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Act. 329 CTOINFORMACION Folios: 32

REF: Expediente 07-079-737

TÍTULO SOLICITADO: COMBINACIÓN SINÉRGICA DE XOLAIR/
OMALIZUMAB/E25 CON AGENTE
INMUNOSUPRESOR.

PUBLICACIÓN: Gaceta: 592 de 30/05/2008, N° de publicación: 390.

PRIORIDAD: GB 0502358.5 de 04/02/2005

SOLICITANTE: NOVARTIS AG.

APODERADO: CARLOS R. OLARTE.

TRÁMITE: SUSTENTACION DE OPOSICIÓN

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, obrando en calidad de apoderado de la sociedad **LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A.**, dentro del trámite de la referencia, en ejercicio de lo dispuesto por el artículo 42 inciso 2° de la Decisión 486 de 2000, por medio del presente escrito, procedo a sustentar la oposición presentada oportunamente ante ese Despacho, en los siguientes términos:

I. COMPLEMENTO DE INFORMACIÓN

Comendidamente me permito presentar los argumentos que demuestran que la solicitud de la referencia incumple los requisitos de patentabilidad establecidos por los artículos 14, 16, 18 y 20 literal d) de la Decisión 486 de 2000, y que por ello no merece recibir el beneficio patentario.

La solicitud colombiana **07-079-737** que reivindica una composición farmacéutica que comprende como ingredientes activos, un anticuerpo anti-IgE (Omalizumab) y cuando menos un agente inmunosupresor, en donde los ingredientes activos están presentes en cada caso en forma libre o en la forma de una sal farmacéuticamente aceptable, y opcionalmente cuando menos un vehículo farmacéuticamente aceptable para su uso simultaneo, separado o secuencial, carece de novedad y nivel inventivo como se argumenta a continuación:

➤ En primer término, existen diversas publicaciones de carácter científico que exponen la utilidad de Omalizumab en el tratamiento de trastornos alérgicos, veamos:

✓ **Omalizumab Improves Asthma-Related Quality Of Life In Patients With Severe Allergic Asthma¹.**

Abstract: BACKGROUND: We have previously shown that omalizumab, a recombinant humanized monoclonal anti-IgE antibody, reduces asthma exacerbations and decreases inhaled corticosteroid (ICS) requirement in patients with severe allergic asthma who were symptomatic despite moderate-to-high doses of ICSs. OBJECTIVE: The aim of the present study was to assess the effects of omalizumab on asthma-related quality of life (QOL). METHODS: These analyses were part of a multicenter, 52-week, randomized, double-blind, placebo-controlled study assessing the efficacy, safety, and tolerability of subcutaneous omalizumab (> or =0.016 mg/kg of IgE [in international unit per milliliter] per 4 weeks) in 525 adults with severe allergic asthma. A 16-week steroid-stable phase was followed by a 12-week steroid-reduction phase and a 24-week double-blind extension phase. The effect of treatment on asthma-related QOL was evaluated by using the Asthma Quality of Life Questionnaire (AQLQ) administered at baseline and at weeks 16, 28, and 52. RESULTS: The 2 treatment groups were comparable in terms of baseline AQLQ scores. At weeks 16, 28, and 52, omalizumab-treated patients demonstrated statistically significant improvements across all AQLQ domains, as well as in overall score. Moreover, a greater proportion of patients receiving omalizumab achieved a clinically meaningful improvement in asthma-related QOL during each phase of the study. Greater than 50% of both patients and investigators rated treatment similarly with omalizumab as excellent or good compared with less than 40% of placebo recipients. CONCLUSION: In patients requiring moderate-to-high doses of ICSs for severe allergic asthma, the measurably improved disease control afforded by add-on omalizumab therapy is paralleled by clinically meaningful improvements in asthma-related QOL.

✓ **Efficacy And Tolerability Of Anti-Immunoglobulin E Therapy With Omalizumab In Patients With Poorly Controlled (Moderate-To-Severe) Allergic Asthma².**

Abstract: BACKGROUND: Patients with poorly controlled asthma have greater morbidity and mortality. This study evaluated the efficacy and tolerability of

¹ Finn A, Gross G, van Bavel J, Lee T, Windom H, Everhard F, Fowler-Taylor A, Liu J, Gupta N. J Allergy Clin Immunol. 2003 Feb;111(2):278-84.
² Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H. Allergy. 2004 Jul;59(7):701-8.

omalizumab in patients with poorly controlled, moderate-to-severe allergic asthma.

METHODS: This was a randomized, open-label, multicentre, parallel-group study. A total of 312 patients (12-73 years) receiving ≥ 400 microg/day (adolescent) or ≥ 800 microg/day (adult) inhaled beclomethasone dipropionate, or equivalent were included. Patients received best standard care (BSC) with or without omalizumab [at least 0.016 mg/kg/IgE (IU/ml) every 4 weeks] for 12 months. **RESULTS:** The annualized mean number of asthma deterioration-related incidents was reduced from 9.76 with BSC alone ($n = 106$) to 4.92 per patient-year with omalizumab ($n = 206$) ($P < 0.001$). Mean clinically significant asthma exacerbation rates were 2.86 and 1.12 per patient-year, respectively ($P < 0.001$). Omalizumab-treated patients (41.4%) required rescue medication < 1 day/week compared with 20.7% for BSC alone ($P < 0.001$). Omalizumab improved absolute forced expiratory volume in 1 s (FEV(1)) compared with BSC alone (2.48 and 2.28 l, respectively; $P < 0.05$) and reduced symptom scores relative to BSC alone (decrease of 6.5 and 0.7 respectively; $P < 0.001$). Omalizumab was well-tolerated. **CONCLUSIONS:** Omalizumab administered as add-on therapy to BSC benefits patients with poorly controlled, moderate-to-severe allergic asthma.

✓ The Anti-IgE Antibody Omalizumab Reduces Exacerbations And Steroid Requirement In Allergic Asthmatics³.

Abstract: The clinical benefit and steroid-sparing effect of treatment with the anti-immunoglobulin-E (IgE) antibody, omalizumab, was assessed in patients with moderate-to-severe allergic asthma. After a run-in period, 546 allergic asthmatics (aged 12-76 yrs), symptomatic despite inhaled corticosteroids (500-1,200 microg daily of beclomethasone dipropionate), were randomized to receive double-blind either placebo or omalizumab every 2 or 4 weeks (depending on body weight and serum total IgE) subcutaneously for 7 months. A constant beclomethasone dose was maintained during a 16-week stable-steroid phase and progressively reduced to the lowest dose required for asthma control over the following 8 weeks. The latter dose was maintained for the next 4 weeks. Asthma exacerbations represented the primary variable. Compared to the placebo group, the omalizumab group showed 58% fewer exacerbations per patient during the stable-steroid phase ($p < 0.001$). During the steroid-reduction phase, there were 52% fewer exacerbations in the omalizumab group versus the placebo group ($p < 0.001$) despite the greater reduction of the beclomethasone dosage on omalizumab ($p < 0.001$). Treatment with omalizumab was well tolerated. The incidence of adverse events was similar in both groups. These results indicate that omalizumab therapy safely improves asthma control in allergic asthmatics who remain symptomatic despite regular use of inhaled corticosteroids and simultaneous reduction in corticosteroid requirement.

✓ Omalizumab, Anti-IgE Recombinant Humanized Monoclonal Antibody, For The Treatment Of Severe Allergic Asthma⁴.

³ Solèr M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, Thirlwell J, Gupta N, Della Cioppa G. Eur Respir J. 2001 Aug;18(2):254-61.

⁴ Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, van As A, Gupta N. J Allergy Clin Immunol. 2001 Aug;108(2):184-90.

Abstract: BACKGROUND: A recombinant humanized anti-IgE mAb, omalizumab, forms complexes with free IgE, blocking its interaction with mast cells and basophils; as a consequence, it might be effective in the treatment of asthma. OBJECTIVE: The purpose of this study was to evaluate the efficacy and safety of omalizumab in the treatment of inhaled corticosteroid-dependent asthma. METHODS: In this phase III, double-blinded, placebo-controlled trial, 525 subjects with severe allergic asthma requiring daily inhaled corticosteroids were randomized to receive placebo or omalizumab subcutaneously every 2 or 4 weeks, depending on baseline IgE level and body weight. Inhaled corticosteroid doses were kept stable over the initial 16 weeks of treatment and tapered during a further 12-week treatment period. RESULTS: Omalizumab treatment resulted in significantly fewer asthma exacerbations per subject and in lower percentages of subjects experiencing an exacerbation than placebo treatment during the stable steroid phase (0.28 vs 0.54 [P =.006] and 14.6% vs 23.3% [P =.009], respectively) and during the steroid reduction phase (0.39 vs 0.66 [P =.003] and 21.3% vs 32.3% [P =.004], respectively). Beclomethasone dipropionate reduction was significantly greater with omalizumab treatment than with placebo (median 75% vs 50% [P <.001]), and beclomethasone dipropionate discontinuation was more likely with omalizumab (39.6% vs 19.1% [P <.001]). Improvements in asthma symptoms and pulmonary function occurred along with a reduction in rescue beta-agonist use. Omalizumab was well tolerated, with an adverse-events profile similar to that of placebo. CONCLUSION: The addition of omalizumab to standard asthma therapy reduces asthma exacerbations and decreases inhaled corticosteroid and rescue medication use.

✓ Effect Of Omalizumab On Symptoms Of Seasonal Allergic Rhinitis⁵.

