6

Treatment of Allergic Rhinitis: Anticholinergics, Glucocorticotherapy, Leukotriene Antagonists, Omalizumab and Specific-Allergen Immunotherapy

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1. Introduction

Throughout history, various classifications of rhinitis have emerged, many of which originated from expert groups. We would have to go back to 1994 to find the "*International Consensus Report on Diagnosis and Management of Rhinitis*" (International Rhinitis Management Working Group, 1994), which was subsequently modified in the 2000 "*Consensus statement on the treatment of allergic rhinitis. EAACI Position paper*" (Van Cauwenberge et al, 2000). Of particular interest is the "*Executive Summary of Joint Task Force Practice Parameters on Diagnosis and Management of Rhinitis*" of 1998 (Dykewicz & Fineman, 1998). In 2001, a group of experts, the "*Allergic Rhinitis and its Impact on Asthma (ARIA) Workshop Expert Panel*", met to develop guidelines on the diagnosis and treatment of rhinitis, which also dealt with other inflammatory processes interrelated/associated with asthma. The acronym "ARIA" comes from "Allergic Rhinitis and its Impact on Asthma". ARIA is a document from a non-governmental organisation of the World Health Organization (WHO), endorsed by numerous scientific societies, such as the International Association of Allergology and Clinical Immunology (IAACI) and the World Allergy Organization (WAO) (Bousquet et al, 2001).

It was established as an educational program as the "Guidelines for recommendations for the diagnosis and comprehensive handling of patients with rhinitis", associated with asthma and other interrelated processes (sinusitis, conjunctivitis and otitis).

In this chapter, we revised others modalities of treatment for AR; anticholinergics, glucocorticotherapy, leukotriene antagonists, omalizumab and specific-allergen immunotherapy.

2. Anticholinergics

Ipratropium bromide is an anticholinergic compound related to atropine. It is poorly absorbed, but has high topical activity. It inhibits secretion for at least 4 hours, without the appearance of systemic symptoms.

Mechanism of action: It is capable of significantly reducing rhinorrhoea by acting selectively on the muscarinic receptors, which, when activated by acetylcholine released by the parasympathetic nervous system, induce the secretion of mucus by the nasal seromucous glands.

Systemic cholinergic collateral effects rarely appear, but include changes in vision, tachycardia, urinary retention and dry mouth. However, it should be administered with caution to patients with glaucoma or prostatic hypertrophy.

Ipratropium bromide is used in aqueous solution for topical nasal use in doses of two inhalations of 0.02 mg each three times a day in each nostril. The recommended dose should not be increased if there is no improvement.

It has been used for allergic (Kaiser et al, 1995) and non-allergic (Bronsky et al, 1995) perennial rhinitis, and acts by improving hydrorrhoea, with a maximum peak 1-4 hours after administration. It has barely any effect on nasal obstruction and sneezing, and its most frequent side effects are epistaxis, nasal dryness and headache (Kaiser et al, 1995; Bronsky et al, 1995).

3. Glucocorticotherapy

In the literature review we performed, we found only one published article that covers the treatment of seasonal AR with systemic corticosteroids (Myging et al, 2000). They report that they could find only 5 studies published between 1960 and 1993 on systemic corticosteroids and AR, compared to more than 100 published studies on topical corticosteroids. There are several publications that compare topical corticosteroids with each other and with other drugs.

According to the 1994 Consensus (International Rhinitis Management Working Group, 1994), first-line therapy for the handling of seasonal AR in moderate cases with intermittent symptoms are antihistamines, and intranasal corticosteroids in severe cases with daily symptoms. In case of exacerbations during the pollen season, it is currently common practice to administer a short cycle of oral or intramuscular corticosteroids. It seems that systemic corticosteroids are highly effective for nasal blockage, but not so much for rhinorrhoea and sneezing. One high oral dose of 30 mg daily seems effective in controlling all nasal symptoms. Subcutaneous atrophy has been reported at the injection site, as well as local reactions, changes of pigmentation, etc.

The lack of reliable comparative studies and the fear of severe side effects have pushed studies and treatment towards therapy with inhaled corticosteroids.

3.1 Systemic glucocorticosteroids

Brown et al published the first placebo-controlled study of the use of systemic corticosteroids for the treatment of AR. They report that the use of 3 injections of 240 mg of

methylprednisolone in one-week intervals, achieved significant improvement of symptoms (Brown et al, 1960).

In the decade of the 70´s, other authors prescribed 2 injections of 80 mg of methylprednisolone with 14-day intervals to 8 patients with seasonal AR. Cortisol levels decreased after the injection, and patients began to recover and return to normal after 3 weeks (Ganderton & James, 1970).

McMillin scheduled an 80 mg injection of triamcinolone acetonide to 18 patients with severe AR, and measured morning plasmatic cortisol levels for 21 days. Although the levels descended on several occasions, the initial values were recovered after 3 weeks (Mc Millim, 1971).

In the decade of the 80´s, various clinicians studied the results of administering an injection of 5 mg of betamethasone dipropionate, another of 3 mg of betamethasone phosphate, with 3 mg of betamethasone acetate, and a third of 40 mg of methylprednisolone. These injections were administered to 60 patients with significant AR, who were divided into 3 groups depending on the type of injection (Ohlander et al, 1980)

Methylprednisolone and beclomethasone dipropionate (BDP) reduced the production of endogenous cortisol for at least 14 days, while the combination of phosphate and betamethasone acetate did not suppress plasma cortisol in 12 days. Glycaemia increased in the 3 groups in the first two days following the injection.

Hedner et al, prescribed an injection of 80 mg of methylprednisolone to 14 patients with AR. Baseline cortisol and plasma cortisol response to hypoglycaemia had moderate but significant reductions at 2 weeks, although they returned to normal in 4 weeks (Hedner & Persson, 1981).

Almost in parallel, Borum et al performed two trials in 24 patients with AR. In the first, they gave an injection of 80 mg of methylprednisolone at the start of the pollen season, and in the second, they gave it at the peak of the pollen season (Borum et al, 1987). In the first group, the effect lasted the entire season (at least 5 weeks), with all symptoms disappearing. In the second group, the injection had a rapid effect on nasal obstruction, which disappeared and did not return in the remaining 5 weeks of pollen season. Rhinorrhoea and sneezing did not disappear as noticeably as in the first group and reappeared in a few weeks. The use of rescue anti-Hl, however, was clearly inferior in both groups, compared to placebo.

Laursen et al studied the effect of a 5 g injection of betamethasone dipropionate and 2 mg of betamethasone, immediately before the start of the birch pollen season (study was performed in Denmark). They found that these patients had fewer symptoms, especially nasal obstruction, than patients treated with placebo, with the effect lasting 4 weeks (Laursen et al, 1987).

In 1988, the following year, these same authors performed a double-blind placebo-controlled trial with 30 adults with rhinoconjunctivitis (RC) who were allergic to seasonal birch pollen (Laursen et al, 1988). The patients were treated with 100 micrograms of BDP in each nostril twice a day for 4 weeks. Patients received either a placebo or an injection of 5 mg of BDP and 2 mg of betamethasone phosphate, immediately before the start of the birch pollen season. The authors concluded that an injection of BDP and betamethasone phosphate immediately before the birch pollen season produced a significant reduction in rhinoconjunctivitis symptoms, compared to placebo and topical steroid treatment.

