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Effect of Simvastatin on Transforming Growth Factor BETA-1-Induced Myofibroblast Differentiation and Collagen Production in Nasal Polyp-Derived Fibroblasts

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Background: Statins are the most commonly prescribed drugs for the treatment of hypercholesterolemia. Statins exert not only lipid-lowering but also other cellular effects, including anti-fibrotic properties. The purposes of this study were to determine the effect of simvastatin on Transforming growth factor (TGF)-β1-induced myofibroblast differentiation and collagen production in nasal polyp-derived fibroblasts (NPDFs) and to verify the mechanism of the effect of simvastatin in TGF-β1-induced myofibroblast differentiation in NPDFs.

Methods: NPDFs were pre-treated with simvastatin with or without mevalonate or Y-27632 for 2 hours prior to induction by TGF-β1. The expression of α-smooth muscle actin (SMA) and collagen type IV mRNA was determined by a reverse transcription-polymerase chain reaction, and the expression of α-SMA protein was determined by immunofluorescent cytochemical staining. Total soluble collagen production was analyzed by the SirCol collagen dye-binding assay. Phosphorylation of Smad 2/3 was evaluated by Western blot analysis.

Results: In TGF-β1-induced NPDFs, simvastatin significantly inhibited the expression of α-SMA and collagen type IV mRNA and reduced α-SMA and collagen protein levels. Pre-treatment with mevalonate reversed the effect of simvastatin. The expression of α-SMA mRNA and protein was significantly decreased by pre-treatment with Y-27632. The TGF-β1-induced expression of pSmad 2/3 protein was notably decreased by pre-treatment with simvastatin.

Conclusions: We showed that simvastatin inhibits TGF-β1-induced myofibroblast differentiation (expression of α-SMA) and collagen production in NPDFs and Rho/ROCK and TGF-β1/Smad signaling is involved as an underlying mechanism. The results of our study suggest that simvastatin is a possible candidate for the suppression of nasal polyp formation.

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A 26-Week Study Evaluating the Safety and Efficacy of Ciclesonide Hydrofluoralkane Nasal Aerolos in Subjects with Perennial Allergic Rhinitis

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Background: Ciclesonide hydrofluoralkane nasal aerosol (CIC-HFA) is currently in development as a potential treatment for allergic rhinitis. The objective of this study was to determine the long-term safety and efficacy of CIC-HFA compared to placebo in subjects with perennial allergic rhinitis (PAR).

Methods: Subjects ≥12 years of age with a ≥2 year history of PAR were randomized in a placebo-controlled, double-blind, parallel group, multicenter study to CIC-HFA 74 μg (N = 298), CIC-HFA 148 μg (N = 505), or placebo (N = 307) QD AM for 26 weeks. Subject-reported change from baseline in reflective total nasal symptom score (rTNSS) and instantaneous total nasal symptom score (iTNSS) averaged every 2 weeks over the 26 weeks of the treatment period were secondary endpoints and were calculated as a sum of the individual nasal symptoms of congestion, runny nose, sneezing, and nasal itching. Change from baseline in the individual reflective and instantaneous nasal symptom scores averaged every 2 weeks over the 26 weeks of treatment period were also evaluated. Treatment-emergent adverse events (TEAEs) were assessed throughout the study.

Results: CIC-HFA 74 μg and CIC-HFA 148 μg doses demonstrated improvement in rTNSS (LS mean change 0.65 & 0.52 respectively, P ≤ 0.01 for both), iTNSS (LS mean change 0.51 & 0.42 respectively, P ≤ 0.05 for both), and improvements in the individual reflective and instantaneous nasal symptoms (P ≤ 0.05 for all except instantaneous sneezing for the CIC-HFA 74 μg dose) at 26 weeks from baseline. P-values were adjusted for multiplicity. The overall incidence of TEAEs was comparable between the CIC-HFA treatment groups and placebo. The most frequently reported TEAEs (≥5% of subjects in any treatment group) were headache, nasopharyngitis, upper respiratory tract infections, viral upper respiratory tract infections, sinusitis, and epistaxis.

Conclusions: In this study, once-daily treatment with CIC-HFA 74 μg or CIC-HFA 148 μg demonstrated improvements in the nasal symptoms of PAR. Both active treatments were well tolerated.

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Omalizumab Improves Asthma but not Nasal Symptoms in Japanese Patients With Severe Allergic Asthma and Rhinitis

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Background: There is evidence that humanized monoclonal antibody against IgE (Omalizumab) is effective in severe allergic asthma. In this study, we examined the effectiveness of omalizumab on asthma and nasal symptoms in Japanese patients with severe allergic asthma and rhinitis.