Abstract: Context: Seasonal allergic rhinitis is a common IgE-mediated disorder that produces troublesome symptoms. A recombinant humanized monoclonal anti-IgE antibody (omalizumab) forms complexes with free IgE, blocking its interaction with mast cells and basophils and lowering free IgE levels in the circulation. Objective: To assess the efficacy and safety of omalizumab for prophylaxis of symptoms in patients with seasonal allergic rhinitis. Design: Randomized, double-blind, dose-ranging, placebo-controlled trial conducted from July 25 through November 21, 1997. Setting: Twenty-five outpatient centers throughout the United States. Patients: Five hundred thirty-six patients aged 12 to 75 years with at least a 2-year history of moderate to severe ragweed-induced seasonal allergic rhinitis and a baseline IgE level between 30 and 700 IU/mL. Interventions Patients: were randomly assigned to receive omalizumab, 50 mg (n = 137), 150 mg (n = 134), or 300 mg (n = 129), or placebo (n = 136) subcutaneously just prior to ragweed season and repeated during the pollen season every 3 weeks in patients with baseline IgE levels of 151 to 700 IU/mL (4 total treatments) and every 4 weeks in patients with baseline IgE levels of 30 to 150 IU/mL (3 total treatments). Main Outcome Measures: Self-assessed daily nasal symptom

⁵ Thomas B. Casale, MD; John Condemi, MD; Craig LaForce, MD; Anjuli Nayak, MD; Michael Rowe, MD; Marc Watrous, PhD; Margaret McAlary, MS; Angel Fowler-Taylor, RPh; Amy Racine, PhD; Niroo Gupta, MD, PhD; Robert Fick, MD; Giovanni Della Cioppa, MD; for the Omalizumab Seasonal Allergic Rhinitis Trial Group. JAMA. 2001;286:2956-2967. Vol. 286 No. 23, December 19, 2001.

severity scores (range, 0-3), rescue antihistamine use, and rhinitis-specific quality of life during the 12 weeks from the start of treatment. Results: Nasal symptom severity scores were significantly lower in patients who received 300 mg of omalizumab than in those who received placebo (least squares means, 0.75 vs 0.98, respectively; $P = .002$). A significant association was observed between IgE reduction and nasal symptoms and rescue antihistamine use. Rhinitis-specific quality of life scores were consistently better in patients who received 300 mg of omalizumab than in those who received lower dosages or placebo and did not decline during peak season. The frequency of adverse events was not significantly different among the omalizumab and placebo groups. Conclusion: Omalizumab decreased serum free IgE levels and provided clinical benefit in a dose-dependent fashion in patients with seasonal allergic rhinitis.

Es evidente que en estos documentos se evalúa y se demuestra el efecto terapéutico que tiene Omalizumab sobre trastornos alérgicos, específicamente sobre Asma y Rinitis; una persona medianamente versada en la materia reconociendo el mecanismo de acción y la acción terapéutica comprobada de dicho anticuerpo, fácilmente podría llegar a la conclusión de que combinando Omalizumab con agentes inmunosupresores, podría obtenerse un tratamiento efectivo para este tipo de trastornos alérgicos. Lo anterior también se pone en evidencia en algunos de los artículos científicos mencionados anteriormente, donde se demuestra que el uso concomitante de Omalizumab con corticosteroides, reduce la cantidad necesaria de dichos agentes antiinflamatorios (también con características inmunosupresoras) en pacientes asmáticos. En otras palabras, la solicitud colombiana en trámite carece de nivel inventivo, puesto que para cualquier persona medianamente versada en la materia resultaría obvia la combinación farmacológica entre Omalizumab con agentes inmunosupresores para el tratamiento de trastornos de carácter alérgico.

➤ En el mismo sentido, existen documentos que revelan con anterioridad este tipo de combinaciones farmacológicas en formulaciones farmacéuticas útiles para el tratamiento de los mismos trastornos reivindicados por la solicitud colombiana en trámite, veamos:

- La publicación internacional WO 03/057249 publicada el 17 de Julio de 2003 y titulada "COMBINATION TREATMENTS FOR ALLERGIC DISEASE COMPRISING ADMINISTERING AN ANTI-IGE ANTIBODY AND ANTIALLERGIC COMPOUND" revela:

1. A pharmaceutical composition comprising as active ingredients an anti-IgE antibody and at least one further antiallergic compound selected from the group consisting of anti-inflammatory agents, leukotriene modifiers, bronchodilators, antihistamines, interleukin antagonists, mast cell inhibitors, and immunotherapeutical agents, in which the active ingredients are present in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

(...)

3. The composition according to claims 1 or 2 wherein the anti-IgE antibody is Omalizumab.

4. The composition according to claim 3, characterized in that Omalizumab is administered in a concentration dependent on the baseline IgE level of the patient to be treated.

(...)

7. The composition according to claim 6, characterized in that the immunotherapeutical agent is a macrolide T-cell immunomodulator or immunosuppressant.

(...)

13. The composition according to claim 12 wherein the anti-IgE antibody and antiallergic compound are present in respective amounts which are jointly therapeutically effective against asthma.

(...)

28. Use of the composition according to any one of claims 1 to 13 for the prevention or treatment of allergic disease.

Como se puede apreciar claramente, en esta anterioridad se revelan formulaciones farmacéuticas que contienen una combinación entre un **anticuerpo Anti-IgE** -específicamente Omalizumab-, junto con **agentes inmunosupresores** útiles para el tratamiento de trastornos alérgicos -específicamente asma-, y que pueden ser administrados separados o secuencialmente. Así mismo la administración de dichas formulaciones se hace en una concentración dependiente del nivel de IgE de la línea base del paciente a tratar, de la misma manera que lo reivindica la solicitud colombiana en su reivindicación 9.

- Por su parte la patente americana US 6,723,833 publicada el 20 de Abril de 2004 y titulada "THERAPEUTIC COMPOSITIONS COMPRISING ANTI-IGE ANTIBODIES AND IMMUNOSUPPRESSIVE AGENT" revela:

1. A composition of an improved anti-IgE antibody or IgE binding fragment thereof in combination with an adjunct immunosuppressive agent, wherein the improved anti-IgE antibody or IgE binding fragment thereof comprises:

- (a) the heavy and light chains of E26 (SEQ ID NOs:15-16);
- (b) the heavy and light chains of E27 (SEQ ID NOs:17-18); or
- (c) antigen binding fragments of (a) or (b).

2. The composition of claim 1, wherein the immunosuppressive agent is selected from the group consisting of azathioprine, cyclophosphamide, bromocryptine and glutaraldehyde.

3. The composition of claim 1, wherein the immunosuppressive agent is a glucocorticosteroid.

4. The composition of claim 1, wherein the immunosuppressive agent is selected from the group consisting of: cyclosporin A; an anti-CD3 antibody; an anti-CD4 antibody and an anti-CD4a antibody.

5. The composition of claim 1, wherein the immunosuppressive agent is selected from the group consisting of: a soluble peptide containing an LFA-3 binding domain; streptokinase; TGF- β ; streptodornase; deoxyspergualin, rapamycin and a T-cell receptor.

6. The composition of claim 1, wherein the improved anti-IgE antibody comprises the heavy and light chain sequences of E26 (SEQ ID NOs:15-16).

7. The composition of claim 1, wherein the improved IgE binding fragment comprises an E26 sequence selected from the group consisting of: an Fab fragment (SEQ ID NOs:19-20); an sFv fragment (SEQ ID NO:22) and an F(ab')₂ fragment (SEQ ID NOs: 24-25).

8. The composition of claim 1, wherein the improved IgE binding fragment comprises an E27 sequence selected from the group consisting of: an Fab fragment (SEQ ID NOs: 19 and 21); an sFv fragment (SEQ ID NO:23) and an F(ab')₂ fragment (SEQ ID NOs: 24 and 26).

9. The composition of claim 1, wherein the improved anti-IgE antibody comprises the heavy and light chains of E27 (SEQ ID NOs: 17-18).

10. The composition of claim 1, wherein the immunosuppressive agent is a 2-amino-5-aryl-substituted pyrimidine.

Por su parte, esta anterioridad revela formulaciones farmacéuticas que contienen una combinación entre un anticuerpo Anti-IgE y diversos agentes inmunosupresores, dentro de los cuales se encuentran varios de los reivindicados por la solicitud colombiana.

En otras palabras, estas dos anterioridades demuestran irrefutablemente la falta de novedad de la solicitud colombiana en trámite, ya que revelan las características esenciales que sustentan la invención de dicha solicitud, como es: una composición farmacéutica que comprende un anticuerpo anti-IgE y al menos un agente inmunosupresor adicional y un vehículo adecuado para su administración ya sea simultánea, separada o secuencial.

➤ Por ultimo, pero no por esto menos importante, y ante una revelación textual del uso de la combinación farmacológica entre un anticuerpo anti-IgE y agentes inmunosupresores en el tratamiento de un trastorno de carácter alérgico, tales como asma, es necesario resaltar que dicha revelación es inaceptable a la luz de la Decisión 486.

En efecto, a la luz de la normativa subregional resulta inaceptable pretender atribuirse exclusiva sobre un "Uso", categoría no incluida en el concepto de "Productos o Procedimientos" que establece el artículo 14 de la Decisión 486 de 2000. Lo anterior, además, en consonancia con la reiterada interpretación de la SIC sobre este punto.

Sin perjuicio de lo anterior me permito hacer notar que aún si los usos o métodos terapéuticos fueran permitidos en nuestro medio, éstos deberían cumplir necesariamente con los requisitos materiales de patentabilidad, novedad, nivel Inventivo y Aplicación Industrial.