That same year, other authors found a significant reduction in plasma cortisol 3 weeks after an injection of 80 mg of methylprednisolone, but not during treatment with 200 micrograms of intranasal budesonide. They found no differences between the two therapies in terms of nasal obstruction, but there was a tendency to favour topical treatment with budesonide in terms of sneezing and rhinorrhoea (Pichler et al, 1988).

Brooks et al, treated 31 patients with rhinitis for 5 days with placebo or methylprednisolone in daily doses of 6, 12 or 24 mg, divided into 3 daily doses. They achieved significant improvement in nasal obstruction with 6 mg, and with all symptoms except for sneezing with 24 mg (Brooks et al, 1993)

Based on the literature, systemic corticosteroids seem to have a significant effect on nasal obstruction, but less so on sneezing and rhinorrhoea. These studies demonstrated a reduction in cortisol plasma levels after an IM injection of corticosteroids. The effect is greatest at 3 days and disappears after 3 weeks.

We have not found any published study on whether systemic corticosteroids should be added due to a lack of improvement with topical corticosteroids or other drugs.

3.2 Topical (intranasal) glucocorticosteroids

Several studies have shown the inhibitory efficacy of topical corticosteroids in the delayed response of allergic reactions. Symptoms that occur 2-11 hours after nasal provocation by an allergen are completely eliminated with their administration. Initially, it was thought that topical corticosteroids did not inhibit the early response; however, there is clear evidence that they also act on symptoms immediately. Studies have shown their efficacy in reducing both specific and non-specific nasal hyperreactivity.

It has been shown that the effective dose of antihistamines (loratadine oral) can be reduced with the use of fluticasone in nasal spray, in the treatment of seasonal AR. The conclusion is that the efficacy and decreased inflammation is greater with fluticasone (decreases eosinophilic cationic proteins and the number of eosinophils, and improves scores on quality-of-life questionnaires).

A reduction has been shown in the number of subepithelial cells (CD3+, CD4+, CD8+) in patients treated with topical corticosteroids. Recent studies have demonstrated a reduction in the expression of adhesion molecules (ICAM-l) in patients treated over long periods of time. Their anti-inflammatory effects are increased by the decrease in chemotaxis and the activation of eosinophils. In terms of symptoms, this translates into decreased obstruction, pruritus, sneezing and rhinorrhoea. Currently, various compounds are used.

3.2.1 Beclometasone dipropionate

Introduced in 1973 for topical nasal treatment, beclometasone dipropionate (BDP) is a potent local steroid, with absorption at therapeutic doses. It was the first steroid that proved effective in the topical treatment of hay fever.

BDP acts by penetrating the cell membrane and binding with cytoplasmic receptors. The compound formed is transferred to the nucleus, where it binds to the DNA molecule. It seems to act by emptying histamine deposits, reducing the number of mast cells and

inhibiting their synthesis of histamines. It lowers the number of eosinophils, lessening the release of cytotoxic proteins, and reduces mucosal oedema by decreasing vascular permeability.

BDP may cause non-serious local side effects, such as epistaxis, nasal pruritus and, rarely, mycotic infection, but it is doubtful that it causes mucosal atrophy in long-term treatments.

It is used in nasal spray, with a standard dose of 100 micrograms every 6 hours. It has an anti-inflammatory effect 5000 times more powerful than hydrocortisone.

Cockcroftf performed a study for 42 days on patients with AR. At 35 days, there was a decrease in clinical symptoms in 86% (P<.05) of patients who had been treated with BDP, compared to 13% who had received placebos (Cockcroft et al, 1976)

In a 4-week study, Peluchi compared azelastine at doses of 0.56 mg/day with BDP at doses of 200 micrograms/day and placebo. Both drugs were effective, reducing eosinophilia more in patients who had received the corticosteroid (Peluchi et al, 1995).

3.2.2 Budesonide

A non-halogenated corticosteroid, budesonide is an anti-inflammatory drug 2-3 times more powerful than BDP (Bryson & Faulds, 1992). It has a half-life of 2 hours, and is inactivated in the liver by oxidative metabolism after systemic absorption. It has the same mechanism of action as BDP, and may cause temporary epistaxis, nasal pruritus and sneezing as collateral effects.

The average recommended dose is 100 micrograms every 12 hours in each nostril. Prophylactic administration protects against immediate allergic reactions. Therefore, treatment of seasonal rhinitis should be started before exposure to the allergen.

Cimetidine influences the pharmacokinetics and pharmacodynamics of budesonide after concomitant oral and intravenous administration, although it is of little clinical significance.

3.2.3 Fluticasone propionate

A fluorinated glucocorticoid with significant topical activity, fluticasone propionate (FP) (Flixonase; GlaxoSmithKline, London, UK) is structurally similar to cortisol, with certain variations that increase its lipophilic properties and its potency of action. It has high selectivity and affinity for glucocorticoid receptors.

FP possesses an anti-inflammatory potency twice than that of BDP which is linked to its effect on various cellular elements and the mediators of the inflammation (Barnes, 1992). It reduces the number of activated eosinophils in the nose during antigenic stimulation in allergic individuals.

FP significantly reduces the number of T lymphocytes, and reduces the number of non-activated basophils, neutrophils and eosinophils. Meltzer studied nasal eosinophilia in 497 patients treated with fluticasone or placebo, and found a decrease (P<.01) in patients treated with fluticasone (Melzer et al, 1990).

The lipolytic character of topical corticosteroids is significant, since it leads to increased drug retention in the tissues. The recommended dose is 200 mg/day (two applications of 50

μg per nostril, once a day). For children between the ages of 4-11 years, half the dose is recommended. Side effects are similar to those of the other inhaled corticosteroids described above (LaForce et al, 1994).

FP is eliminated from systemic circulation at a rate approximately equal to hepatic blood flow. It is metabolised through hydrolysis with the formation of 17-ß-carboxylic metabolic acid, which has insignificant anti-inflammatory and systemic activity due to incomplete absorption in the gastrointestinal tract and to extensive metabolism during the first hepatic step.

Comparative studies of BDP at similar doses have shown that both steroids have a similar efficacy for controlling nasal symptoms, in all cases superior to that of placebo. The speed of action is greater in fluticasone, as evidenced by the fact that significant improvement in symptoms is seen by the second day of treatment, while the delay in the onset of improvement for those treated with BDP was three days (Scadding et al, 1994).

Same authors found that after nasal provocation with an allergen, treatment with FP decreased obstruction in 45%, sneezing in 73%, pruritus in 78% and hydrorrhoea in 80% (Scadding et al, 1994).

Kaszuba demonstrated the efficacy of antihistamines (loratadine oral) with the use of fluticasone in nasal spray, in the treatment of seasonal AR. The conclusion was that the efficacy and decreased inflammation was greater with FP (decreased ECP, the number of eosinophils and improved scores on quality-of-life questionnaires) (Kaszuba et al, 2001).