Methods: An open-label study that enrolled 7 patients with both severe allergic asthma and rhinitis who visited Allergy Center, Saitama Medical University was performed. All patients presented uncontrolled asthma despite medication including high-dose inhalational corticosteroids, long-acting beta2-agonist, leukotriene receptor antagonist, theophylline, and oral prednisolone. Omalizumab was added on their treatments and symptoms score using Asthma Control Test (ACT), peak expiratory flow rate (PEFR), exhaled nitric oxide (eNO), sputum eosinophils and nasal symptoms were evaluated before and 12 to 16 weeks after omalizumab.

Results: Omalizumab significantly improved ACT scores especially dose of rescue use of short-acting beta2-agonist (P < 0.05) and PEFR (P < 0.05). Furthermore, omalizumab significantly decreased exhaled both eNO (P < 0.05) and the percentage of eosinophils in induced sputum. On the other hand, nasal symptoms were not change following induction of omalizumab.

Conclusions: Clinical effectiveness of omalizumab was confirmed in Japanese population of severe allergic asthma, but not rhinitis. The therapeutic potency of omalizumab on asthma likely involves anti-inflammatory properties such as decreasing eNO or airway eosinophilia.

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Economic Evaluation of Grass Tablets for Immunotherapy (oral) Compared to Placebo in Adults and Children in Italy

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Diseases. Universita Degli Studi Di Genova, Genoa, Italy; 6Department of Medical and Surgical Specialties and Public Health, Perugia, Perugia, Italy. **Background:** Specific immunotherapy is based on the regular administration over time of a maintenance dose of allergen extracts to allergic patients in order to modify the immune response, thus achieving a decrease in symptoms/drug intake and an improvement in quality of life, possibly on the long-term. Grass pollen tablet, Oralair (Stallergenes, Antony Cedex, France), were developed and registered for rhinoconjunctivitis allergy induced by grass pollen. There is sufficient evidence for the clinical efficacy of the product, but pharmacoeconomy data are lacking.

**Methods:** An economic analysis, using a rescue medication adjusted score (AASS) was performed, based on the available registration trials—to assess the magnitude of Oralair effect if patients had not taken any rescue medication. In the present study the results of an adult and a pediatric study are pooled together with economic data in order to perform a cost-effectiveness analysis from the third party payer perspective. Medical visits, diagnostic exams, skin prick test, and drugs were valorized in euros according to the National tariffs and the standard drug prices in the Italian setting. The estimated ROC also enabled us to quantify the effectiveness in terms of Quality Adjusted Life Years (QALY). A decision tree was structured in order to model possible outcomes and costs, according to a low, moderate and high AASS in adults and pediatric patients. A probabilistic sensitivity analysis was finally conducted to test the robustness of the results as well as the consistency with an assumed cost effectiveness threshold of euros 30,000/QALY.

**Results:** The results showed a relative difference of 1.84 in favor of the active treatment versus placebo in absolute value in adult study and of 1.64 in pediatric study. The results also show how the Oralair administration costs 1024 euro/QALY with high and moderate AASS. Including also the loss of productivity the incremental cost-effectiveness ratio (ICER) in adults is 700 euro/QALY. The 95% of the simulation performed by sensitivity analysis shows an ICER below the threshold of 30,000 euro/QALY.

**Conclusions:** In conclusion our results show that Oralair grass tablet is a cost effective strategy in adults and pediatric patients with moderate and severe AASS.

**SUBLINGUAL IMMUNOTHERAPY 1**

157 The Post-Treatment Efficacy of House Dust Mite Sublingual Allergen Immunotherapy Tablets in Adults With Allergic Rhinitis Karl-Christian Bergmann, MD, 1 Pascal Demoly, MD, PhD, 2 Margitta Wong, 1,3 Wystieck Fokkens, 2 Tabar Ann, 1 Nguyen Helene, 1 Olivier de Beaumont, 6 Michel Melac, 3 Marine Freux, 2 and Robert K Zeldin 6, 1 Allergy-Centre-Charité, Charité - Universitätsmedizin Berlin, Berlin, Germany; 2 Allergy, University Hospital of Montpellier, Montpellier, France; 3 Dermatology, Charité University Clinic, Berlin, Germany; 5 Department of Otorhinolaryngology, AMC, Amsterdam, Netherlands; 6 Department of Allergy, Complejo Hospitalario de Navarra, Pamplona, Spain; 7 Stallergenes SA, Antony, France.

**Background:** The efficacy and safety of 2 doses of sublingual allergen immunotherapy house dust mite (HDM) tablets administered for 12 months were demonstrated in a randomized, double-blind, placebo-controlled study of adults suffering from HDM-related allergic rhinitis. Here we report the efficacy during the 12-month, treatment-free, follow-up period.