Aunque a la ausencia de ellos nos hemos referido ya, cabe desde ahora anotar que el último resulta de imposible cumplimiento, en tanto la reproducción industrial del uso separado, combinado o secuencial de medicamentos para tratar ciertas patologías es del resorte de la profesión médica y no de las actividades industriales.

En el mismo sentido, también es relevante resaltar que la solicitud colombiana en trámite, no solo carece de novedad y de nivel inventivo como se ha demostrado con los argumentos anteriores, sino que además incurre en una improcedencia directa de patentabilidad dado el hecho que en su capítulo reivindicatorio, específicamente en sus reivindicaciones 7 y 12 a 15, describe un método

terapéutico, lo cual es inaceptable a la luz de la Decisión 486 del año 2000 la cual expone explícitamente en su artículo 20 literal d) que *“No serán patentables (...) Los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales.”*

Por todo lo anterior reitero que la solicitud de la referencia, en todas sus reivindicaciones, incumple los requisitos materiales de patentabilidad establecidos por la Decisión 486 de 2000, razón por la cual no puede ser objeto de privilegio de patente de invención.

VI. ANEXOS

- Abstracts de todas las publicaciones científicas mencionadas en el acápite de Complemento de Información.
- La publicación internacional WO 03/057249 publicada el 17 de Julio de 2003 y titulada “COMBINATION TREATMENTS FOR ALLERGIC DISEASE COMPRISING ADMINISTERING AN ANTI-IGE ANTIBODY AND ANTIALLERGIC COMPOUND” capítulo reivindicatorio.
- La patente americana US 6723833 publicada el 20 de Abril de 2004 y titulada “THERAPEUTIC COMPOSITIONS COMPRISING ANTI-IGE ANTIBODIES AND IMMUNOSUPPRESSIVE AGENT” capítulo reivindicatorio.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

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[All: 1](#) [Review: 0](#)☐ 1: J Allergy Clin Immunol. 2003 Feb;111(2):278-84. [Click here to read](#) [Links](#)**Omalizumab improves asthma-related quality of life in patients with severe allergic asthma.****Finn A, Gross G, van Bavel J, Lee T, Windom H, Everhard F, Fowler-Taylor A, Liu J, Gupta N.**

National Allergy, Asthma and Urticaria Centers of Charleston, Charleston, South Carolina, USA.

BACKGROUND: We have previously shown that omalizumab, a recombinant humanized monoclonal anti-IgE antibody, reduces asthma exacerbations and decreases inhaled corticosteroid (ICS) requirement in patients with severe allergic asthma who were symptomatic despite moderate-to-high doses of ICSs.

OBJECTIVE: The aim of the present study was to assess the effects of omalizumab on asthma-related quality of life (QOL). **METHODS:** These analyses were part of a multicenter, 52-week, randomized, double-blind, placebo-controlled study assessing the efficacy, safety, and tolerability of subcutaneous omalizumab ($>$ or $=0.016$ mg/kg of IgE [in international unit per milliliter] per 4 weeks) in 525 adults with severe allergic asthma. A 16-week steroid-stable phase was followed by a 12-week steroid-reduction phase and a 24-week double-blind extension phase. The effect of treatment on asthma-related QOL was evaluated by using the Asthma Quality of Life Questionnaire (AQLQ) administered at baseline and at weeks 16, 28, and 52. **RESULTS:** The 2 treatment groups were comparable in terms of baseline AQLQ scores. At weeks 16, 28, and 52, omalizumab-treated patients demonstrated statistically significant improvements across all AQLQ domains, as well as in overall score. Moreover, a greater proportion of patients receiving omalizumab achieved a clinically meaningful improvement in asthma-related QOL during each phase of the study. Greater than 50% of both patients and investigators rated treatment similarly with omalizumab as excellent or good compared with less than 40% of placebo recipients. **CONCLUSION:** In patients requiring moderate-to-high doses of ICSs for severe allergic asthma, the measurably improved disease control afforded by add-on omalizumab therapy is paralleled by clinically meaningful improvements in asthma-related QOL.

PMID: 12589345 [PubMed - indexed for MEDLINE]

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The anti-IgE antibody omalizumab improves asthma-related quality of life in patients with allergic asthma. [Allergy. 2002]

Omalizumab improves asthma-related quality of life in children with allergic asthma. [Pediatrics. 2002]

Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). [Pediatrics. 2001]

Review Spotlight on omalizumab in allergic asthma. [BioDrugs. 2004]

Review Omalizumab: a review of its use in the management of allergic asthma. [Treat Respir Med. 2004]

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Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with poorly controlled (moderate-to-severe) allergic asthma.**Ayres JG, Higgins B, Chilvers ER, Ayre G, Blogg M, Fox H.**

Department of Environmental and Occupational Medicine, Liberty Safe Work Research Centre, Aberdeen, UK.

BACKGROUND: Patients with poorly controlled asthma have greater morbidity and mortality. This study evaluated the efficacy and tolerability of omalizumab in patients with poorly controlled, moderate-to-severe allergic asthma. **METHODS:** This was a randomized, open-label, multicentre, parallel-group study. A total of 312 patients (12-73 years) receiving ≥ 400 microg/day (adolescent) or ≥ 800 microg/day (adult) inhaled beclomethasone dipropionate, or equivalent were included. Patients received best standard care (BSC) with or without omalizumab [at least 0.016 mg/kg/IgE (IU/ml) every 4 weeks] for 12 months. **RESULTS:** The annualized mean number of asthma deterioration-related incidents was reduced from 9.76 with BSC alone ($n = 106$) to 4.92 per patient-year with omalizumab ($n = 206$) ($P < 0.001$). Mean clinically significant asthma exacerbation rates were 2.86 and 1.12 per patient-year, respectively ($P < 0.001$). Omalizumab-treated patients (41.4%) required rescue medication < 1 day/week compared with 20.7% for BSC alone ($P < 0.001$). Omalizumab improved absolute forced expiratory volume in 1 s (FEV(1)) compared with BSC alone (2.48 and 2.28 l, respectively; $P < 0.05$) and reduced symptom scores relative to BSC alone (decrease of 6.5 and 0.7 respectively; $P < 0.001$). Omalizumab was well-tolerated. **CONCLUSIONS:** Omalizumab administered as add-on therapy to BSC benefits patients with poorly controlled, moderate-to-severe allergic asthma.

PMID: 15180756 [PubMed - indexed for MEDLINE]

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Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. [Allergy. 2004]

Efficacy and safety of a recombinant anti-immunoglobulin E antibody (omalizumab) in severe allergic asthma. [Allergy. 2004]

Benefits of omalizumab as add-on therapy in patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. [Allergy. 2005]

Review Spotlight on omalizumab in allergic asthma. [BioDrugs. 2004]

Review Anti-IgE for chronic asthma in adults and children. [Cochrane Database Syst Rev. 2006]

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Eur Respir J. 2001 Aug;18(2):249-50.

The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics.

Solèr M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, Thirlwell J, Gupta N, Della Cioppa G.

Pulmonary Division, University Hospital, Basel, Switzerland.

The clinical benefit and steroid-sparing effect of treatment with the anti-immunoglobulin-E (IgE) antibody, omalizumab, was assessed in patients with moderate-to-severe allergic asthma. After a run-in period, 546 allergic asthmatics (aged 12-76 yrs), symptomatic despite inhaled corticosteroids (500-1,200 microg daily of beclomethasone dipropionate), were randomized to receive double-blind either placebo or omalizumab every 2 or 4 weeks (depending on body weight and serum total IgE) subcutaneously for 7 months. A constant beclomethasone dose was maintained during a 16-week stable-steroid phase and progressively reduced to the lowest dose required for asthma control over the following 8 weeks. The latter dose was maintained for the next 4 weeks. Asthma exacerbations represented the primary variable. Compared to the placebo group, the omalizumab group showed 58% fewer exacerbations per patient during the stable-steroid phase ($p < 0.001$). During the steroid-reduction phase, there were 52% fewer exacerbations in the omalizumab group versus the placebo group ($p < 0.001$) despite the greater reduction of the beclomethasone dosage on omalizumab ($p < 0.001$). Treatment with omalizumab was well tolerated. The incidence of adverse events was similar in both groups. These results indicate that omalizumab therapy safely improves asthma control in allergic asthmatics who remain symptomatic despite regular use of inhaled corticosteroids and simultaneous reduction in corticosteroid requirement.

PMID: 11529281 [PubMed - indexed for MEDLINE]

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Treatment of childhood asthma with anti-immunoglobulin E antibody (omalizumab). [Pediatrics. 2001]

Exhaled nitric oxide in children with asthma receiving Xolair (omalizumab), a monoclonal anti-immunoglobulin E antibody. [Pediatrics. 2004]

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Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma.

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BACKGROUND: A recombinant humanized anti-IgE mAb, omalizumab, forms complexes with free IgE, blocking its interaction with mast cells and basophils; as a consequence, it might be effective in the treatment of asthma. **OBJECTIVE:** The purpose of this study was to evaluate the efficacy and safety of omalizumab in the treatment of inhaled corticosteroid-dependent asthma. **METHODS:** In this phase III, double-blinded, placebo-controlled trial, 525 subjects with severe allergic asthma requiring daily inhaled corticosteroids were randomized to receive placebo or omalizumab subcutaneously every 2 or 4 weeks, depending on baseline IgE level and body weight. Inhaled corticosteroid doses were kept stable over the initial 16 weeks of treatment and tapered during a further 12-week treatment period. **RESULTS:** Omalizumab treatment resulted in significantly fewer asthma exacerbations per subject and in lower percentages of subjects experiencing an exacerbation than placebo treatment during the stable steroid phase (0.28 vs 0.54 [$P = .006$] and 14.6% vs 23.3% [$P = .009$], respectively) and during the steroid reduction phase (0.39 vs 0.66 [$P = .003$] and 21.3% vs 32.3% [$P = .004$], respectively). Beclomethasone dipropionate reduction was significantly greater with omalizumab treatment than with placebo (median 75% vs 50% [$P < .001$]), and beclomethasone dipropionate discontinuation was more likely with omalizumab (39.6% vs 19.1% [$P < .001$]). Improvements in asthma symptoms and pulmonary function occurred along with a reduction in rescue beta-agonist use. Omalizumab was well tolerated, with an adverse-events profile similar to that of placebo. **CONCLUSION:** The addition of omalizumab to standard asthma therapy reduces asthma exacerbations and decreases inhaled corticosteroid and rescue medication use.