3.2.4 Fluticasone furoate

Fluticasone furoate (FF) (Avamys; GlaxoSmithKline, London, UK) is the most recent intranasal glucocorticosteroid available for the treatment of AR (allergic rhinitis). It possesses a distinctive combination of pharmacodynamic and physico-chemical properties, which confers a high affinity for the glucocorticosteroid receptor and a potent anti-inflammatory activity. This allows its effectiveness in treating both nasal and ocular symptoms to be complemented by a favorable safety and tolerance profile. In addition, the new nasal delivery device was designed according to the needs experienced and expressed by patients, which assures an optimal dispensation that promotes its extensive use. (Allen et al, 2007; Rosenblut et al, 2007; Baumann et al, 2009).

The compliance of the patients in treatment with intranasal corticosteroids may be influenced by both the sensorial properties of the drug and the delivery device. FF has been formulated to release a low volume (50 μl) in the form of a fine mist, with a favorable profile of sensory characteristics in terms of reduction in odor, in the posterior aftertaste, and in the retro-nasal dripping down the throat (Mahadevia et al, 2004; Meltzer et al, 2008).

In addition to the greater affinity for the glucocorticosteroid receptor, FF shows a high selectivity for the same as compared to other intranasal glucocorticosteroids; for each FF molecule which binds to the mineralocorticoid receptor, other 800 will bind to the glucocorticosteroid receptor, which considerably limits the potential undesirable side effects.

FF has demonstrated superior efficacy when compared to placebo in the treatment of nasal symptoms of seasonal allergic rhinitis in adults and children, and demonstrated a significant

improvement in overall relief of associated eye symptoms. Symptomatic relief of allergic rhinitis begins 8 hours after administration and lasts for 24 hours (Máspero et al, 2008; Nathan RA et al, 2008; Vasar et al, 2008; Baroody et al, 2009; Meltzer et al, 2009).

The efficacy of FF administered for 4 weeks versus placebo has also been assessed in adolescents and adults with perennial allergic rhinitis, with significant improvement in nasal symptoms and extraocular manifestations (such as pharyngeal or palatal itching) and in the RQLQ scores (Keith & Scadding, 2009; Keith & Scadding, 2010).

The recommended dose of FF in Spain for patients older than 12 years is 110 μg, which equals two sprays in each nostril once a day. It may be reduced to one spray in each nostril once symptoms are controlled. For children between 6 and 12 years of age, the recommended dose is one spray in each nostril once daily (55 μg), but can be increased to two sprays if it fails to control the symptoms. In Europe FF is not approved in children less than 6 years of age (GlaxoSmithKline, 2011).

FF (like the rest of intranasal corticosteroids) has proven effective for controlling nasal symptoms in allergic rhinitis. But unlike other intranasal corticosteroids, which show contradictory effects on ocular symptoms, FF is the only intranasal corticosteroid that demonstrates a consistent positive effect on ocular symptoms in seasonal allergic rhinitis in a large number of patients from different studies, across different pollen seasons and geographical locations (Keith & Scadding, 2009; Keith & Scadding, 2010).

3.2.5 Flunisolide

Introduced in 1978, flunisolide is a poorly water-soluble drug, which is therefore dissolved in propylene glycol and water (Horan & Johnson, 1978; Schulz et al, 1978). Rhinoscopy is recommended once a year for prolonged treatment.

3.2.6 Mometasone furoate

A corticosteroid available worldwide in dermatological preparations, mometasone furoate (MF) has been classified as a powerful corticosteroid according to European Union directives. It has few systemic side effects when applied topically to the skin. Solutions of MF in aqueous suspension are prepared for subsequent administration with a nasal nebulizer, and have been marketed for several years now. The absorption rate for MF is 8%, and absolute bioavailability has been estimated at less than 1% of the adjusted dose, due to hepatic metabolism.

MF, a potent, topically active, synthetic, 17-heterocyclic corticosteroid was originally introduced for the treatment of dermatological conditions (Lundbland et al, 2001). MF aqueous nasal spray (Nasonex; Schering-Plough, Inc., Kenilworth, NJ, USA) was shown to be effective in several inflammatory conditions of the upper respiratory tract, including AR (van Drunen et al, 2005) and non-AR (Lundbland et al, 2001), nasal polyps (Small et al, 2005; Stjarne et al, 2006), adenoidal hypertrophy (Berlucchi et al, 2007) and uncomplicated rhinosinusitis (Meltzer et al, 2005). Safety and pharmacokinetic evaluations of MF have shown a lack of systemic activity when applied to the nasal mucosa, even in pediatric patients (Zitt et al, 2007). There is no clinical evidence that MF nasal spray suppresses the function of the hypothalamic–pituitary–adrenal axis when the drug is administered at

clinically relevant doses (100-400 μg/day) (Small et al, 2005), and there are no reports of any influence on children´s growth (Schenkel et al, 2000; Meltzer et al, 2005). Histological studies after long-term use of MF nasal spray have shown no signs of atrophy of the nasal mucosa (Minshall et al, 1998).

3.3 Side effects, safety and tolerance of glucocorticosteroids

We performed a literature review of articles published between 1994 and 2012, and found numerous articles that studied the effectiveness, side effects, safety and tolerance of inhaled corticosteroids, and then compared them with each other and with other drugs. We have summarised these articles below.

Edwards compared BDP with hydrocortisone, prednisolone, dexamethasone and betamethasone, which cause suppression of the hypothalamic-pituitary-adrenal cortex axis and adverse systemic reactions. The undesirable action of the topical corticosteroid is reduced at the application site (Edwards, 1995)

It is metabolised quickly and has longer duration of action. The study concluded by declaring the safety and efficacy of intranasal treatment with BDP as an indicated treatment for patients with AR.

Other authors tested the usefulness and efficacy of topical corticosteroids, with a reduction in the number of Langerhans cells in nasal mucosa, as well as the number of eosinophils. Moreover, they demonstrated the corticosteroids' efficacy, since these reduced three of the major symptoms of AR: sneezing, rhinorrhoea and nasal blockage (Mygind & Dahl, 1996).

Howland tested the advantages of FP in nasal spray over oral antihistamines in the treatment of seasonal AR, in doses of 200 micrograms once a day. After a follow-up of one year, the study found no side effects on bone mineralisation, subcapsular cataracts, glaucoma or the pituitary axis (Howland, 1996).

The same year they published a similar study in another journal: Efficacy of 200 micrograms of FP in aqueous nasal spray once a day. The study observed mild local topical effects and no indirect effects after systemic absorption (Howland et al, 1996).

Other clinicians observed that intranasal FP is an effective treatment for AR, is well tolerated and is indicated over other treatments using intranasal corticosteroids, antihistamines or intranasal cromolyn sodium, when administered once a day. It has better cost-effectiveness than the antihistamines loratadine and terfenadine (Wiseman & Benfield, 1997).

Finally, it confirmed that topical nasal corticosteroids decrease nasal blockage more effectively than antihistamines (Mygind et al, 1977).

The topical corticosteroids, such as triamcinolone, are the most powerful and effective agents in the treatment of AR, and have little systemic absorption (Naclerio, 1998). Oral antihistamines do not always control nasal congestion. Vasoconstrictors can cause drug-induced rhinitis, if used for a prolonged period of time, which is typical. Anti-leukotrienes need more studies; cromolyn sodium is effective in AR, but less so than topical corticosteroids.

Storms concluded that the benefits of FP exceed the risk in studies on the treatment of asthma and AR, using intranasal doses of 200 micrograms once a day. There were no cases of adrenal suppression or osteoporosis due to its use (Storms, 1998).

