suspect drug and dose, concomitant medication, duration of treatment).

Data sources used in this thesis

In Chapter 4.1, data were collected alongside an open-label randomized clinical trial (January 1, 2002, to January 1, 2006) (MZ CR NI/7470-3).

For the conduct of pharmacovigilance studies in Chapters 5.1, 5.2, and 5.3, we used data from the WHO database - Vigibase. The Uppsala Monitoring Centre (UMC) maintains the WHO international pharmacovigilance programme since 1978, in collaboration with 81 national pharmacovigilance centres around the world (10). Yearly the UMC receives 250 000 case reports of suspected adverse drug reactions from the participating national centres that are stored in the WHO database. Vigibase currently contains over 3.7 million case reports. The WHO Adverse Drug Reaction Terminology and WHO Drug Dictionary are used for coding of clinical information in relation to drug therapy and reported drugs on the reports (21, 22). The reports contain information related to the patient, the drugs and the adverse event. The case reports are anonymous and heterogeneous and vary as regards source, documentation and relationship likelihood. Reporters are physicians, pharmacists and other health care professionals. In a few countries, in particular the USA, reports directly from patients are also accepted.

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4

Study on pharmacoeconomic aspects of specific allergen immunotherapy

4.1

Economic evaluation of sublingual vs subcutaneous allergen immunotherapy

Pokladnikova Jitka, MSc Pharm[1], Krcmova Irena, MD[2], Doc.Vlcek Jiri, CSc.[1]

1. Department of Social and Clinical Pharmacy, Faculty of Pharmacy, Charles University in Prague, Hradec Kralove, Czech Republic
2. Department of Allergology and Clinical Immunology, University Hospital and Faculty of Medicine, Charles University in Prague, Hradec Kralove, Czech Republic

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ABSTRACT

Background: Sublingual allergen immunotherapy (SLIT) is a commonly used alternative route of administration to standard subcutaneous immunotherapy (SCIT) in Europe. Despite its wide use, the cost-effectiveness of SLIT vs SCIT has not been well established.

Objective: To evaluate the cost and effectiveness of SLIT compared with SCIT in patients with allergic rhinoconjunctivitis during a 3-year specific allergen immunotherapy (SIT) from a third-party payer's, a patient's, and society's perspectives.

Methods: We performed an open-label randomized clinical trial of patients receiving SLIT (n=19), patients receiving SCIT (n=23), and a control group (n=22). The outcome measures were Rhinoconjunctivitis Quality of Life Questionnaire score, visual analog scale score, symptomatic medication reduction, and direct and indirect costs.

Results: SLIT offered clinical benefits to patients comparable to those provided by SCIT. From the perspective of a third-party payer, the total average direct medical cost per patient of 3-year SIT was estimated at €416 vs €482 in the SLIT and SCIT group, respectively. A patient who received SLIT paid less than a patient who received SCIT for all out-of-pocket costs (€176 for SLIT vs €255 for SCIT) but more for sole allergen extracts (€72 for SLIT vs €55 for SCIT). When both direct and indirect costs were considered, the 3-year SIT expenditures per patient reached €684 vs €1,004 in the SLIT and SCIT groups, respectively.

Conclusions: SLIT represents a less expensive alternative relative to subcutaneous administration from all perspectives. However, from a patient's perspective, SCIT offers a less expensive alternative for patients who do not experience loss of income and travel costs associated with treatment.

5

Studies on the safety of intranasal corticosteroids

5.1

Intranasally administered corticosteroids and neuropsychiatric disturbances: a review of the International Pharmacovigilance Programme of the World Health Organisation

MSc Pharm Jitka Pokladnikova,[2] Ronald H.B. Meyboom MD,PhD[1,3] Doc.Jiri Vlcek[2],CSc and Prof.Ralph I. Edwards[1]

1. WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, Uppsala, Sweden
2. Department of Social and Clinical Pharmacy, Faculty of Pharmacy, Charles University in Prague, HRADEC KRALOVE, The Czech Republic
3. Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, UTRECHT, The Netherlands

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ABSTRACT

Background: The systemic use of corticosteroids is connected with a variety of psychiatric and neurologic effects. Corticosteroids for intranasal administration (INCs) are considered to act locally and to exert minimal systemic effects. An unexpected cluster of case reports of neuropsychiatric disorders during intranasal corticosteroid use was reported to the World Health Organization Uppsala Monitoring Centre.