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Effect of Omalizumab on Symptoms of Seasonal Allergic Rhinitis

A Randomized Controlled Trial

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ALLERGIC RHINITIS IS AN IGE-mediated condition manifested by upper respiratory tract, lower respiratory tract, and ocular symptoms.¹⁻³ This disease affects at least 10% to 20% of US and northern European populations, and its prevalence in urban areas is increasing.⁴⁻⁷ It is a common reason for seeking outpatient medical care⁸ and frequently complicates concomitant conditions such as allergic asthma, chronic sinusitis, otitis media, and nasal polyposis.⁹⁻¹¹ Allergic rhinitis is also associated with diminished quality of life, lost work productivity, and school absenteeism.¹²⁻¹⁴ The total economic burden of allergic rhinitis and its com-

Context Seasonal allergic rhinitis is a common IgE-mediated disorder that produces troublesome symptoms. A recombinant humanized monoclonal anti-IgE antibody (omalizumab) forms complexes with free IgE, blocking its interaction with mast cells and basophils and lowering free IgE levels in the circulation.

Objective To assess the efficacy and safety of omalizumab for prophylaxis of symptoms in patients with seasonal allergic rhinitis.

Design Randomized, double-blind, dose-ranging, placebo-controlled trial conducted from July 25 through November 21, 1997.

Setting Twenty-five outpatient centers throughout the United States.

Patients Five hundred thirty-six patients aged 12 to 75 years with at least a 2-year history of moderate to severe ragweed-induced seasonal allergic rhinitis and a baseline IgE level between 30 and 700 IU/mL.

Interventions Patients were randomly assigned to receive omalizumab, 50 mg (n=137), 150 mg (n=134), or 300 mg (n=129), or placebo (n=136) subcutaneously just prior to ragweed season and repeated during the pollen season every 3 weeks in patients with baseline IgE levels of 151 to 700 IU/mL (4 total treatments) and every 4 weeks in patients with baseline IgE levels of 30 to 150 IU/mL (3 total treatments).

Main Outcome Measures Self-assessed daily nasal symptom severity scores (range, 0-3), rescue antihistamine use, and rhinitis-specific quality of life during the 12 weeks from the start of treatment.

Results Nasal symptom severity scores were significantly lower in patients who received 300 mg of omalizumab than in those who received placebo (least squares means, 0.75 vs 0.98, respectively; $P=.002$). A significant association was observed between IgE reduction and nasal symptoms and rescue antihistamine use. Rhinitis-specific quality of life scores were consistently better in patients who received 300 mg of omalizumab than in those who received lower dosages or placebo and did not decline during peak season. The frequency of adverse events was not significantly different among the omalizumab and placebo groups.

Conclusion Omalizumab decreased serum free IgE levels and provided clinical benefit in a dose-dependent fashion in patients with seasonal allergic rhinitis.

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See also p 3005 and Patient Page.

plications in the United States is estimated at \$6 billion per year.¹⁵

Symptoms of allergic rhinitis are triggered by exposure to allergens. Patients who are very sensitive to pollen exhibit symptoms almost as soon as pol-

Author Affiliations and Financial Disclosures are listed at the end of this article.

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lination begins, with symptoms becoming more severe when pollen concentrations are highest and waning with the end of the pollen season.¹⁶ Presently, allergen avoidance, pharmacotherapy, and immunotherapy are the treatments available for allergic rhinitis.^{17,18} Despite these therapeutic options, there remains a group of patients whose symptoms are not controlled and for whom alternative therapies are needed. At least 50% of patients are likely to require primary care management with combined therapies, such as an intranasal corticosteroid and an oral antihistamine for optimal control throughout the pollen season.¹⁹ A survey of 526 patients prescribed these combined therapies showed that only 142 (27%) were using both types of drug regularly, and 88 (62%) of those patients described symptom control as partial or poor.²⁰

A recombinant humanized monoclonal anti-IgE antibody (omalizumab) was recently developed.²¹ This antibody binds specifically to a unique epitope, the FcεRI binding site on human IgE, and thereby blocks the binding of IgE to mast cells and basophils. Given the fundamental role of IgE in the pathogenesis of seasonal allergic rhinitis, decreasing free serum IgE in atopic patients was expected to decrease seasonal rhinitis symptoms during the pollen season.

We assessed the efficacy of omalizumab, formerly rhuMAb-E25, for the prophylaxis of symptoms in patients with ragweed-induced seasonal allergic rhinitis, determined the agent's effect on rhinitis-specific quality of life, and evaluated the relationship between free IgE levels (serum IgE not bound up in the IgE-omalizumab complex) and clinical efficacy measures.

METHODS

Patients

Individuals aged 12 to 75 years with no or mild symptoms during the preceding month but with at least a 2-year history of moderate to severe seasonal allergic rhinitis due to ragweed were eligible for the study. The history of moderate to severe ragweed-induced allergic rhinitis was defined as having a

score of 2 or more on a 0- to 3-point scale (0, no symptoms and 3, severe symptoms), in 4 of 8 symptom categories (sneezing, itchy nose, running nose, stuffy nose, watery eyes, red eyes, itchy eyes, or itchy throat) based on patient recall of the previous ragweed season. Skin test sensitivity to ragweed pollen and a baseline total IgE level of between 30 and 700 IU/mL also were required. A positive skin test result was defined as presence of both wheal and erythema. In the absence of wheal, an erythema response equal to the positive control (1 mg/mL histamine base) and 1 grade larger than the negative control (extract diluent) at 15 to 20 minutes after skin testing was considered a positive skin test result. The erythema response was graded as follows: 0, no erythema; 1, 20 mm or less; or 2, more than 20 mm.²² The lower limit of baseline total IgE level was established to ensure that serum IgE levels would be sufficiently high to be detectable, and the upper limit was based on dosing considerations. Prior to drug therapy, total IgE is equivalent to free IgE; after drug therapy, total IgE is equivalent to free IgE plus IgE bound to omalizumab.

Exclusion criteria included history of severe idiopathic anaphylactic reaction; immunotherapy within 2 years for seasonal ragweed allergic rhinitis; prior exposure to omalizumab; parasitic infection; history of perennial, vasomotor, or structurally related rhinitis; recent history (<3 months) of drug-induced rhinitis or acute infectious sinusitis; regular treatment with β-adrenergic antagonists, tricyclic antidepressants, or monoamine-oxidase inhibitors; treatment with short-acting antihistamines within 3 days, cetirizine hydrochloride or loratadine within 5 days, or astemizole within 3 months; systemic corticosteroids within 3 months; inhaled or intranasal corticosteroids within 15 days or anytime during the trial; travel for at least 5 consecutive days outside the regions of the study; current or recent serious systemic disease; clinically significant ECG abnormality; and pregnancy or lactation.

The study was performed in accordance with the Declaration of Helsinki and its amendments. Patients gave written informed consent before enrollment. The institutional review board at each center approved the study.

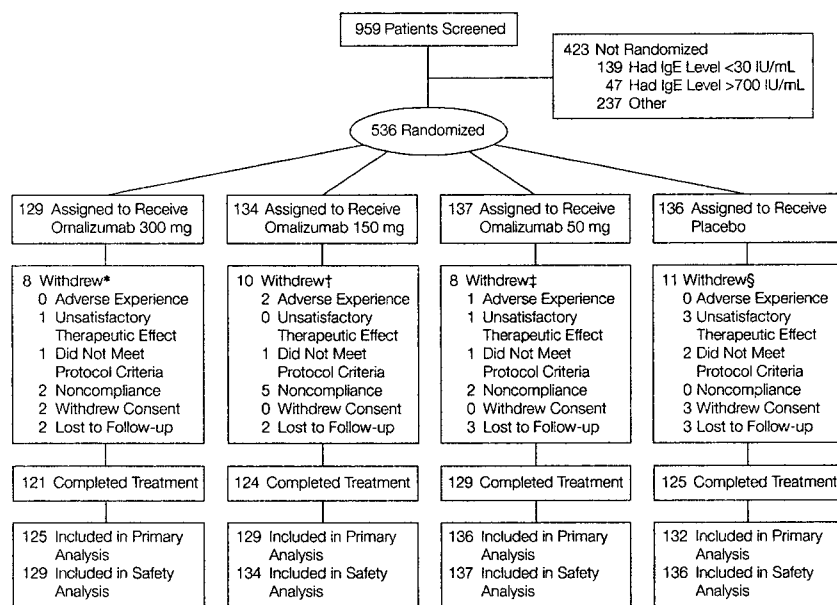
Study Design

This was a double-blind, placebo-controlled, dose-ranging trial conducted from July 25 through November 21, 1997, at 25 centers in the Northeast, Southeast, Midwest, West, and Great Lakes regions of the United States. Blinded study participants included investigators, patients, and study monitors. At trial completion, drug codes were broken and made available for data analysis. Ragweed-induced seasonal allergic rhinitis was chosen as the study condition because ragweed is the most common cause of seasonal allergic rhinitis in North America,¹⁶ and the timing of ragweed season is uniform in these regions, usually peaking in late August or early September.²³ Daily ragweed pollen counts were used to determine the pollen season (the start and end defined as the first and last sequence of >10 grains/m³ for ≥2 consecutive days) and the severe pollen season (the start and end defined as the first and last sequence of >100 grains/m³ for ≥2 consecutive days) for each center. Pollen data, collected with a rotation impaction sampler, were measured locally at each center.