Corren stated that the use of intranasal corticosteroids has been shown to be an effective and safe form of therapy for AR. In terms of side effects, MF and FP seem to be safer and have less potential for systemic effects, even in cases of prolonged use and use in children, making them the ideal drugs for allergic rhinitis (Corren, 1999)

Lumry considered MF and FP as the best drugs for the treatment of AR, although there is lesser systemic involvement with mometasone. A case has been reported of suppression of nocturnal cortisol levels with FP, indicating suppression of the hypothalamic-pituitary-adrenal axis (Lumry, 1999).

Other authors tested the superiority of treatment with intranasal FP (200 micrograms once a day) over levocabastine in nasal spray and placebo nasal spray. The antihistamine improved symptoms of nasal blockage and rhinorrhoea. The placebo improved symptoms of sneezing, nasal blockage, rhinorrhoea and pruritus (Di Lorenzo et al, 1999). Furthermore, it is recommended the use of triamcinolone as the intranasal corticosteroid of choice in AR at a recommended dose of 220 micrograms once a day (Gawchik & Saccar, 2000).

Allen, from his perspective as an endocrinologist, observed that intranasal corticosteroids have been established as the first-line treatment of AR. They are safe and have few reported side effects due to excessive and prolonged doses, or to several concomitant inhaled corticosteroids (Allen, 2000).

However, Szefler warned that topical administration of corticosteroids may reduce the total required dose of corticosteroid for treating patients with minimal side effects (Szefler, 2001). This has prompted the development of intranasal corticosteroids as treatment for allergic and perennial rhinitis.

It has been shown that intranasal MF does not cause adverse side effects, and can even be used in children, as it does not affect bone growth. Therefore, we can say that the side effects of intranasal corticosteroids are minimal at the recommended doses.

Transrud stated that intranasal corticosteroids accepted as first-line treatment of AR are safe and effective. They reduce nasal congestion, pruritus, rhinorrhoea and sneezing that occur in the early and late phases of the allergic response. They join other studies that demonstrated an almost complete prevention of late phase symptoms. Adverse reactions are usually limited to nasal mucosa, along with headache and epistaxis in 5%-10% of patients (Trangsrud et al, 2002).

Wang reported that there was no difference between the efficacy of anti-Hl and topical corticosteroids in the treatment of AR, with both drugs recommended despite their different pharmacological characteristics. The greater benefit of topical corticosteroids is in its longer lasting anti-inflammatory action, compared with the speed of action of anti-Hl (Wang, 2002).

Finally, it is confirmed the greater efficacy of an intranasal treatment with FP over oral loratadine and a leukotriene inhibitor (montelukast) in seasonal AR. The results were significantly better in the fluticasone group in the reduction of nasal symptoms (Saengpanich et al, 2003).

Other authors showed that both intranasal corticosteroids and intranasal antihistamines were effective topical therapies in the treatment of AR (Salib & Howarth, 2003). Intranasal therapy represents a better form of treatment in AR, with a highly favourable risk/benefit

ratio. It is the preferred route of administration of corticosteroids in the treatment of the disease, as well as an important option compared to therapy with antihistamines, especially when quick symptom relief is needed.

Using meta-analysis, Waddell compared the efficacy of intranasal corticosteroids and oral antihistamines in the treatment of AR, and found a clear benefit in favour of intranasal corticosteroids. However, there is no clear evidence that one corticosteroid spray is more effective and safer than another in the treatment of rhinitis. It has not been demonstrated that either FP, MF or triamcinolone are more effective, or they are more expensive than BDP, budesonide and dexamethasone (Waddell et al, 2003).

Conversely, it was demonstrated that intranasal FP, in doses of 200 micrograms once a day, improves ocular symptoms in patients with AR, without the need for adding oral antihistamines or topical eye drops (De Wester, 2003).

Towards the end of 2003, Borish stated that an effective therapy in the treatment of rhinitis is that which is direct and decreases inflammation and its systemic manifestations. Antihistamines quickly resolve nasal symptoms, but not inflammation, at least not significantly. Oral corticosteroids are highly effective, but have significant systemic side effects. Local intranasal corticosteroids act on the level of local inflammatory processes of rhinitis, reducing local inflammatory cells, but without direct involvement of other tissues (Borish, 2003). Anti-leukotrienes have systemic anti-inflammatory effects and an acceptable safety profile.

They compared the efficacy of antihistamines versus intranasal corticosteroids in AR, with the studies favouring corticosteroids. Antihistamines also do not seem to be superior in the treatment of conjunctivitis associated with AR (Nielsen & Dahl, 2003).

Other author warned that it would be best to avoid allergens during pregnancy (Keleç, 2004). If cromolyn is not tolerated or is ineffective, first- or second-generation anti-H1 (cetirizine and loratadine) may be used. Intranasal corticosteroids may be added for treatment of significant nasal obstruction. There are no studies on the use of new intranasal corticosteroids (FP, FF, flunisolide, triamcinolone, MF) during the first trimester of pregnancy. Kim confirmed that intranasal corticosteroids are safe and effective for treating AR in adults (Kim et al, 2004). The administration of budesonide aqueous nasal spray for 6 weeks is well tolerated and safe, with no suppression of the pituitary-adrenal axis, even in children aged 2 to 5 years with AR.

Patel et al stated that the use of betamethasone suppresses the adrenal axis, which does not happen with MF nasal spray. The concentration of cortisol in morning saliva is a tool for monitoring adrenal function (Patel et al, 2004).

Gradually, it has been established that AR and asthma often coexist and represent 2 manifestations of the same disease, which has recently been called CARAS (combined allergic rhinitis and asthma syndrome) (Taramarcaz & Gibson, 2004). The benefit of using intranasal corticosteroids in CARAS has been shown, although there is still a lack of studies. Currently, the best practice is to treat conventional asthma with bronchial corticosteroids (inhaled) with or without ß-agonists and adding intranasal corticosteroids to avoid symptoms specific to rhinitis.

4. Oral Cys-LT cysteinyl leukotriene receptor-1 antagonist

Allergic rhinitis is a common airways hypersensitivity disease. Histamine and leukotrienes are involved in the pathogenesis of allergic rhinitis. Conventional treatments include topical steroids and antihistamines. Due to the adverse effects of these treatments, new drugs like leukotriene receptor antagonists are being investigated for the treatment of allergic rhinitis (Modgill et al, 2010).

The cysteinyl leukotrienes (LTC4, LTD4, LTE4) are products of arachidonic acid metabolism and are released from various cells, including mast cells and eosinophils. These eicosanoids bind to cysteinyl leukotriene (CysLT) receptors. The CysLT type-1 (CysLT1) receptor is found in the human airway (including airway smooth muscle cells and airway macrophages) and on other pro-inflammatory cells (including eosinophils and certain myeloid stem cells). CysLTs have been correlated with the pathophysiology of asthma and AR. In asthma, leukotriene-mediated effects include airway edema, smooth muscle contraction, and altered cellular activity associated with the inflammatory process. In allergic rhinitis, CysLTs are released from the nasal mucosa after allergen exposure during both early- and late-phase reactions and are associated with symptoms of allergic rhinitis (Lipworth, 1999).