**Methods:** Of the 509 patients randomized, 412 were included in the year 2 full analysis set (500 IR = 132, 300 IR = 134, Placebo = 146). The primary efficacy variable was the Average Adjusted Symptom Score (AAdSS, scale 0–12) an average of the daily score based on the severity of 4 rhinitis symptoms (sneezing, rhinorrhea, nasal pruritus and nasal congestion) and adjusted for rescue medication usage. The AAdSS was analyzed, at the end of the post-treatment period, using an ANCOVA and at 3, 6, 8 and 12 months after treatment cessation in a secondary analysis, using repeated measures ANCOVA.

**Results:** At the end of the post-treatment period, the 500 IR group showed a significant improvement in AAdSS vs. placebo ($P = 0.021$) with a LS Means difference of $-0.70$ (95% CI [–1.29, –0.11]), corresponding to $-19.1$%. The LS Means difference of $-0.62$ (95% CI [–1.20, –0.05]) between the 300 IR and placebo groups was also significant ($P = 0.034$), corresponding to $-17.0$%. The difference between the active treatment groups was not statistically significant. Eight months after treatment cessation, which corresponds to the autumn peak in HDM, the relative LS mean difference was $-20.9$% ($P = 0.0079$) for the 500 IR and was $-25.5$% ($P = 0.0011$) for the 300 IR group.

**Conclusions:** During the 12-month post-treatment period, house dust mite sublingual immunotherapy tablets at doses of 500 IR and 300 IR provided sustained symptom relief, demonstrating their efficacy after treatment cessation.

158 Efficacy of Immunotherapy with an Oral Bacterial Lysate and Vitamin C in the Primary Prevention of Acute Respiratory Tract Infections in Children Miguel Socci, MD, Pablo Shullitel, MD, and Luciano Cortigiani, MD. Sociedad Argentina de Alergia e Immunologia, SanJusto, Argentina.

**Background:** Airway infections are of great importance worldwide and nearly half of the pediatric consultations in industrialized countries are caused by respiratory tract infections (RTIs). Acute respiratory tract infections (ARTIs) are among the main causes of morbidity and mortality in children and recurrent infections of the respiratory tract are the most frequent cause of pharmacotherapy in pediatric practice. The aim of this study was to evaluate the efficacy and tolerability of immunotherapy with oral bacterial lysates + vitamin C in the prevention of ARTIs in children.

**Methods:** 109 children with ages between 4 and 16 years with frequent respiratory tract infections (2–5 infections the previous winter) were evaluated. Participants were randomly allocated in 2 groups: 52 patients (mean age 6.8 ± 2.9 years; 20 males 32 females) received no preventive therapy (NPT group) and 57 (mean age 9.0 ± 3.3 years; males 36 females 21) received immunotherapy with oral bacterial lysates + vitamin C (VC group) at the recommended dosage. Patients were followed up for 6 months, including the administration period. Primary end points were the type and number of ARTIs. Secondary end points (after the infection occurred) included: time to clinical cure, severity of infection, absenteeism from school due to an ARTI, number of antibiotic courses or other drugs prescribed, and duration of concomitant drug treatment.

**Results:** There were significant differences between groups in the cumulative number of acute infectious episodes: 170 in NPT group (141 upper ARTIs, 29 lower ARTI, and 26 otitis episodes) vs 55 in VC group (50 upper ARTIs, 5 lower ARTI and 4 otitis episodes). Patients in the NPT group received 127 antibiotic courses compared to 28 in the VC group ($P < 0.0001$). Patients in the NPT group had 475 days of absenteeism from school compared to 100 days in the VC group ($P < 0.0001$). No adverse events related to the trial medications were reported.

**Conclusions:** Immunotherapy with oral bacterial lysates and vitamin C appears to be very effective in the prevention of infectious episodes in pediatric patients with frequent respiratory tract infections. Future studies are needed to further explore the role of oral bacterial lysates in ARTIs prevention.

**SUBLINGUAL IMMUNOTHERAPY 2**

159 Therapeutic Effect and Safety of the Sublingual Immunotherapy With Tropical House Dust Mite Allergen Vaccines in Asthmatic Cuban Adult Patients Raúl Lázaro Castro Almarares, MD, 1 Mercedes Ronquillo, MD, 2 Alexis Labrada, PhD, 3 Mirta Alvarez Castello, MD, 4 Mayda González, MD, 3 José Rodríguez, MD, 6 Irene Enriquez, MD, 6 Bárbara I Navarro Vilas, MD, 7 Yunia Oliva DiazLic, 8 and Maytee Mateo 8, 7 National Center