Eligible patients with baseline IgE levels between 151 and 700 IU/mL were randomly assigned (FIGURE 1) to receive either 50, 150, or 300 mg of omalizumab or placebo subcutaneously at 3-week intervals for a total of 4 treatments administered at baseline and at weeks 3, 6, and 9. Patients with baseline IgE levels between 30 and 150 IU/mL were randomly assigned to receive 1 of the 3 omalizumab dosages or placebo every 4 weeks, for a total of 3 treatments administered at baseline and weeks 4 and 8. The treatment schedules were based on data showing the pharmacokinetic and pharmacodynamic relationship between baseline IgE levels and omalizumab and the ex-

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Figure 1. Participant Flow Diagram



Asterisk indicates 3 patients withdrew prior to the pollen season; dagger, 2 withdrew prior to the pollen season; double dagger, 0 withdrew prior to pollen season; and section mark, 2 withdrew prior to the pollen season. Noncompliance includes failure to meet scheduled appointments, to comply with completing diary, or to follow concomitant medication use instruction.

pected suppression of IgE necessary for clinical benefit.²⁴⁻²⁶

A computer-generated randomization scheme was used to provide balanced blocks of patient numbers for each of the 4 treatment groups within each baseline IgE stratum, and patients were assigned a sequential randomization number. Placebo was sterile, white, preservative-free lyophilized powder excipient identical to excipient in the vials that contained study drug. Clinical assessments were performed at each visit for study drug administration and at the end of the trial (week 12). Blood levels of anti-omalizumab antibody were determined approximately 12 weeks after the final visit.

Patients could take 4 mg of chlorpheniramine maleate as needed for severe allergic rhinitis symptoms. Patients unable to tolerate chlorpheniramine were permitted to use alternative antihistamines as rescue medication. Oral or topical decongestants were allowed on a restricted basis, after consulting with the study physician, for temporary relief of

severe nasal congestion, as were eye drops for ocular symptoms.

Efficacy Parameters

The primary efficacy parameter was the average daily nasal symptom severity score. Secondary efficacy measures included average daily ocular symptom severity, average daily nasal and ocular symptom duration, proportion of days with minimal nasal symptoms, proportion of days with rescue or concomitant antihistamine use, rescue or concomitant seasonal allergic rhinitis medication use index, number of tablets of rescue medication taken, patient's and investigator's global evaluation of treatment effectiveness, Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scores,²⁷ and pharmacoeconomic assessments.

Each evening, patients recorded self-assessed symptom severity and duration scores in a daily diary. Nasal symptoms included sneezing and itchy, runny, or stuffy nose; ocular symptoms included itchy, watery, or red eyes. Sym-

ptoms were scored on a scale from 0 to 3 (for symptom severity, 0, no symptoms; 1, mild; 2, moderate; 3, severe; for symptom duration, 0, no symptoms; 1, symptoms present for <3 hours; 2, symptoms present for 3-8 hours; 3, symptoms present >8 hours). A minimal nasal symptom day was defined as a day when the total nasal symptom severity score was 2 or less and no rescue medications were taken to alleviate allergic rhinitis symptoms. Concomitant medications used for symptomatic relief of allergy symptoms were recorded. The average number of tablets of rescue chlorpheniramine taken per day was calculated by adding up the number of tablets per day and dividing by the number of days within the pollen season. Alternative rescue antihistamines were equated to chlorpheniramine based on the recommended dosing frequency (every 6 hours) of chlorpheniramine (eg, 1 tablet of loratadine daily equals 4 chlorpheniramine tablets). A rescue antihistamine or concomitant medication use index was calculated for each patient by adding the total number of different kinds of rescue antihistamines or concomitant medications used each day during the pollen season and dividing it by the total number of days in the pollen season.

Using the RQLQ,²⁷ quality of life was assessed at randomization before receiving the initial treatment, before each subsequent treatment, and at the end of the trial, week 12. The RQLQ is a 28-item questionnaire assessing an overall quality-of-life score and 7 domains of rhinitis-related quality of life (activity limitations, sleep impairment, non-nasal or nonocular symptoms, practical problems, nasal symptoms, eye symptoms, and emotional function). The recall period for each question was the previous 7 days. Baseline measurements on the day that patients received their first treatment represent their status 2 to 3 weeks before the start of the pollen season. Each domain was scored on a 0- to 6-point scale (0, not troubled to 6, extremely troubled).

The number of days missed from work or school, perceived effective-

ness at performing daily work or school activities (missing 1 day, 0%-25%; 2, 26%-50%; 3, 51%-75%; 4, 76%-100%) and medical resource use (unscheduled health care visits and contacts, changes in allergy treatments) were also recorded. At the end of the 12-week trial, investigators and patients rated global evaluation of treatment effectiveness on a 5-point scale (1, excellent control of symptoms to 5, worsening of symptoms).

Evaluation of IgE levels

Blood samples for measurement of IgE levels were obtained at each treatment visit, at week 12, and 12 weeks after the end of the trial (week 24). Assays to determine total IgE levels were performed at the central laboratory facility using Abbott IMX Microparticle Enzyme Immunoassay, MEIA (Abbott Laboratories, Abbott Park, Ill). Assays to determine ragweed-specific IgE levels were performed using the Pharmacia CAP system RAST FEIA (Pharmacia, Uppsala, Sweden).²⁵ Free IgE levels were measured using a solid-phase enzyme-linked immunosorbent assay²⁵ with a fluorometric technique and human serum as standard. The coefficients of variation of the assay were from 5.4% to 11.2%. The upper limit of quantitation of this assay was 62.5 IU/mL and the lower limit of quantitation was 0.3 IU/mL.

Detection of Antibodies to Omalizumab

Serum samples were screened for the presence of anti-omalizumab antibodies before patients received their first treatment and 12 weeks after the end of the trial (week 24) using a previously described antibody assay.²⁴

Adverse Events

Adverse events were classified at each visit according to modified World Health Organization Adverse Reaction Terminology²⁸ and assessed by the investigators as mild, moderate, or severe and related or not related to treatment. Patients were instructed to record all skin reactions at the trial drug

injection sites after each treatment, using a 0 (none) to 3 (severe) scale for symptoms such as burning, itching, and redness. Laboratory values measured were complete blood cell count with differential, serum chemistry panel, and urinalysis.

Statistical Analysis

Symptom severity and duration scores were averaged over the 12-week trial for each patient. In the analyses of average symptom scores and global effectiveness evaluations, a step-down method was used to control the type I error rate of the multiple comparisons. It first tested the highest dose vs placebo and would only test the second highest dose if the first test was significant. Each significance test was performed at a .025 level (1-sided). This procedure was adopted because it was valid regardless of the variables analyzed and statistical models used. Statistical tests for quality of life and minimal symptom days were performed at a .05 significance level (2-sided).

The data were analyzed with SAS software version 6.08 (SAS Institute Inc, Cary, NC). The primary efficacy analysis was based on all patients who received at least 1 dose of trial medication, did not withdraw from the trial prior to the onset of the pollen season, and who had any diary data during the pollen season. Average symptom scores and medication use were analyzed using an analysis of variance model. The factors included in the model were treatment, center, treatment schedule, as well as treatment by center and treatment by treatment schedule interactions. In addition, a post hoc analysis of minimal symptom days was conducted. Wilcoxon rank sum test was used to compare the number of minimal symptom days during the entire pollen season in each omalizumab group vs placebo.

The patients' and investigators' global evaluation scores at week 12, as well as change in RQLQ score from baseline to the visit closest to the peak of the ragweed season, were analyzed using van Elteren test stratified by center.²⁹ Each domain of the RQLQ score and the

overall score were grouped into 3 categories: meaningful improvement (decrease in score ≥ 0.5), no meaningful change (decrease or increase < 0.5), and meaningful deterioration (increase of ≥ 0.5).³⁰

An analysis of covariance model was used to investigate the relationship between free IgE level and clinical efficacy. This model fitted the average nasal symptom severity score with covariate baseline total IgE level and factors baseline IgE strata (equivalent to treatment schedule) and free IgE category. Four free IgE categories (≤ 10.4 , > 10.4 -20.8, > 20.8 -62.5, and > 62.5 IU/mL) were defined according to measurements taken at the treatment visit when the pollen count was the highest. According to the Bonferroni rule, an α level of .0016 was used to adjust for multiple comparisons of each of the lower free IgE categories to the highest free IgE category.

A sample size of 100 efficacy-evaluable patients per treatment arm was required to detect mean differences in average nasal symptom severity score of 0.1, 0.2, and 0.3 between placebo and the low, medium, and high doses of omalizumab, respectively. Approximately 20% more patients were randomized in anticipation of dropouts.