There are two different LT inhibitors/modifiers:

- LT receptor antagonists [LTRAs; montelukast (Singulair®, Merck Sharp & Dohme Inc, NJ, USA), zafirlukast (Accolate®,AstraZeneca farmacéutica, Madrid, Spain), and pranlukast (Azlaire®, Schering Plough Inc, NJ, USA).
- 5-Lypoxigenase inhibitor of LT synthesis [zileuton® (Zyflo®)].

Montelukast and zafirlukast block binding of cysteinil LTs to the cysLT1 receptor in the extracellular space. Zileuton inhibits 5-lipoxygenase and therefore all LT synthesis within inflammatory cells. By blocking the actions of LTs, it promotes bronchodilation and decreases the inflammatory response. Anti-LTs also have been used successfully by some authors to control allergic diseases such as AR, atopic dermatitis, chronic urticaria and allergic conjunctivitis. The FDA has approved montelukast for the treatment of AR (Scow et al, 2007).

4.1 Montelukast

Montelukast is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older; for prevention of exercise-induced bronchoconstriction in patients 15 years of age and older; and for the relief of symptoms of seasonal allergic rhinitis in patients 2 years of age and older and perennial allergic rhinitis in patients 6 months of age and older (this last indication is available in the USA but not in Spain) (Merch, Sharp & Dohme, 2011).

For AR, montelukast should be taken once daily. Efficacy was demonstrated for seasonal AR when montelukast was administered in the morning or the evening without regard to time of food ingestion. The time of administration may be individualized to suit patient needs. The following doses for the treatment of symptoms of seasonal AR are recommended: 10 mg for adults and adolescents 15 years of age and older; 5 mg for pediatric patients 6 to 14 years of age; and one 4 mg for pediatric patients 2 to 5 years of age (Merch, Sharp & Dohme, 2011).

Safety and effectiveness in pediatric patients younger than 2 years of age with seasonal AR have not been established. The following doses for the treatment of symptoms of perennial allergic rhinitis are recommended: 10 mg for adults and adolescents 15 years of age and older; 5 mg for pediatric patients 6 to 14 years of age; 5 mg for pediatric patients 2 to 5 years of age; 4 mg for pediatric patients 6 to 23 months of age. Safety and effectiveness in pediatric patients younger than 6 months of age with perennial AR have not been established.

Montelukast is an orally active compound that binds with high affinity and selectivity to the CysLT1 receptor (in preference to other pharmacologically important airway receptors, such as the prostanoid, cholinergic, or β-adrenergic receptor). Montelukast inhibits physiologic actions of LTD4 at the CysLT1 receptor without any agonist activity.

The efficacy of montelukast for the treatment of persistent and seasonal AR was investigated in different studies and clinical trials.

Evidence in persistent AR:

- Montelukast alone or in combination with antihistamines (desloratadine or levocetirizine) gave a gradual increase in nasal symptom improvement within 6 weeks of treatment in patients with persistent AR (Ciebiada et al, 2011).
- A multicenter, randomized, double-blind, placebo-controlled study was conducted in the US among 1992 patients to evaluate montelukast for treatment of perennial AR. The study was conducted during the winter, and all patients had positive skin tests for at least 2 perennial allergens. The investigators conclude that montelukast provides statistically significant symptomatic relief of persistent AR over 6 weeks of treatment (Patel et al, 2005).
- A randomized, double-blind, placebo-controlled, parallel-group study was performed to compare the effects of oral montelukast 4 mg once daily at bedtime with those of oral cetirizine 5 mg once daily at bedtime for 12 weeks in 60 children with perennial AR. The results revealed that both montelukast and cetirizine were significantly efficacious compared with placebo in nasal airway resistance, eosinophil percentage in nasal smears, Pediatric Rhinoconjunctivitis Quality of Life Questionnaire (PRQLQ), Total Symptom Score (TSS) and all symptom items except nasal itching, throat itching and tearing. For nasal itching, only cetirizine was significantly efficacious (Chen et al, 2006).

Evidence in persistent AR:

- Weinstein et al analyzed data from 4 phase III clinical trials to determine the onset of action of montelukast in seasonal allergic rhinitis. The 4 trials were double-blind, parallel-group, multicenter studies conducted in Fall 1999 (Study 1), Spring 2000 (Study 2), Fall 2000 (Study 3), and Spring 2001 (Study 4). Over the entire 2 weeks treatment period, pooled data indicated that montelukast was significantly better than placebo in decreasing symptom scores. The authors conclude that in patients with seasonal allergic rhinitis, montelukast reduces daytime and nighttime symptoms by the 2nd day of once-daily therapy (Weinstein et al, 2005).
- A multicenter, randomized, double-blind, placebo-controlled, parallel-group study was performed to compare the effects of montelukast 10 mg once daily at bedtime with those of loratadine 10 mg once daily at bedtime for 2 weeks during the allergy season in 1302 patients with seasonal AR. Quality of life scores (including measures of activity, sleep, nasal symptoms, eye symptoms, other symptoms, practical problems, and

emotions) also improved significantly in the montelukast and loratadine groups (P=0.003 and P≤0.001, respectively, versus placebo) (Philip et al, 2002).

- A multicenter, randomized, double-blind, double-dummy, placebo- and active-controlled study was performed in the US and Canada to evaluate the effects of montelukast 10 mg once daily in 1214 patients with spring seasonal AR. Therapy with montelukast significantly improves assessments of symptom severity as well as quality-of-life parameters for patients with seasonal AR (van Adelsberg et al, 2003).

4.2 Zafirlukast

Donnelly et al performed a study with 164 patients who were administered increasing doses of oral Zafirlukast (10, 20, 40, 100 mg and placebo). They found a significant decrease in nasal obstruction, sneezing and rhinorrhoea in patients who received doses starting from 20 mg (Donnelly et al, 1995)

5. Omalizumab (anti-IgE monoclonal antibody)

Several therapeutic anti-IgE antibodies, able to reduce free IgE levels and to block the binding of IgE to FcεRI without cross-linking IgE and triggering degranulation of IgE-sensitized cells have been developed. At present omalizumab is the only monoclonal antibody (mAb) - based drug approved for the treatment of asthma. A new mAb specific for human IgE has been shown to possess a unique set of binding specificities. This mAb, 8D6, binds to a conformational epitope on the CH3 domain of human IgE and can compete with omalizumab for binding to IgE. Like omalizumab, it does not bind to IgE already bound to the high-affinity IgE Fc receptor (FcεRI) on basophils and mast cells. It also does not cause activation and degranulation of IgE-pulsed, human FcεRI-expressing rat basophilic leukemic cells (RBL SX-38). This mAb can inhibit IgE binding to recombinant α chain of human FcεRI in ELISA and to human FcεRI-expressing RBL SX38 cells in fluorescence flow cytometric analysis. However, unlike omalizumab, 8D6 can bind to IgE already bound by the low-affinity IgE Fc receptors (FcεRII, or CD23). Since earlier investigators have shown that anti-CD23 mAbs can inhibit the synthesis of IgE in lymphocyte culture in vitro and can down-regulate IgE production in treated patients, 8D6 may offer pharmacological mechanisms in addition to those mediated by omalizumab, for controlling IgE in patients with allergic diseases. (Shiung et al, 2001).

