In spite of the fact that pharmacological therapy and allergen avoidance are effective means of managing allergic disease, allergen-specific immunotherapy is able to treat not only the symptoms, but also the underlying causes of the disease. Allergen-specific sublingual immunotherapy is now recognized to be an efficacious and well-tolerated treatment for allergic rhinitis.

According to Incorvaia C (2009) specific immunotherapy is the only treatment targeting the causes, and not only the symptoms, of allergic diseases. Sublingual immunotherapy (SLIT) was introduced and developed to solve the problem of the adverse reactions, uncommon but possibly severe and rarely fatal, to the traditional subcutaneous immunotherapy (SCIT). The evidence of SLIT efficacy concerns rhinitis and asthma caused by sensitization to polens and to house dust mites, but there are increasing data suggesting that SLIT could be applied in forms of allergy hardly feasible for SCIT because of its poor safety (this is true for food allergy and latex allergy) or could be considered for new applications, such as atopic dermatitis or baker’s asthma. In particular, there are placebo-controlled trials indicating good efficacy and safety of SLIT in patients allergic to latex and foods and in children with atopic dermatitis, that indicate SLIT as a real treatment option in such clinical entities.

Sublingual immunotherapy (SLIT) has been shown to be effective in patients with allergic diseases. It has demonstrated long-term clinical benefits and shown the potential to modify the course of allergic disease in children with rhinitis, conjunctivitis, and asthma. The precise mechanisms of SLIT remain unclear, but antigen-presenting cells in the oral mucosa may induce regulatory T-cells that suppress the allergic immune response by increasing production of interleukin-10. SLIT has also been shown to increase allergen-specific IgG antibodies that antagonize and block the allergic response. SLIT was well tolerated in all reported, double-blinded, placebo-controlled, randomized trials. SLIT is an ideal mean of treating the pediatric population because of its excellent safety and good compliance. However, the optimal dose and duration of SLIT require further investigation.

Several trials have also shown a potential immunomodulatory effect of sublingual immunotherapy, with evidence of a reduction in the progression from allergic rhinitis to asthma and reduced new aeroallergen sensitisation. Sublingual immunotherapy has been used extensively in Europe and possesses most of the benefits of subcutaneous immunotherapy along with increased safety, tolerability, and convenience. The authors of the present review have prescribed 210 sublingual immunotherapy treatments in children and adults suffering of allergic rhinitis in several places of Greece. The product which was used was Sarm Allergeni sublingual drops. The patients maintained the treatment for three years without any medical supervision, but only written advice and telephone communication with the prescribing physician. No side effects have been reported. No one patient abandoned the treatment due to intolerance or acute allergic reactions. Sarm sublingual immunotherapy was a resultful and safe treatment of allergic rhinitis in our hands. Our patients are free of allergic symptoms or in some cases they had need of the conventional antiallergic drugs for very short periods of time. Finally, we mention the information needed for the patient, in order to keep the safe orders of use of the sublingual allergens drops.

1. Name of the medicinal product
Specific sublingual immunotherapy contain...
ing allergen extracts.

2. Composition
Specific allergenic extract:
• Starting therapy: four vials containing 6ml of the following allergen concentrations: 40-200-1000-1000B.U./ml
• Paediatric starting therapy: five vials containing 6ml of the following allergen concentrations: 8-40-200-1000-1000B.U./ml
• Pre-seasonal therapy: five vials containing 6ml of the following allergen concentrations: 40-200-1000-1000B.U./ml
• Rapid induction therapy: three vials containing 8ml of solution at 1000B.U./ml
• Maintenance therapy: three vials containing 6ml of solution at 1000B.U./ml.

Other ingredients in 1ml: sodium chloride 9mg, glycerine 0.5ml, ultrapure water sufficient to reach 1ml.

3. Pharmaceutical form
Oral solution that must be administered in sublingual form.

4. Product properties
The administration of allergens by sublingual means with regular intervals induces a persistent reduction of allergic symptomatology. The reduction degree depends on the individual sensitivity and on the administered doses.

5. Clinical particulars
5.1. Therapeutic indications: Treatment therapy for allergic disease caused by inhalant agents.

5.2. Contra-indications: Immunotherapy is contraindicated in the acute and serious diseases that affect general conditions, and in all pathologies and therapies that depress the immune system. Besides, it is contraindicated for patients with continuous lesions of the mouth mucosa, for patients with gastrointestinal disturbances, both current and temporary, for patients with an acute allergic reaction and for patients who cannot use adrenaline.