Objective: To investigate the possible connection between intranasal corticosteroid use and the development of neuropsychiatric disorders, as reported to the International Pharmacovigilance Programme.

Methods: All reports containing adverse event terms indicating neuropsychiatric disturbances in suspected connection with intranasal corticosteroids were retrieved from Vigibase and evaluated (April 2006). The case reports are heterogeneous and vary regarding source, documentation quality, and relationship likelihood.

Results: A total of 429 reports were received from 16 countries (1980-April 2006), of neuropsychiatric events occurring in patients using INCs, representing 7.6% of the total of reports regarding these drugs in the same period. Frequently reported events were nervousness, anxiety, agitation, insomnia, emotional lability, depression, somnolence, confusion, convulsions, and migraine. Most reports concerned fluticasone propionate, beclometasone dipropionate, mometasone furoate, or budesonide. In 370 reports (86.2%), the INC was the sole suspect drug and in 220 (51.3%) it was the only drug used. In 97 of 108 patients who had discontinued the intranasal corticosteroid, the reaction abated. Of 41 patients, 32 had a relapse when the drug was reintroduced.

Conclusions: The data collected by the International Pharmacovigilance Programme suggest that the intranasal use of corticosteroids can be complicated by neuropsychiatric adverse reactions. Further study is needed to confirm the connection and to determine the frequency and risk factors of such reactions.

5.2

Can intranasal corticosteroids cause migraine-like headache?

MSc Pharm Jitka Pokladnikova,[2] Ronald H.B. Meyboom MD,PhD[1,3] Doc.Jiri Vlcek[2],CSc and Prof.Ralph I. Edwards[1]

1. WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, Uppsala, Sweden
2. Department of Social and Clinical Pharmacy, Faculty of Pharmacy, Charles University in Prague, HRADEC KRALOVE, The Czech Republic
3. Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht University, UTRECHT, The Netherlands

Cephalalgia (*in press*).

ABSTRACT

Intranasal corticosteroids (INCs) act predominantly locally and are considered to exert minimal systemic effects. On reviewing the international data collected in the WHO's global pharmacovigilance programme an unexpected cluster was found of 38 case reports of migraine in suspected connection with INCs. These reports came from 5 countries (May 2007) and concerned 6 different drugs. In all reports the INC was the sole suspect drug. In eight reports the recurrence of the event was recorded after reexposure to the drug. INCs are mainly used for rhinitis, on the other hand, and there is a known connection between rhinitis and migraine. International pharmacovigilance data suggest that the use of INCs may cause or trigger migraine or migraine-like headache. Further study is needed to determine if the reported association is true or not and, if so, what the possible mechanism is.

5.3

Intranasal corticosteroids and gynaecomastia

MSc Pharm Jitka Pokladnikova,[1] and the Centre[2]

1. Department of Social and Clinical Pharmacy, Faculty of Pharmacy, Charles University in Prague, HRADEC KRALOVE, The Czech Republic
2. WHO Collaborating Centre for International Drug Monitoring, Uppsala Monitoring Centre, Uppsala, Sweden

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6

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6 LIST OF PUBLICATIONS

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7

Summary

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. Those drug-related safety issues need to be communicated to the professional community, health care providers as well as patients. Further studies are needed to confirm drug-adverse event associations and determine the risk factors that predispose individuals to such reactions.

- **Neuropsychiatric disorders** - Data collected in international pharmacovigilance suggest that the intranasal use of corticosteroids can be complicated by neuropsychiatric side effects. Of the data regarding INCs a substantial proportion concerns neuropsychiatric events: psychiatric excitatory reactions with nervousness, anxiety, insomnia, agitation and aggression, mood disorders (depression, euphoria, mania), sedation and cognitive impairment (somnolence, confusion, amnesia), psychotic episodes with hallucinations and paranoid reactions, and neurologic disorders such as convulsions and benign intracranial hypertension. The reporting pattern is generally the same as that for systemic corticosteroids. The use of systemic corticosteroids is also associated with a variety of side effects affecting the central nervous system, ranging from changes in mood and cognition to psychosis. Most common effects are mild euphoria or depression; other effects include insomnia, night mares, anxiety, agitation, emotional lability, somnolence, and more serious are panic reactions, mania, behavioural abnormalities, hallucinations, severe depression, psychosis and delirium. Confusion and amnesia may occur and corticosteroid-induced pseudo-dementia has also been reported. The incidence of severe psychiatric symptoms is about 5 % and generally increases in relation with the increased daily glucocorticoid dose (in particular in doses exceeding the equivalent of 40 mg of prednisone). Nevertheless, the occurrence of neuropsychiatric effects has been shown also in patients with inhaled corticosteroids. Today, the minimum of corticosteroid dose that may in an individual patient trigger a neuropsychiatric disorder is not known. Most of the available information on neuropsychiatric side effects concerns systemic corticosteroid exposure.