Chu et al, have explored the effects of IgE sequestration versus IgE suppression by comparing omalizumab to FcγRIIb-optimized anti-IgE antibodies in humanized mouse models of immunoglobulin production. By using a murine anti-IgE antibody as a template, the authors humanized, increased IgE binding, and modified its Fc domain to increase affinity for FcγRIIb. Relative to omalizumab, this new mab, XmAb7195, has a 5-fold higher affinity for human IgE and more than 400-fold higher affinity for FcγRIIb. In addition to sequestering soluble IgE, XmAb7195 inhibited plasma cell differentiation and consequent human IgE production through coengagement of IgE B-cell receptor with FcγRIIb. In peripheral blood mononuclear cells-engrafted mice, XmAb7195 reduced total human IgE (but not IgG or IgM) levels by up to 40-fold relative to omalizumab (Chu et al, 2012).

Omalizumab represents an important clinical advance in the management of allergic diseases and can be considered to be safe in children with seasonal allergic rhinitis

undergoing specific immunotherapy simultaneously (Kamin et al, 2010). Rush IT (RIT) carries a greater risk of acute allergic reactions (including anaphylaxis) than standard subcutaneous IT. In RIT, the accelerated dosing schedule can cause early increases in total and specific IgE concentrations that could predispose individuals to allergic reactions. The effect of omalizumab on the safety and efficacy of RIT was studied in adult patients with ragweed-AR. (Table 1).

Study	Patients and type of AR	Type of study	Comments
Casale et al, 1997	240 patients with ragweed AR	comparison omalizumab-placebo	Decrease dose-dependent in serum free IgE correlation between symptoms and IgE levels
Ädelroth et al, 2000	251 patients with birch pollen AR	comparison omalizumab-placebo	Decrease serum free IgE levels with omalizumab association between free IgE levels and clinical outcome mean daily NSSS, concomitant medication use, RRQoL was significantly better with omalizumab
Casale et al, 2001	536 patients with ragweed AR	comparison omalizumab-placebo	Significant association between IgE reduction, nasal symptoms and rescue medication use; significantly lower NSSS, lower need for rescue medication, better RRQoL scores, 75% reduction in days missed from work in patients receiving 300 mg omalizumab
Kopp et al, 2002	92 children with birch and grass pollen AR	Four treatment groups: -grass IT + omalizumab -grass IT + placebo -birch IT + omalizumab -birch IT + placebo	Symptom load was significantly reduced in both omalizumab groups compared to placebo. In vitro sulfidoleukotriene release was significantly lower with IT + omalizumab compared to IT + placebo, parallel to the reduction in symptoms and the use of rescue medication.
Kuehr et al, 2002	221 children with birch and grass pollen AR	Four treatment groups: -grass IT + omalizumab -grass IT + placebo -birch IT + omalizumab -birch IT + placebo	Significant reduction in symptom load and rescue medication use in the omalizumab + IT group compared to IT alone. Omalizumab reduced symptom load regardless of IT and had a protective effect independent of the type of allergen and additional clinical benefit to IT.
Chervinsky et al, 2003	289 patients with perennial AR	comparison omalizumab-placebo	Significantly lower NSSS and rescue antihistamines; improved RRQoL in the omalizumab group patient evaluation of efficacy significantly favored omalizumab.

Study	Patients and type of AR	Type of study	Comments
Nayak et al, 2003	287 patients with ragweed AR	retreatment with omalizumab	Decrease in serum free IgE levels.
Bez et al, 2004	225 children with birch and grass pollen AR	Four treatment groups: -grass IT + omalizumab -grass IT + placebo -birch IT + omalizumab -birch IT + placebo	Combination of IT and omalizumab: no pollen-induced increase in ECP and decrease in tryptase in nasal secretions; significantly lower tryptase levels in the omalizumab group.
Rolinck-Werninghaus et al, 2004	Further analyses during grass pollen season after previous study (Van Cauwenberge, 2005)	Four treatment groups: -birch IT + placebo -birch IT + omalizumab -grass IT + placebo -grass IT + omalizumab	Significantly diminished rescue medication use and reduction in the number of symptomatic days with omalizumab monotherapy. Superior efficacy of the omalizumab + IT combination on symptom severity compared to IT or omalizumab alone.
Vignola et al, 2004	405 patients with asthma and persistent AR	comparison omalizumab-placebo	Significant improvement in RRQoL in the omalizumab-treated patients
Casale et al, 2006	159 patients with ragweed AR	Four treatment groups: -omalizumab + placebo -omalizumab + RIT -placebo + placebo -placebo + RIT	Significant improvement in severity scores during the ragweed season with omalizumab + IT compared to IT alone

ECP = eosinophilic cationic protein; NSSS = nasal symptom severity scores; RIT = rush immunotherapy; RRQoL = rhinitis-related quality of life.

Table 1. Clinical studies with "omalizumab" and combination "omalizumab-specific immunotherapy" in allergic rhinitis.

6. Allergen-specific Immunotherapy

Two stages have been defined in AR immune pathophysiology. The first stage is named sensitization phase reaction, and is initiated by preferential activation and polarization of the immune response to environmental antigens, that culminates with a generation of a predominant Th2 immune response and production of IgE antibodies; the second stage, named effector phase reaction, is initiated with a second encounter with antigen (Ag) leading to activation of effector mechanisms, such as degranulation of granulocytes and release of histamine (Robles-Contreras et al, 2011). Allergen-induced cell degranulation is the key event in allergic inflammation and leads to early-phase symptoms. Early phase reaction (EPR) has been studied extensively in both humans and animals; EPR is initiated with a second encounter with the antigen by IgE previously attached to IgE receptors (FcεRI, FcεRII or CD23). Cross-linking of IgE receptors induces: a) release of preformed mediators such as histamine, proteases and chemotactic factors; b) activation of transcription factors and cytokine gene expression, and c) production of prostaglandins and leukotrienes by phospholipase A2 pathway (Figure 1).