5.3. Undesirable effects: The administration of immunotherapy may be accompanied by gastro-abdominal pain especially if the dosage has not been optimised and exceeds the patient’s maximum tolerance. Although these effects disappear once the dosage has been readapted. No important general reactions have been advised. However, patients should inform their doctors in the event of any undesirable effect.

5.4. Special warning and special precautions for use: For the hours that follow administration it is important that the patient avoids any sporting activity, physical strain, hot baths and saunas.

5.5. Pregnancy and lactation: Normally, during pregnancy, a hyposensitizing therapy is not initiated. Should the patient become pregnant during an immunotherapy, the contraindication to the vaccine administration would be the difficulty to establish a suitable therapeutic treatment for possible undesired effects. The prescribing doctor shall decide whether or not to proceed with the therapy. There are no contraindications for the administration of the therapy during breast feeding.

5.6. Interaction with other medicaments and other form of interaction: The patient should avoid contact with causative and cross-reacting allergens. The doctor should consider that a parallel treatment with symptomatic anti-allergic drugs (antihistamines, corticosteroids, membrane stabilizers) may alter the patient’s tolerability threshold or complicate the choice for the optimal dose.

5.7. Dosology and method of administration: The doctor managing immunotherapy establishes doses and frequency of the administration, adjusting dosage to each patient’s degree of sensitization and general conditions.

5.7.1. Method of vial preparation
a. Remove the dropper from the wrapping
b. Remove the flip-off ring nut and open the vial
c. Holding the vial with the left hand, put the dropper on the vial with the right hand
d. Finally push with the forefingers and the middle fingers, until the plastic ring nut is completely well-adjusted.

Attention: to avoid liquid leak, after the drop application, the vial must be stored vertically.

5.7.2. Method of administration: Sublingual administration is to be taken before any food, preferably in the morning. Remove the cap from the dropper and put the vial upside down under the tongue. By means of a pronounced pressure in the centre of the dropper, place the recommended dose under the tongue, where it is left for at least two minutes, keeping the mouth slightly open and the tongue raised. To keep a sign of the administered doses we suggest to fill in the tables 1-2-3 “Administered doses” for the doctor.

5.7.3. Indicative administration schedules: The treatment period.

If there are two different therapies to be administered, it is better to separate these by taking one therapy in the morning and the other in the evening.

5.7.4. If there are two different therapies to be administered, it is better to separate these by taking one therapy in the morning and the other in the evening.

5.7.5. Treatment period: The treatment period shall be established by the prescribing doctor in accordance to patient’s clinical trend (approximately 3 years).

5.7.6. Omission of one or more doses: If the therapy is interrupted for more than a 7 day period, then it is wise to decrease dosage. Should the therapy be suspended for a very long period (3-4 weeks), it is advisable to resume therapy by using the concentration previously reached and interrupted.

5.8 Overdose: The administration of an excessive dose of allergen can cause either immediately or after several hours, a fresh outbreak of the allergic symptoms, as gastrointestinal pain which can easily be controlled with suitable pharmacological therapy.

5.9 Special warnings: None

5.10 Effects on ability to drive and use machines: Although none of these effects have been reported, these cannot be excluded.

6. Pharmaceutical particulars
6.1 Incompatibilities: Not reported.

6.2 Shelf-life: 12 months; the expiry date on the pack refers to unopened and undamaged vials that have been stored correctly.

6.3 Special precautions for storage: Store at +2/+8 °C upon receipt.

6.4 Nature and contents of container: Neutral
Surgical treatment of facial paralysis and advances in facial reanimation

The facial paralysis patient suffer serious functional, cosmetic, and the disease often has a significant emotional impact on patients creating psychological problems (mainly depression) and impairment of the ability for social communication.

The management of facial paralysis is one of the most complex areas of reconstructive surgery. Management of the condition has evolved extensively over the past 50 years, relying largely upon neural repair techniques and static techniques prior to the 1940s, followed by heavy emphasis on regional muscle transfer by the 1970s. With the advent of the operating microscope and the development of microinseritment, in the mid-1970s free tissue transfer based became technically feasible, and new techniques quickly ensured that introduced functioning muscle as a viable and valuable option in the management of the paralyzed face. These techniques have been subject to continual refinement to improve their reliability and reduce morbidity. Despite the advances of recent years and the number of new techniques proposed in the literature, facial reanimation remains a challenge for the reconstructive surgeon. Along with the myriad of new surgical techniques in managing facial paralysis comes the...
challenge of selecting the most effective procedure for the patient. Given the wide variety of functional and cosmetic deficits in the facial paralysis patient, the reconstructive surgeon requires a thorough understanding of the surgical techniques available to treat this condition.