  Neuropsychiatric events during INC use were reported in various age groups, probably reflecting the general user population. Nevertheless the relatively frequent occurrence of nightmares, hallucinations, aggression and other behavioural disturbances, intracranial hypertension and convulsions in children may be of particular clinical interest.

  In the light of the small amounts of corticosteroids that are nasally administered, the seriousness of many of the reported reactions is remarkable. In the majority of reports the prescribed daily dose did not exceed the maximum recommended daily dose range with the exception of 12 % patients. Many reactions occurred early in the course of treatment. The most frequently reported INCs were fluticasone and beclometasone. This may likely reflect the drug exposure in the first place. Nevertheless, due to pharmacokinetic and pharmacodynamic determinants fluticasone and beclometasone have a comparatively high potency for systemic adverse effects compared to other INCs.

  Taken together, however, 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 drugs. 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. For example in Sweden, a reporting rate of 0.04 reactions per million defined daily doses per year could be calculated when the number of case-reports of INCs was related to the pharmacy sales data. On the other hand underreporting is vast but unknown and the frequency remains uncertain and likely underestimated.

Since these neuropsychiatric reactions can be serious or embarrassing, further study is needed to clarify the mechanisms underlying the various neuropsychiatric events, identify risk factors and further update the safety profile of intranasally administered corticosteroids.

- **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.

8

Závěr

8 ZÁVĚR

Cílem racionální farmakoterapie je zajistit bezpečnou a nákladově efektivní léčbu pacientů s alergickou rýmou (AR). Tato dizertační práce se zabývá dvěma aspekty léčby alergické rýmy (1) srovnáním účinků a nákladů sublinguální a subkutánní aplikační formy specifické alergenové imunoterapie (SIT) u pacientů s alergickou rýmou, a (2) systémovými nežádoucími účinky intranazálních kortikosteroidů – konkrétně neuropsychiatrickými potížemi a gynekomastií.

(1) Specifická alergenová imunoterapie: účinnost a náklady

- Výsledky naší farmakoekonomické studie prokázaly účinnost obou aplikačních forem SIT ve srovnání se standardní farmakologickou léčbou a to ve smyslu zlepšení klinických příznaků a snížení spotřeby symptomatických léků u pacientů se sezónní alergickou rhinokonjunktivitidou. Ačkoliv se účinnost obou aplikačních forem SIT ve třetím roce její aplikace signifikantně nelišila, zlepšení klinického stavu bylo ve skupině léčené subkutánně výraznější.

  Z ekonomického hlediska, byla SIT aplikována sublinguálně výhodnější než aplikace subkutánní, a to jak z pohledu pacienta a zdravotní pojišťovny, tak i společnosti. Pouze ve specifických případech, kdy pacienti neměli finanční výlohy na cestovné a nepřišli o mzdu z důvodu návštěvy alergologa v pracovní době, byla subkutánní aplikační forma levnější než sublinguální.

  K tomu, abychom mohli potvrdit výhodnost SIT aplikované sublinguálně je nutné provést rozsáhlejší komparativní studie obou aplikačních forem SIT zkoumajících kost-efektivitu, včetně délky trvání účinku, preventivního charakteru SIT, bezpečnosti léčby, kompliance pacientů a ušetření nákladů.

(2) Bezpečnost intranazálních kortikosteroidů

V současné době patří intranazální kortikosteroidy mezi léky první volby u středně silné a silné alergické rinitidy. Většina odborné veřejnosti je vnímá jako bezpečná léčiva s minimálním výskytem systémových nežádoucích účinků. Výsledky našich farmakovigilačních studií však naznačují, že léčba intranazálními kortikosteroidy může být komplikována výskytem nežádoucích jevů jako jsou neuropsychiatrické potíže či gynekomastie.