RESULTS

Demographics

Five hundred thirty-six of 959 screened patients from 25 centers met the eligibility criteria and were randomized as shown in Figure 1. Seven patients were excluded from the analysis because they had no data within the pollen season. No statistically significant differences were detected among the study groups at baseline (TABLE 1). Ninety-two percent to 96% of patients were white, 21% to 29% had a history of asthma, and 12% to 15% had a history of atopic dermatitis. Thirty-seven patients either withdrew or were excluded from the study: 10 were lost to follow-up; 9 were excluded for noncompliance (failure to meet scheduled appointments or to comply with study procedure); 5 withdrew consent; 5 did not meet protocol criteria; 5 failed to respond to treat-

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OMALIZUMAB FOR SYMPTOMS OF SEASONAL ALLERGIC RHINITIS

ment (based on investigator's medical judgment); and 3 withdrew because of adverse events (Figure 1). The 37 patients were equally distributed across the treatment groups.

Recruitment started June 30, 1997. All patients received the first dose of study drug between July 25 and August 4, 1997. The last treatment was administered between October 16 and 24, 1997. The start date of the pollen season was between August 6 and September 3, 1997, and the end date was between September 5 and October 5, 1997. Fifteen of the 25 centers reported a severe pollen season between August 6 and September 24, 1997. The duration and severity of the pollen season varied among

participating study centers, but exposure to the pollen season and severe pollen season was similar across the treatment groups (Table 1). Sixty-four percent of patients in the 300-mg, 63% in the 150-mg, and 64% in the 50-mg omalizumab groups and 61% in the placebo group were exposed to the severe pollen season.

All patients received the first treatment approximately 2 weeks before the ragweed pollen season. The mean (median) number of days before the onset of the pollen season after the first treatment was 19.8 (19.0) in the 300-mg, 19.8 (19.5) in the 150-mg, and 20.0 (20.0) days in the 50-mg omalizumab groups and 19.9 (19.0) days in the pla-

cebo group. Ninety-eight percent of patients in the 300-mg, 97% in the 150-mg, and 97% in the 50-mg omalizumab groups and 97% in the placebo group received treatment more than a week before the start of pollen season. No patient started study drug after the start of the pollen season.

Efficacy

Average nasal and ocular symptom severity and duration scores over the entire pollen season were consistently and significantly lower in the omalizumab 300-mg group than in the placebo group (TABLE 2). During the severe pollen season, average nasal symptom severity scores were also significantly lower in the

Table 1. Characteristics and Pollen Season Exposure of Study Population

Characteristic	Omalizumab, mg			Placebo (n = 134)	Overall (N = 529)
	300 (n = 126)	150 (n = 132)	50 (n = 137)		
Age, mean (SD), y	36.2 (11.9)	33.7 (13.3)	33.6 (10.6)	34.7 (13.8)	34.5 (12.5)
Sex, No. (%)					
Men	58 (46)	62 (47)	62 (45)	58 (43)	240 (45)
Women	68 (54)	70 (53)	75 (55)	76 (57)	289 (55)
Weight, mean (SD), kg	71.8 (15.4)	71.7 (14.9)	74.3 (14.0)	73.3 (13.6)	72.8 (14.5)
Height, mean (SD), cm	168.2 (11.0)	169.9 (10.3)	169.8 (10.6)	169.7 (9.5)	169.4 (10.3)
Ragweed pollen allergy history total score, mean (SD)*	17.2 (3.2)	16.8 (3.5)	16.6 (3.3)	16.6 (3.7)	16.8 (3.4)
History of asthma, No. (%)	31 (25)	38 (29)	29 (21)	39 (29)	137 (26)
IgE IU/mL, No. (%)					
≤150	75 (60)	75 (57)	79 (58)	79 (59)	308 (58)
>150	51 (40)	57 (43)	58 (42)	55 (41)	221 (42)
Baseline IgE level, mean (SD), IU/mL					
≤150	81.9 (32.4)	76.7 (33.1)	74.3 (34.6)	83.2 (35.5)	79.0 (34.0)
>150	324.4 (151.8)	302.5 (143.4)	296.2 (121.4)	300.5 (138.2)	305.4 (138)
Ragweed-specific IgE, mean (SD), IU/mL					
Ragweed-short	10.3 (16.88)	10.7 (17.28)	8.5 (12.23)	10.0 (16.98)	9.9 (15.84)
Ragweed-long	9.6 (16.20)	9.8 (16.22)	8.2 (11.14)	8.9 (16.51)	9.1 (15.02)
Preseason nasal symptom severity score, mean (SD), [No.]†	0.63 (0.6) [123]	0.76 (0.61) [129]	0.69 (0.54) [135]	0.78 (0.61) [134]	0.71 (0.59) [521]
RQLQ score, mean (SD), at baseline‡					
Activity limitations	2.19 (1.43)	2.27 (1.57)	2.08 (1.56)	2.13 (1.67)	2.17 (1.56)
Sleep impairment	1.34 (1.23)	1.32 (1.25)	1.12 (1.32)	1.18 (1.27)	1.24 (1.27)
Non-nasal symptoms	1.23 (1.03)	1.34 (1.28)	1.15 (1.18)	1.25 (1.33)	1.24 (1.20)
Practical problems	1.73 (1.28)	1.96 (1.50)	1.77 (1.46)	1.82 (1.53)	1.82 (1.44)
Nasal symptoms	1.63 (1.19)	1.95 (1.39)	1.80 (1.36)	1.80 (1.50)	1.79 (1.36)
Eye symptoms	1.33 (1.21)	1.55 (1.40)	1.28 (1.23)	1.51 (1.46)	1.42 (1.32)
Emotional function	0.95 (1.01)	1.13 (1.25)	0.94 (1.11)	1.05 (1.33)	1.02 (1.17)
Overall score	1.49 (0.99)	1.65 (1.20)	1.46 (1.17)	1.53 (1.28)	1.53 (1.16)
Exposure to pollen season, mean (SD), d	48.1 (12.3)	47.2 (13.5)	45.7 (14.9)	44.6 (15.1)	46.4 (14.0)
Exposure to severe pollen season, mean (SD), d	15.5 (12.3)	15.4 (12.2)	14.4 (11.7)	14.5 (11.8)	14.9 (11.9)

*Using a 4-point scale, patients evaluated the severity of sneezing, itchy nose, runny nose, stuffy nose, itchy eyes, watery eyes, red eyes, and itchy throat (0, no symptoms; 3, severe symptoms). Total score is the sum of individual scores: the best is 0; the worst, 24.

†Score from daily diary on day of first treatment.

‡The following 7-point Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) scale was used: 0, not troubled; 1, hardly troubled; 2, somewhat troubled; 3, moderately troubled; 4, quite a bit troubled; 5, very troubled; 6, extremely troubled.

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300-mg (0.84 vs 1.20; $P = .001$) and 150-mg (0.95 vs 1.20; $P = .01$) omalizumab groups than in the placebo group. A linear dose-response relationship was observed (slope for dose -0.001 ; $P < .001$) for average daily nasal symptom severity scores (FIGURE 2). Weekly nasal symptom severity scores over the entire pollen season showed minimal change in the 300-mg omalizumab group compared with the other omalizumab groups and with placebo (FIGURE 3), even when pollen counts increased. Patients in the 300-mg (41% vs 18%, $P < .001$) and patients in the 150-mg (29% vs 18%, $P = .04$) omalizumab groups had a significantly greater percentage of days with minimal nasal symptoms than did those in the placebo group (FIGURE 4).

The proportion of days during the pollen season with rescue antihistamine or concomitant medication use was significantly lower in the 300-mg (0.12 vs 0.21 days, $P = .005$) and 150-mg (0.13 vs 0.21 days, $P = .01$) omalizumab groups than in the placebo group, as was the rescue antihistamine or concomitant medication use index (least squares mean [SD], 0.13 [0.34] for the 300-mg and 150-mg omalizumab groups vs 0.22 [0.35] for placebo; $P = .006$ and $P = .01$, respectively). The corresponding values (least squares mean) for the omalizumab 50-mg group were 0.18 days ($P = .20$) and 0.19 (0.35) rescue medication index ($P = .23$).

Most patients who used rescue antihistamines other than chlorpheniramine used fexofenadine (10 of 12 in the 300-mg, 21 of 22 in the 150-mg, and 22 of 24 in the 50-mg omalizumab groups and 29 of 35 in the placebo group). The daily average number of tablets of rescue antihistamine medication taken was 0.17 in the 300-mg vs 0.37 for placebo ($P = .001$) and 0.20 in the 150-mg omalizumab groups vs 0.37 for placebo ($P = .004$). The difference between the number of tablets taken by those in the 50-mg omalizumab group vs the placebo group did not reach statistical significance (0.29 vs 0.37 tablets, $P = .097$). Average daily rescue antihistamine use decreased in congruence with average daily nasal symptom severity scores

(FIGURE 5), with the lowest nasal symptom severity scores and daily rescue antihistamine medication use being obtained with omalizumab 300 mg.

Treatment effectiveness was globally rated as good or excellent by 70.7% in the 300-mg ($P < .001$), 60.0% in the 150-mg ($P < .001$), and 51.9% in the 50-mg ($P = .007$) omalizumab groups compared with 40.8% in the placebo group. The respective values for investigators were 65.3% ($P < .001$), 51.9%

($P = .001$), and 50% ($P = .004$) compared with 35.4% for placebo.