The surgeon must select the treatment options available for acute facial paralysis (<3 weeks duration), intermediate duration facial paralysis (3 weeks to 2 years) and chronic facial paralysis (>2 years). The options for dynamic reanimation of the paralyzed face must be examined in the context of several patient factors, including age, overall health, and patient desires.

With the advent of microsurgery, reanimation of the paralyzed face took a major leap forward with the use of cross facial nerve grafts, nerve transfers, and free muscle transplantation. Today, nerve transfers represent the backbone of facial reanimation, especially in cases where reconstruction of the affected facial nerve is not feasible. The suitability of each nerve transfer is related to the type of facial palsy, time elapsed since injury, and the age and general health of the patient. The selected motor nerve must provide strong muscle contraction and allow the patient to control the facial movements.

For acute facial paralysis, the main surgical therapies are facial nerve decompresion and facial nerve repair. For facial paralysis of intermediate duration, nerve transfer procedures are appropriate. For chronic facial paralysis, treatment typically requires regional or free muscle transfer. Static techniques of facial reanimation can be used for acute, intermediate, or chronic facial paralysis as these techniques are often important adjuncts to the overall management strategy. The best functional results are obtained with direct facial nerve anastomosis and interpositional nerve grafts. In long-standing facial paralysis, temporalis muscle transfer gives a dependable and quick result. Microvascular free tissue transfer is a reliable technique with reanimation potential whose results continue to improve as microsurgical expertise increases. Postoperative results can be improved with ancillary soft tissue procedures, as well as botulinum toxin.

Long-standing facial paralysis requires the introduction of viable, innervated dynamic muscle to restore facial movement. The options include regional muscle transfer and microvascular free tissue transfer. There are advantages and disadvantages of each. Briefly, the regional muscle transfer procedures are reliable and provide immediate return of movement. However, the movement is not of a spontaneous mimetic nature. Free tissue transfer, in contrast, offers the possibility of synchronous, mimetic movement. It does, however, require a prolonged healing time in comparison with that of regional muscle transfer. The choice is made by physician and patient together, taking into account their preferences and biases. Muscle-alone free tissue transfer is the our preferred option for reanimation of uncomplicated facial paralysis without skin or soft tissue deficits. Combined muscle and other tissue (most are skin flaps) is another preferred option for more challenging complex facial paralysis with skin or soft tissue deficits after tumor excision. Gracilis flap is the first choice of muscle transplantation for both reconstructions according to Mehta RP (2009).

From 1986 to 2006, gracilis functioning free muscle transplantation (FFMT) was performed by Mehta RP (2009) at Chang Gung Memorial Hospital for facial reanimation in 249 cases of facial paralysis. The main etiology was postoperative complication and Bell’s palsy. The innervating nerve came mostly from contralateral facial nerve branches, few from ipsilateral facial nerve due to tumor ablation, and from ipsilateral motor branch to masseter or spinal accessory nerve due to Möbius syndrome. Mehta RP had evolutionarily used a short nerve graft (10 to 15cm) to cross the face in the first stage; after a 6- to 9-month waiting period, gracilis FFMT was performed for the second stage of the reconstruction. The technique of evolution has shown encouraging results to achieve the goal of rapid restoration and fewer scars on the donor leg. In the modern era of evidence-based medicine, the field of facial nerve management has expanded exponentially with critical questions that will help future facial reanimation surgeons refine the approach for patients with acute and long-standing facial paralysis.

References
Obstructive sleep apnea (OSA) is characterized by repetitive nocturnal upper airway obstructions that are associated with sleep disruption and cyclic intermittent hypoxia (CIH). The cyclic oscillations in oxygen saturation are thought to contribute to cardiovascular and other morbidity but animal and patient studies of the pathogenic link between CIH and these diseases have been complicated by species differences and by the effects of confounding factors such as obesity, hypertension, and impaired glucose metabolism.

Sleep apnea has been investigated from various aspects for over 32 years since this concept was first proposed. Attention has been focused on the influence of sleep apnea on the circulatory system. It has been reported that sleep apnea is often associated with circulatory disorders and that it is related to hypertension, pulmonary hypertension, right heart failure, arrhythmias, cerebrovascular disease, and nocturnal sudden death.