Z toho důvodu je nutné tyto poznatky komunikovat s odbornou veřejností, poskytovateli zdravotní péče a pacienty. Další farmakoepidemiologické studie by měly potvrdit či vyvrátit

kauzální vztah mezi intranazálními kortikosteroidy a výše zmíněnými nežádoucími jevy a stanovit rizikové skupiny pacientů.

- **Neuropsychiatrické potíže** - Sledováním nežádoucích účinků léčiv na mezinárodní úrovni byl zjištěn nečekaný výskyt neuropsychiatrických potíží během užívání intranazálních kortikosteroidů. Spontánní hlášení případů se týkalo neuropsychiatrických stavů jako jsou afektivní poruchy - nervozita, úzkost, nespavost, agitace a agrese, deprese, euforie, mánie, dále sedace a kognitivní poruchy (somnolence, zmatenost, amnézie), psychotické epizody s halucinacemi a paranoidními reakcemi, neurologickými poruchami jakou jsou konvulze a benigní intrakraniální hypertenze. Škála uvedených nežádoucích jevů přitom odpovídá těm, které se vyskytují při aplikaci systémových kortikosteroidů. Léčení systémovými kortikosteroidy může být doprovázeno podobnými nežádoucími účinky zasahujícími centrální nervový systém jako jsou změny nálad a kognitivních funkcí včetně psychózy. K nejběžnějším nežádoucím účinkům patří mírná euforie nebo deprese, insomnie, úzkost, agitace, emoční labilita, somnolence a závažnější stavy jako jsou panické poruchy, manie, poruchy chování, halucinace, těžká deprese, psychóza a delirium. Hlášeny byly také zmatenost, amnézie a pseudo-demence. Incidence těžkých psychiatrických symptomů se přitom odhaduje na 5 % a ve většině případů roste se zvyšující se denní dávkou glukokortikosteroidů (dávky přesahující 40 mg prednisonu denně). Na druhé straně, výskyt neuropsychiatrických účinků byl zaznamenán i během léčby inhalačními glukokortikosteroidy. Minimální dávka glukokortikosteroidu, která by mohla vyvolat neuropsychiatrickou reakci není doposud známa. Většina dostupných informací o nežádoucích účincích glukokortikosteroidů vychází ze studií, kde byly glukokortikosteroidy podávány systémově.

  Výskyt neuropsychiatrických stavů během užívání intranazálních kortikosteroidů bylo hlášeno v různých věkových skupinách, což pravděpodobně souvisí s charakteristikou populace, která intranazální kortikosteroidy užívá. Z klinického hlediska je u dětí zajímavý relativně častý výskyt těžkých snů, halucinací, agrese a jiných poruch chování.

  Závažnost těchto nežádoucích jevů u vysokého počtu hlášených případů je vzhledem k nízké dávce glukokortikosteroidu překvapující. Ve většině případů předepsaná denní dávka nepřesáhla maximální doporučenou denní dávku s výjimkou 12 % pacientů. Většina nežádoucích jevů se objevila brzy po zahájení terapie glukokortikosteroidy. V souvislosti s nahlášenými nežádoucími jevy bylo nejčastěji zmiňováno užívání flutikazonu a beklometazonu. Je samozřejmě možné, že tento fakt souvisí s preskripčními zvyklostmi. Nicméně je nutné podotknout, že u obou léčiv je

vzhledem k jejich farmakokinetickým a farmakodynamickým vlastnostem riziko systémových nežádoucích účinků vyšší.

Výsledky naší analýzy – např. počet hlášených případů, typ hlášených nežádoucích jevů a podobnost s tím, co je známo i hlášeno v souvislosti s užíváním systémových kortikosteroidů – naznačuje souvislost mezi nežádoucími jevy a užíváním těchto léčiv. To také potvrzuje množství hlášených případů, u kterých neuropsychiatrické problémy odezněly po vysazení léku či se znovu objevily po jeho nasazení.