RQLQ and Other Outcomes

At baseline, the mean overall RQLQ and domain scores did not differ among the 4 treatment groups. The RQLQ scores were consistently lower (indicating better rhinitis-related quality of life) throughout the pollen season in those receiving 300 mg of omalizumab (FIGURE 6). Patients receiving pla-

Table 2. Average Daily Symptom Severity and Duration Scores During the Pollen Season*

Therapy	No. of Patients	Average Score (Least Squares Mean [SE]†)	Difference in Scores vs Placebo (95% CI)	P Value‡
Nasal Symptom Severity				
Omalizumab, mg				
300	125	0.75 (0.06)	-0.23 (-0.38 to -0.08)	.002
150	129	0.86 (0.05)	-0.13 (-0.27 to 0.02)	.27
50	136	0.88 (0.05)	-0.10 (-0.25 to 0.05)	.09
Placebo	133	0.98 (0.05)		
Nasal Symptom Duration				
Omalizumab, mg				
300	125	0.78 (0.06)	-0.25 (-0.41 to -0.08)	.002
150	129	0.90 (0.06)	-0.12 (-0.28 to 0.03)	.06
50	136	0.93 (0.06)	-0.09 (-0.25 to 0.07)	.12
Placebo	133	1.03 (0.06)		
Ocular Symptom Severity				
Omalizumab, mg				
300	125	0.41 (0.05)	-0.25 (-0.40 to -0.10)	.001
150	129	0.45 (0.05)	-0.22 (-0.36 to -0.07)	.002
50	136	0.49 (0.05)	-0.17 (-0.32 to -0.03)	.01
Placebo	133	0.67 (0.05)		
Ocular Symptom Duration				
Omalizumab, mg				
300	125	0.41 (0.06)	-0.25 (-0.41 to -0.10)	.001
150	129	0.46 (0.05)	-0.20 (-0.35 to -0.05)	.005
50	136	0.52 (0.05)	-0.14 (-0.29 to 0.01)	.03
Placebo	133	0.66 (0.05)		
Overall Symptom Severity§				
Omalizumab, mg				
300	125	0.61 (0.05)	-0.24 (-0.38 to -0.10)	<.001
150	129	0.68 (0.05)	-0.17 (-0.30 to -0.03)	.009
50	136	0.71 (0.05)	-0.13 (-0.27 to 0.00)	.03
Placebo	133	0.85 (0.05)		
Overall Symptom Duration§				
Omalizumab, mg				
300	125	0.62 (0.05)	-0.25 (-0.39 to -0.10)	<.001
150	129	0.71 (0.05)	-0.16 (-0.30 to -0.01)	.02
50	136	0.76 (0.05)	-0.11 (-0.26 to 0.03)	.06
Placebo	133	0.87 (0.05)		

*P values compare active treatment and placebo. CI indicates confidence interval.

†The range of possible scores is 0 to 3.

‡Statistically significant difference was set at .025 (1-sided) using a step-down multiple comparison procedure.

§Overall symptom severity and duration scores are the averages of the individual nasal and ocular symptom severity and duration scores.

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cebo or 50 mg of omalizumab experienced a worsening of quality-of-life scores at the peak of the pollen season compared with baseline.

Significant differences in the proportion of patients with meaningful changes (≥ 0.5 points)³⁰ from baseline to peak season in quality-of-life scores were noted between those receiving 300 mg of omalizumab and those receiving

placebo in 4 of the 7 domains, including activity limitations, sleep impairment, non-nasal symptoms, and emotional function, and in overall quality-of-life scores at the peak of the pollen season (TABLE 3). Significant differences in quality of life were observed between the 150-mg omalizumab group and placebo group in 3 of 7 domains, including sleep impairment, non-nasal symptoms, and emotional function scores at the peak of the pollen season (Table 3).

There were no statistically significant differences between the 3 active treatment groups and placebo group with respect to performance effectiveness and the number of additional contacts with health care professionals. The mean (SD) number of days missed from work, school, or both among those receiving 300 mg of omalizumab was 0.1 (0.4) compared with 0.4 (1.6) in those receiving placebo ($P=.005$).

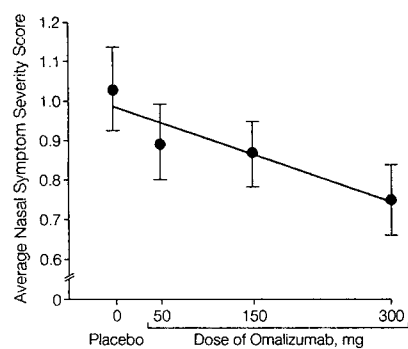
IgE Levels and Clinical Efficacy

A dose-dependent decrease in serum free IgE levels (serum IgE not bound up in the IgE-omalizumab complex) occurred

after omalizumab treatment (TABLE 4). Analysis of the relationship between suppression of serum free IgE levels at peak season and efficacy measures showed a significant association between free IgE levels and daily nasal symptom severity and rescue antihistamine use during the pollen season. Patients with the lowest trough free IgE levels had the lowest symptom scores and least rescue antihistamine use (TABLE 5). The proportion of patients achieving a serum free IgE level <10.4 IU/mL after the first dosing interval was 63% in the 300-mg, 33% in the 150-mg, 4% in the 50-mg omalizumab groups and 3% in the placebo group.

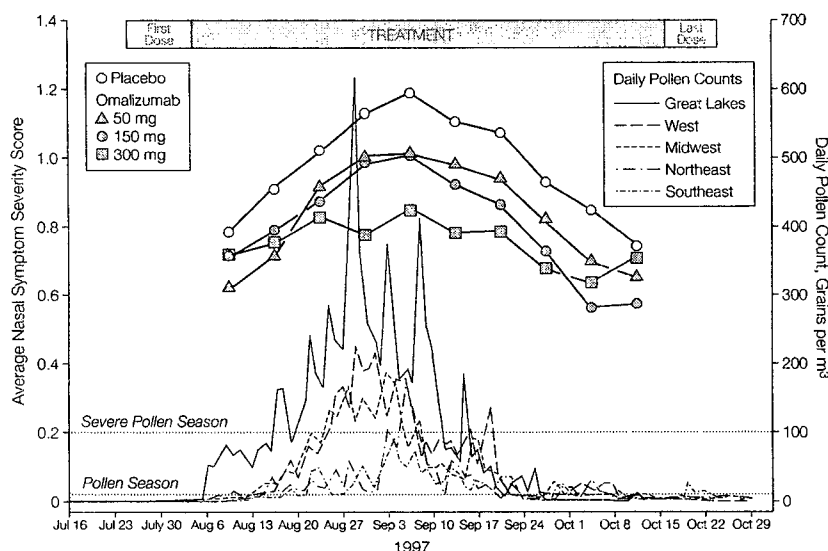
Ragweed pollen-specific IgE levels were measured at baseline and 12 weeks after the final visit (week 24). At baseline, the levels were comparable between all treatment groups (ragweed-short, 8.5-10.7 IU/mL; ragweed-long 8.2-9.8 IU/mL). At the 24-week follow-up, concentrations were higher in omalizumab-treated patients compared with placebo. The increase was dose related and thought to represent ragweed-specific IgE bound up in the IgE-omalizumab complexes as the result of the longer

Figure 2. Linear Dose-Response Relationship Between the Average Daily Nasal Symptom Severity Score (Arithmetic Means) and Dose of Omalizumab



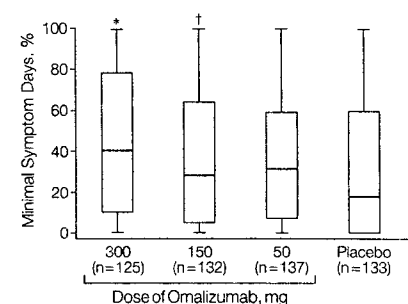
Ninety-five percent confidence intervals are shown. Slope for dose: -0.001 ($P<.001$).

Figure 3. Average Weekly Nasal Symptom Severity Scores and Daily Pollen Counts During the Pollen Season



Patients received the first dose of study drug between July 25 and August 4, 1997, and the last dose between October 16 and October 24, 1997.

Figure 4. Median Percentage of Days With Minimal Symptoms During the Pollen Season



A minimal nasal symptom day was defined as a day when the sum of the 4 individual nasal symptom severity scores was 2 or less out of a maximum of 12 and no rescue medications were taken to alleviate ragweed allergic rhinitis symptoms. Central horizontal bars indicate median, upper and lower ends of the boxes indicate 75th and 25th interquartile range, and error bars indicate maximal and minimal values.

* $P<.001$ comparing omalizumab with placebo.

† $P<.05$ comparing omalizumab with placebo.

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serum half-life of the complexes compared with free IgE.^{25,31-33}

Adverse Events

Headache, upper respiratory infection, and viral infection were the most frequently reported adverse events in the omalizumab groups but were reported less frequently in the 300-mg omalizumab group than in the other omalizumab groups (TABLE 6). Headache, sinusitis, upper respiratory infection, and viral infection were the most frequently reported adverse events in the placebo group. Asthma worsened in 4 patients (2.9%) in the placebo group compared with 3 patients (1%) in the omalizumab groups. Sinusitis was also more common in the placebo group than in the omalizumab group (Table 6). The most commonly reported trial drug-related adverse events in all treatment groups, including placebo, were weight gain (all groups, $\leq 3.0\%$) and headache (all groups, $\leq 2.2\%$). Trial drug-related urticaria was reported in 1 patient receiving 150 mg of omalizumab, who was subsequently withdrawn from treatment, and in 1 receiving 50 mg of omalizumab. Trial drug-related severe adverse events included sprains and strains (1, 300-mg omalizumab), and nausea (1, 50-mg omalizumab).

Injection site reactions were mild and infrequent. The mean symptom score for injection site reaction (eg, burning, itching, redness) was the same in each treatment group (the average frequency of reactions per injection given was 0.2% per patient). There were no clinically significant alterations in laboratory values in any group, and no reactivity for antibodies to the Fab fragment of omalizumab was observed. There was no evidence of immune complex-related adverse events.