Obstructive sleep apnea syndrome (OSAS), due to the collapse of the upper airways, is a common but still underestimated condition. The ‘dose-response’ type relationship between OSAS and hypertension (HT) has now been clearly proven. Therefore, blood pressure must be tested in every apneic patient, especially in those who are treated for obstructive sleep apnea. Several mechanisms explain the relationship, the main one being an increase in sympathetic activity during the apnea episodes. HT associated with OSAS has not been evidenced. Antihypertensive drugs do not change the respiratory parameters during OSAS [4]. Following obstructive apneas there is a transient uncoupling of coronary blood flow (CBF) from myocardial work and an increase in coronary vascular resistance (CVR). This disturbed flow–metabolic coupling may lead to nocturnal myocardial ischemia in patients with both OSA and coronary artery disease.

References
Obstructive sleep apnea (OSA) is characterized by repetitive episodes of upper airway occlusion during sleep. The pathogenesis of obstructive sleep apnea (OSA) has been under investigation for over 29 years, during which a number of factors that contribute to upper airway (UA) collapse during sleep have been identified.

In patients with sleep apnea hypopnea (SAH) volumetric MRI studies and computer-based analysis techniques permitted the objective quantification of the volume of the tongue, soft palate, parapharyngeal fat pads, and lateral pharyngeal walls. It has been demonstrated that the upper airway calibre reduction during sleep due to enlargement of the total soft tissue (tongue, uvula, tonsilar pillars, adenoids, soft palate, blood vessels, lymphoid tissue, pharyngeal fat pads, muscles and pharyngeal mucosa) is crucial to the development of OSA in many patients.

Enlargement of the soft tissues through hypertrophy, inflammation, or edema may decrease the diameter of the UA. Soft tissue edema is considered as largely responsible for this thickening, possibly resulting from inflammation. OSA has been shown to be associated with a variable degree of nasal inflammation, uvula mucosal congestion and airway hyperreactivity. The upper airway inflammation, whose clinical importance is uncertain, is characterised by leukocytes infiltration and interstitial oedema. In addition, recent data has shown the presence of neutrophilic infiltration in the lower airways. The current opinion is that airway inflammation is caused by the local, repeated mechanical trauma related to the intermittent airway occlusion typical of the disease. Another potential mechanism involves the intermittent nocturnal hypoxemia that through the phenomenon of the ischaemia-reperfusion injury may induce the production of oxygen free radicals and therefore cause local and systemic inflammation. Finally, a state of low-grade systemic inflammation may be related to obesity per se with the pro-inflammatory mediators synthesised in the visceral adipose cells. Several authors stress the role of circulating and local inflammatory mediators, such as pro-inflammatory cytokines, exhaled nitric oxide, pentane and 8-isoprostanate as the determinants of inflammation in OSA.

MRI studies have demonstrated increased soft tissue mass surrounding the UA and, hence, reduced UA size in the retropalatal and, to a lesser extent, the retroglottal area of OSA patients compared with control subjects. The larger the volumes of the lateral pharyngeal walls, tongue, and total soft tissue, the greater are the odds of OSA. Thickening of the lateral pharyngeal walls appears to be the predominant factor in OSA patients. The impairment of upper airway (UA) mechanoreceptor sensitivity and reflexes that maintain pharyngeal patency and respiratory control system instability, have also been identified as possible mechanisms facilitating UA instability. This suggests that OSA may be a heterogeneous disorder, rather than a single disease entity. Therefore, the extent to which various pathogenic factors contribute to the phenomenon of repetitive collapse of the UA during sleep probably varies from patient to patient. Further elucidation of specific pathogenic mechanisms in individuals with OSA may facilitate the development of new therapies that can be tailored to individual patient needs according to the underlying mechanisms of their disease. More easily and rapidly than MRI, acoustic pharyngometry can be used to assess the UA calibre and its change in OSA patients. Obstructive sleep apnea (OSA) is characterized by repetitive pharyngeal collapse during sleep. Increased intrinsic UA collapsibility that is generally observed in OSA patients is due to decreased transmural pressure and increased pharyngeal wall compliance. Continuous positive airway pressure (CPAP) provides a pulmonary splint for the nasopharyngeal airway and is a safe, simple treatment for the obstructive sleep apnoea syndrome. CPAP eliminates respiratory events and reduces sleepiness in OSA patients. The relative risk of having residual excessive sleepiness (RES) has been found to be 5.3 (95%CI 1.6-22.1), when Epworth Sleepiness Scale (ESS) score before treatment was >or=11. As 230,000 obstructive sleep apnoea patients are currently treated in France by continuous positive airway pressure, more than 13,800 of them might suffer from residual excessive sleepiness.

References