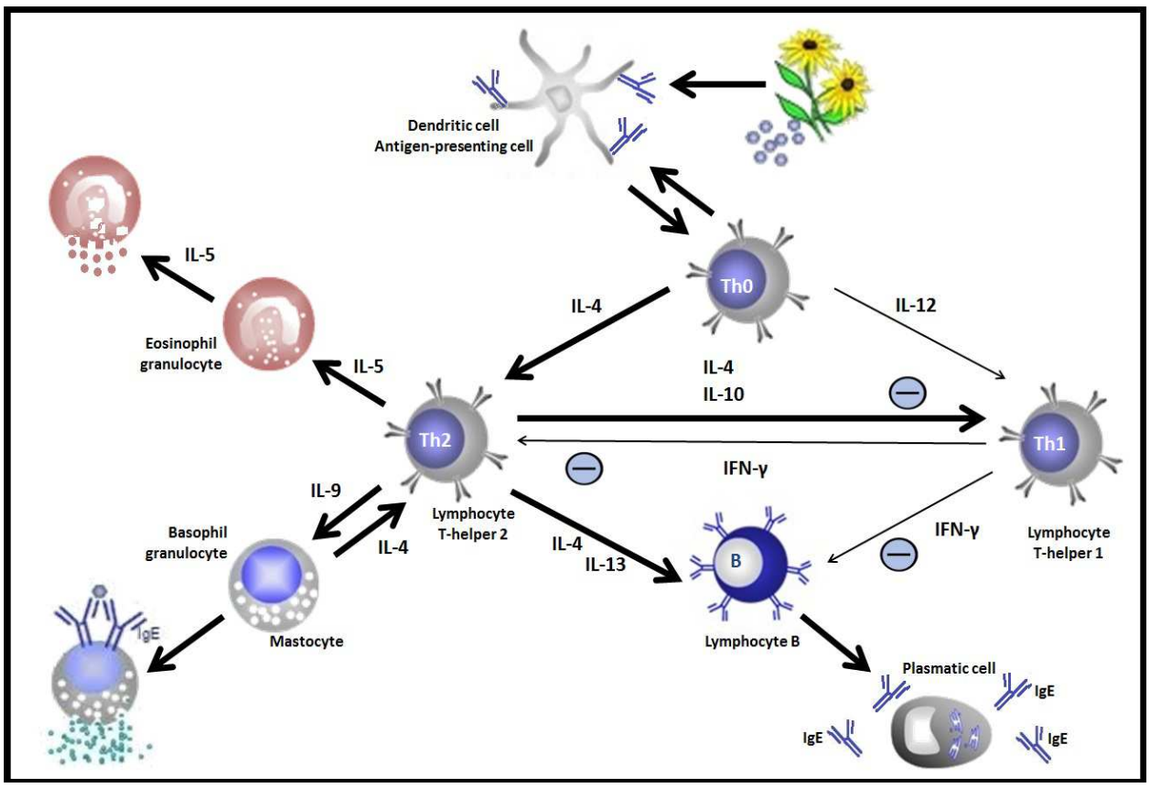

Fig. 1. Mechanism of allergic reaction.

The mechanisms of action of allergen-specific immunotherapy (SIT) include the very early desensitization effects, modulation of T-and B-cell responses and related antibody isotypes, and migration of eosinophils, basophils, and mast cells to tissues, as well as release of their mediators (Figure 2). Regulatory T (Treg) cells have been identified as key regulators of immunologic processes in peripheral tolerance to allergens. Skewing of allergen-specific effector T cells to a regulatory phenotype appears as a key event in the development of healthy immune response to allergens and successful outcome in patients undergoing allergen-specific immunotherapy (Akdis & Akdis, 2011).

Have been reported biomarkers of clinical response to IT:

a. Increase in allergen-specific serum IgG4 (Tari et al, 1990; Tari et al, 1994; Durham et al, 1999; La Rosa et al, 1999; Bufe et al, 2004; Lima et al, 2002; Smith et al, 2004; Til et al, 2004; Tonnel et al, 2004).
b. Increase in serum functional IgG responses:
   - Inhibition of basophil histamine release (Niederberger et al, 2004).
   - Inhibition of IgE-facilitated allergen binding (IgE-FAB) (Shamji et al, 2006).
c. Reduction in immediate and late-phase skin test responses to allergen (Tari et al, 1994; Durham et al, 1999; La Rosa et al, 1999; Tonnel et al, 2004).
d. Suppression of rise in Eosinophil Cationic Protein (ECP) (Gozalo et al, 1997; Passalacqua et al, 1998; Vourdas et al, 1998; Ippoliti et al, 2003) and tryptase (Marcucci et al, 2003) concentrations in nasal lavage during the pollen season

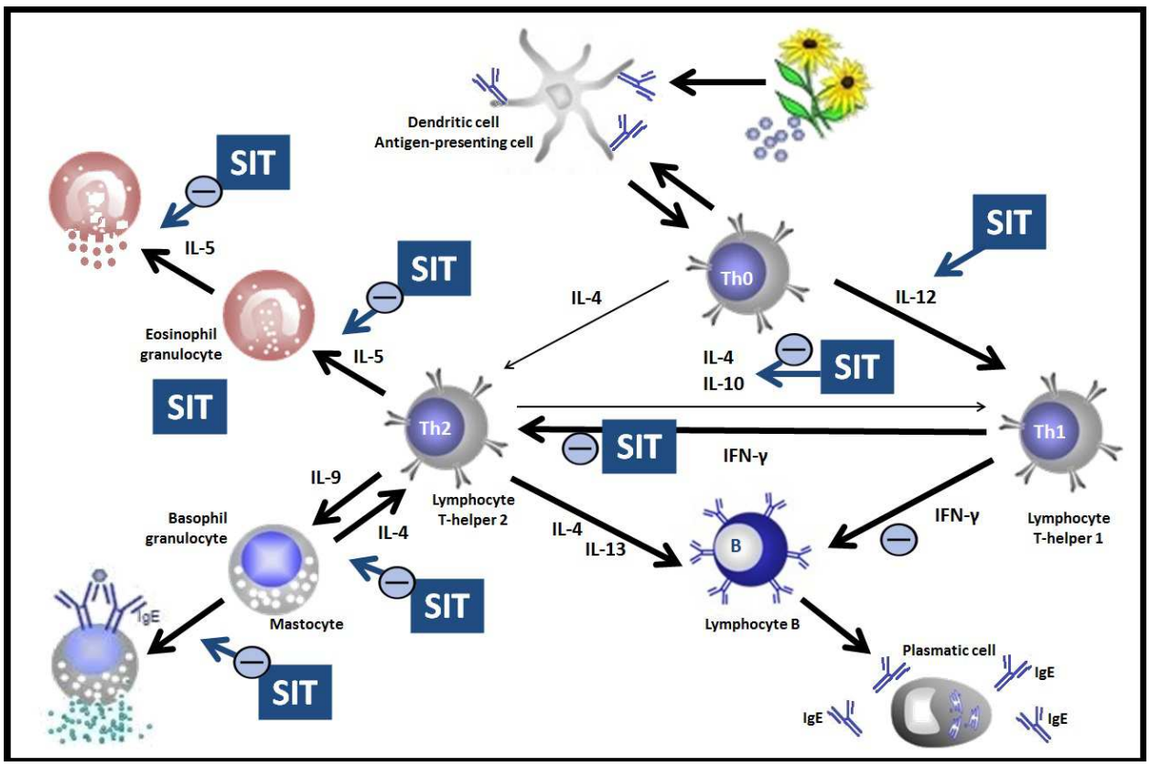

Fig. 2. Mechanisms of action of allergen-specific immunotherapy (SIT).

	Subcutaneous IT for seasonal AR (Calderon et al, 2007)	Sublingual IT for seasonal and perennial AR (Olaguibel & Álvarez-Puebla, 2005)
Participant numbers (active/placebo)	597/466	2333/2256
Symptom scores SMD random (95% CI)	-0.73 (-0.97, -0.50)	-0.49 (-0.64, -0.34)
P-value	<0.00001	<0.00001
Heterogeneity (I^2)	63%	81%
Medication scores SMD random (95% CI)	-0.57 (-0.82, -0.33)	-0.32 (-0.43, -0.21)
P-value	<0.00001	<0.00001
Heterogeneity (I^2)	64%	50%

Heterogeneity: Low = I^2 25%; Moderate = I^2 50%; High = I^2 75%;

Table 2. Efficacy of immunotherapy (IT) in AR (summary of Cochrane meta-analyses)

e. Increased in vitro IL-10 production by peripheral blood mononuclear cells (PBMC) following stimulation with allergen (Nouri-Aria et al, 2004; Francis et al, 2008).
f. Reduction in allergen-induced in vitro PBMC proliferative responses (Fanta et al, 1999).
g. Reduction in bronchial responses to allergen and methacholine challenge (Rak et al, 1988; Cirla et al, 2003).