Vzhledem k rozšířenému užívání intranazálních kortikosteroidů v celosvětovém měřítku je frekvence výskytu nežádoucích jevů pravděpodobně nízká. Například ve Švédsku, frekvence výskytu hlášených nežádoucích jevů byla vypočítána na 0.04 jevu na jeden milion definovaných denních dávek za rok (počet hlášených případů vztažený ke spotřebě těchto léků ve švédské populaci). Na druhé straně jsou obecně nežádoucí účinky „podhlášené“, a tak je stanovení frekvence výskytu těchto nežádoucích jevů nepřesné a pravděpodobně podhodnocené.

Jelikož tyto nežádoucí jevy mohou být závažné a pro pacienty citlivou záležitostí, je nutné se touto problematiku nadále zabývat. Je nezbytné provést další studie, které by zkoumaly mechanizmy těchto rozličných neuropsychiatrických jevů, stanovily rizikové faktory a tím pádem zaktualizovaly bezpečnostní profil intranazálních kortikosteroidů.

- **Migréna** – dle hlášení nežádoucích účinků ve WHO databázi intranazální kortikosteroidy mohou také způsobovat či zhoršovat migrénu či bolest hlavy podobné migréně. Je samozřejmě možné, že bolest hlavy je způsobena probíhajícím zánětem v nosní sliznici či dutinách. Abychom byli schopni blíže porozumět možnému vztahu mezi intranazálními kortikosteroidy a migrénou je důležité, aby zdravotničtí pracovníci hlásili podobné nežádoucí jevy svým národním farmakovigilačním centrům a byly provedeny další studie, které by objasnily vztah mezi intranazálními kortikosteroidy a migrénou/unilaterální migrénou, včetně mechanizmu účinku.

- **Gynekomastie** – osm případů gynekomastie hlášených ve dvou zemích naznačuje možnou souvislost mezi vznikem tohoto nežádoucího jevu a užíváním intranazálních kortikosteroidů. Ačkoliv gynekomastie nebyla v minulosti v literatuře popsána, je nutné poznamenat, že bylo hlášeno i 15 případů gynekomastie v pěti různých zemích v souvislosti s užíváním inhalačních glukokortikosteroidů, a proto je nutné provést další studie k potvrzení kauzalního vztahu mezi gynekomastií a lokálními glukokortikosteroidy.

Cílem léčby alergické rýmy je zlepšit kvalitu života pacienta a obnovit jeho každodenní činnost. Léčebný plán by měl být sestaven individuálně pro každého pacienta a měl by zahrnovat edukaci pacienta, režimová opatření a symptomatickou léčbu. Specifická alergenová imunoterapie by měla být navržena na základě nejnovějších doporučení. Ze závěru našich studií vyplývá, že u pacientů trpících sezónní alergickou rýmou bychom měli zohlednit i bezpečnost a kost-efektivitu terapie.

Za prvé, každý individuální léčebný plán by měl zakomponovat ekonomický rozměr terapeutických alternativ a měl by zohlednit jak její účinnost, tak i finanční možnosti daného pacienta. Zdravotní politika by měla podporovat léčebné postupy, které jsou výhodné jak pro pacienta, tak pro celou společnost. V této souvislosti naše studie poukazuje na to, že sublingualní aplikační forma specifické alergenové imunoterapie je oproti subkutanní výhodnější jak pro zdravotní pojišťovny, tak i pacienty a společnost. Vyjímku tvoří pouze pacienti, kteří nevynakládají finanční prostředky na cestovné a nepřicházejí o mzdu v souvislosti s léčbou. V okamžiku, kdy závěry naší práce budou dále potvrzeny rozsáhlejšími studiemi, představitelé zdravotní politiky by měli nastavit takové podmínky cen a úhrad, které by zvýšily dostupnost sublinguální aplikační formy SIT z důvodu lepšího bezpečnostního a kost-efektivního profilu.

Za druhé, všichni pacienti, kteří užívají intranazální glukokortikosteroidy by měli být sledováni kvůli možnému výskytu systémových nežádoucích účinků glukokortikosteroidů včetně neuropsychiatrických potíží, do té doby dokud nebudou dostupné další informace o těchto nežádoucích jevech. Zvýšené riziko vzniku systémových nežádoucích účinků glukokortikosteroidů můžeme očekávat především u pacientů, kteří užívají několik aplikačních forem glukokortikosteroidů současně.

Lékaři a lékárníci by měli monitorovat bezpečnost léčby alergické rýmy a vybírat nejúčinnější a nejméně nákladný léčebný postup pro maximální přínos pacienta.