The ARIA document clearly states that immunotherapy (IT) is considered effective in AR, and that it is the only treatment that can change the natural course of the disease and prevent its evolution into asthma (Bousquet et al, 2008).

IT, both subcutaneous and sublingual, is an effective treatment for adults and children with severe AR that does not respond to conventional pharmacotherapy and allergen avoidance measures. The efficacy of IT depends on correct patient selection, the type of allergen and the product chosen for treatment. Each vaccine requires individual assessment before recommendation for routine use. In support of the conclusions of recent meta-analyses, data have provided further evidence for the efficacy of Sublingual immunotherapy (SLIT) at least for grass pollen-induced (Table 2).

7. Therapeutic developments in the treatment of allergic rhinitis (AR)

Due to the increased prevalence of AR, its impact on quality of life, its societal costs and the fact that it is a predisposing factor for asthma, new therapeutic options are being sought. Studies are being performed with anti-leukotrienes, anti-immunoglobulin E antibodies, phosphodiesterase inhibitors, and others, which seem to confirm promising results.

Schultz et al state that, in addition to the well established therapeutic guidelines in the treatment of rhinitis with antihistamines, corticosteroids, nasal decongestants, etc., there are an increasingly number of new therapeutic alternatives, such as anti-leukotrienes, anti-immunoglobulin E antibodies, phosphodiesterase inhibitors and intranasal heparin, as well as new specific immunotherapies (recombinant). There are promising results, but more studies are needed to confirm these initial data (Schultz et al, 2003).

Bjermer and Diamant observed that, although inhaled corticosteroids are currently considered first-line drugs in the anti-inflammatory control of asthma and rhinitis, there are studies with anti-leukotrienes and anti-immunoglobulin E that are highly promising. Clinical trials are being performed with modified cytokines (Bjermer & Diamant, 2004).

Koreck et al reported on *low intensity UVB, UVA and visible light phototherapy* as treatment for AR (3 times per week for three weeks). The authors reported that there was a significant reduction in the number of eosinophils, ECP and IL-5 in the nasal lavage. They also found inhibition in the RBL-2H3 mediator release of basophils. Phototherapy is a new option in the treatment of immunologically mediated mucosal diseases, including allergic rhinitis (Koreck et al, 2005).

Kirchhoff et al used the *H1-receptor antagonist dimethindene maleate* topically on patients with seasonal allergic rhinitis for 2 weeks and compared it with placebo. With this antagonist, they achieved statistically significantly better results in the quality of life questionnaires for rhinitis than with placebo (Kirchhoff et al, 2003).

Unal et al investigated the potential benefits of the *toxin botulinum type A* on nasal symptoms of allergic rhinitis, and compared it to an isotonic saline solution as placebo. The results were significantly better in patients treated with botulinum toxin, especially in rhinorrhoea, nasal obstruction and sneezing. In selected cases, the injection of intranasal toxin botulinum may help control allergic rhinitis symptoms (Unal et al, 2003).

Monoclonal antibodies anti-IL-5 seem to be an effective treatment that reduces the number of eosinophils locally in the airway and in peripheral blood in asthmatic patients. Two monoclonal antibodies have been designed to neutralize IL-5 (mepolizumab and reslizumab). Mepolizumab is a fully humanized anti-IL-5 monoclonal IgG1 antibody that binds to free IL-5 with high affinity and specificity to prevent IL-5 from associating with the IL-5 receptor complex alpha-chain on the surface of eosinophils (Leckie et al, 2000).

There are clinical trials with recombinant soluble IL-4 receptor, and recombinant IL-12. Immunomodulatory treatments for IL-9, IL-l0, IL-12 and IL-13 are being studied, as well as immunostimulatory DNA sequences, with encouraging results.

8. Conclusions

Considering the reviewed data, and unifying the above-mentioned opinions on the treatment of AR, we provide the following guidelines:

- Inhaled corticosteroids are effective and safe for the treatment of AR, usually associated with antihistamines in persistent AR. We have found no indication for administering systemic corticosteroids unless there is another associated pathology.
- Histamine and leukotrienes are involved in the pathogenesis of allergic rhinitis. Montelukast is indicated for the prophylaxis and chronic treatment of asthma in adults and pediatric patients 12 months of age and older; for prevention of exercise-induced bronchoconstriction in patients 15 years of age and older; and for the relief of symptoms of seasonal allergic rhinitis in patients 2 years of age and older and perennial allergic rhinitis in patients 6 months of age and older
- Omalizumab represents an important clinical advance in the management of allergic diseases and can be considered to be safe in children with seasonal allergic rhinitis undergoing specific immunotherapy simultaneously.
- Immunotherapy is an effective treatment for adults and children with severe AR that does not respond to conventional pharmacotherapy and allergen avoidance measures. The efficacy of IT depends on correct patient selection, the type of allergen and the product chosen for treatment.
- Encouraging new treatments are currently being studied.

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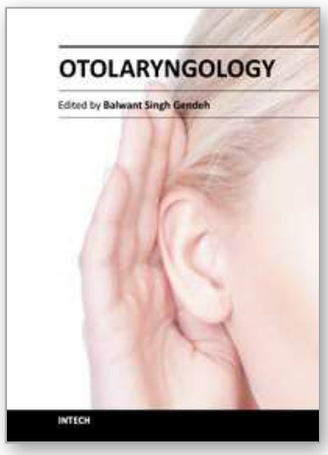

Otolaryngology

Edited by Prof. Balwant Singh Gendeh

ISBN 978-953-51-0624-1
Hard cover, 198 pages
Publisher InTech
Published online 23, May, 2012
Published in print edition May, 2012

This book emphasizes on different aspects of otolaryngology - the medical sciences of diagnosis and treatment of ENT disorders. "Otolaryngology" is divided into various clinical sub-specialities, namely otology, rhinology, laryngology, and head and neck. This book incorporates new developments, as well as future perspectives in otolaryngology. I would like to dedicate this book to those of you who will pick up the torch and by continued research, close clinical observation and the highest quality of clinical care, as well as by publication and selfless teaching, further advance knowledge in otolaryngology from this point forward. It is intended to be a guide to other books to follow. Otolaryngologists, researches, specialists, trainees, and general practitioners with interest in otolaryngology will find this book interesting and useful.

How to reference

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Jesus Jurado-Palomo, Irina Diana Bobolea, Maria Teresa Belver Gonzalez, Alvaro Moreno-Ancillo, Ana Carmen Gil Adrados and Jose Manuel Morales Puebla (2012). Treatment of Allergic Rhinitis: Anticholinergics, Glucocorticotherapy, Leukotriene Antagonists, Omalizumab and Specific-Allergen Immunotherapy, Otolaryngology, Prof. Balwant Singh Gendeh (Ed.), ISBN: 978-953-51-0624-1, InTech, Available from: http://www.intechopen.com/books/otolaryngology/treatment-of-allergic-rhinitis-anticholinergics-glucocorticotherapy-leukotriene-antagonists-omalizum

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