In a follow-up to the primary study, 287 of 374 patients who completed treatment with omalizumab were treated with omalizumab during a second ragweed season.³³ The overall incidence and pattern of adverse events were similar to those reported in the primary study. There were no severe or se-

rious adverse events related to omalizumab treatment. No anti-omalizumab antibodies were detected in any patient, and no significant immune-complex mediated disorders were observed.

COMMENT

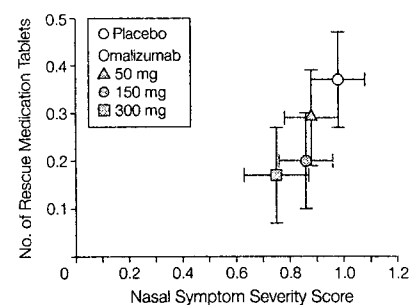
The results of this randomized, placebo-controlled trial provide clinical evidence that lowering systemic free IgE levels with a specific blocker of IgE binding provides clinical benefit in patients with seasonal allergic rhinitis. These findings are consistent with the results of a previously published placebo-controlled trial in 251 adults with birch pollen-induced seasonal allergic rhinitis, in which omalizumab, administered subcutaneously 2 or 3 times during the season (depending on baseline IgE levels) significantly reduced nasal symptom severity scores and use of rescue medication, and improved quality of life scores.³⁴

Treatment with omalizumab was initiated before the onset of the ragweed pollen season to assess whether blocking IgE binding before and during the pollen season could reduce seasonal allergic rhinitis symptoms for an entire pollen season. It was hypothesized that beginning treatment before symptoms develop might prevent the priming

effect of allergic inflammation in the nasal mucosa that leads to increased reactivity to allergen challenge as the season progresses.³⁵

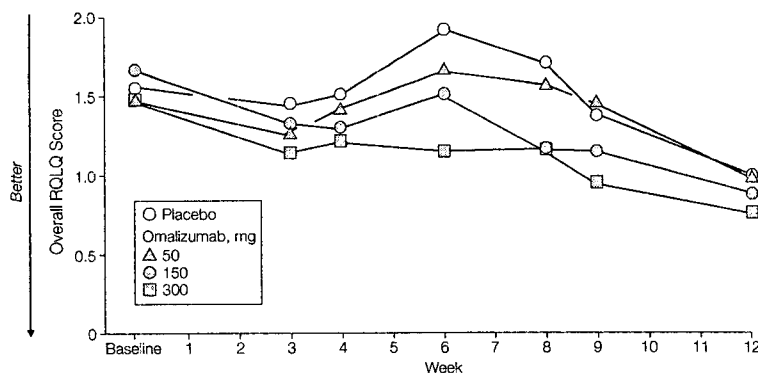
Average daily nasal symptom severity score, the outcome that measures some of the most troublesome symptoms of allergic rhinitis, and the primary efficacy variable for this study, was significantly lower (indicating less severe symptoms) in the 300-mg omalizumab group than in the placebo group over the entire ragweed pollen season (difference in least squares means of -0.23) adjusted for center and treatment schedule. During the severe pol-

Figure 5. Average Daily Amount of Rescue Medication Used vs the Average Daily Nasal Symptom Severity Scores During the Pollen Season



Values displayed as least squares means with 95% confidence intervals.

Figure 6. Mean Overall Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) Scores



Lower scores indicate better quality of life. Data at 3, 6, and 9 weeks are for the every 3-week treatment group; data at 4 and 8 weeks are for the every 4-week treatment group. Data at baseline and 12 weeks include all patients. Data at week 8 (corresponding to the peak of the pollen season) are for 68 patients in the 300-mg omalizumab group; 63 patients in the 150-mg omalizumab group; 70 patients in the 50-mg omalizumab group; and 68 patients in the placebo group.

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Table 3. Meaningful Change in the Rhinoconjunctivitis Quality of Life Questionnaire (RQLQ) Score²⁷ From Baseline to the Peak of the Pollen Season Among Adult Patients*

Change from Baseline†	No. (%) of Patients			
	Omalizumab, mg			Placebo
	300	150	50	
Activity limitations				
≥0.5-Point improvement	56 (54.9)	42 (41.6)	39 (35.1)	45 (41.7)
<0.5-Point change	24 (23.5)	36 (35.6)	31 (27.9)	22 (20.4)
≥0.5-Point decline	22 (21.6)	23 (22.8)	41 (36.9)	41 (38.0)
Total	102 (100.0)	101 (100.0)	111 (100.0)	108 (100.0)
P value‡	.01	0.30	0.80	
Sleep impairment				
≥0.5-Point improvement	40 (39.2)	39 (39.0)	26 (23.4)	25 (23.4)
<0.5-Point change	45 (44.1)	39 (39.0)	39 (35.1)	36 (33.6)
≥0.5-Point decline	17 (16.7)	22 (22.0)	46 (41.4)	46 (43.0)
Total	102 (100.0)	100 (100.0)	111 (100.0)	107 (100.0)
P value‡	<.001	.002	.85	
Non-nasal symptoms				
≥0.5-Point improvement	36 (35.3)	44 (44.0)	31 (27.9)	23 (21.5)
<0.5-Point change	47 (46.1)	35 (35.0)	44 (39.6)	47 (43.9)
≥0.5-Point decline	19 (18.6)	21 (21.0)	36 (32.4)	37 (34.6)
Total	102 (100.0)	100 (100.0)	111 (100.0)	107 (100.0)
P value‡	.002	.001	.37	
Practical problems				
≥0.5-Point improvement	46 (45.1)	43 (43.0)	37 (33.0)	39 (36.8)
<0.5-Point change	29 (28.4)	26 (26.0)	34 (30.4)	27 (25.5)
≥0.5-Point decline	27 (26.5)	31 (31.0)	41 (36.6)	40 (37.7)
Total	102 (100.0)	100 (100.0)	112 (100.0)	106 (100.0)
P value‡	.09	.33	0.86	
Nasal symptoms				
≥0.5-Point improvement	37 (37.0)	41 (41.4)	27 (25.0)	38 (36.2)
<0.5-Point change	30 (30.0)	23 (23.2)	27 (25.0)	19 (18.1)
≥0.5-Point decline	33 (33.0)	35 (35.4)	54 (50.0)	48 (45.7)
Total	100 (100.0)	99 (100.0)	108 (100.0)	105 (100.0)
P value‡	.22	.27	.32	
Eye symptoms				
≥0.5-Point improvement	46 (46.0)	50 (50.5)	32 (29.6)	43 (40.6)
<0.5-Point change	31 (31.0)	23 (23.2)	36 (33.3)	25 (23.6)
≥0.5-Point decline	23 (23.0)	26 (26.3)	40 (37.0)	38 (35.8)
Total	100 (100.0)	99 (100.0)	108 (100.0)	106 (100.0)
P value‡	.13	.08	.22	
Emotional function				
≥0.5-Point improvement	35 (35.0)	42 (42.4)	30 (27.8)	31 (29.2)
<0.5-Point change	41 (41.0)	35 (35.4)	37 (34.3)	35 (33.0)
≥0.5-Point decline	24 (24.0)	22 (22.2)	41 (38.0)	40 (37.7)
Total	100 (100.0)	99 (100.0)	108 (100.0)	106 (100.0)
P value‡	.04	.009	.90	
Overall				
≥0.5-Point improvement	45 (44.1)	42 (41.6)	25 (22.3)	33 (30.6)
<0.5-Point change	36 (35.3)	34 (33.7)	44 (39.3)	37 (34.3)
≥0.5-Point decline	21 (20.6)	25 (24.8)	43 (38.4)	38 (35.2)
Total	102 (100.0)	101 (100.0)	112 (100.0)	108 (100.0)
P value‡	.008	.07	.33	

*Adult patients included in the analysis were aged 18 years or older. Adolescent patients, aged 12 to 17 years (n = 47), completed a different RQLQ instrument (7 in the 300-, 17 in the 150-, and 11 in the 50-mg omalizumab groups, and 12 in the placebo group) and were excluded from this analysis. Data are for the assessment on the visit closest to the maximum pollen count.

†Meaningful improvement or decline was defined by a change in quality of life score of at least 0.5 from baseline.³⁰ A patient with a change in score less than 0.5 would be defined as having experienced no meaningful change.

‡P values (2 sided) are for overall comparisons of the active treatment groups vs placebo and were derived from the van Elteren test adjusted for center.

len season, the difference in least squares means between the 300-mg omalizumab treatment group and placebo was 0.36 (0.84 vs 1.20, respectively; $P = .001$).

Patients reported mild nasal symptoms (<1.0 on a 0- to 3-point scale) on the first day of treatment. Therefore, even though the study investigators considered patients to be asymptomatic at baseline, background symptoms may represent underlying chronic nasal disease or mild perennial allergic rhinitis. Patients receiving 300 mg of omalizumab experienced almost no difference in nasal symptom severity score between the first treatment day and peak season, whereas patients in the placebo group experienced a 50% increase in symptom severity (0.8 and 1.2, respectively, Figure 3). These data suggest that patients generally were protected during the pollen season. In addition, patients receiving 300 mg of omalizumab showed more than a 2-fold difference in proportion of minimal nasal symptom days during the entire pollen season compared with patients receiving placebo (median, 41% vs 18%, $P < .001$).

Daily nasal and ocular symptom severity and duration scores were consistently lower among patients who received 300 mg of omalizumab compared with those in the placebo group (Table 2), despite significantly greater rescue antihistamine use in the placebo group (Figure 5). This combined effect strengthens the efficacy results in this study because the greater use of rescue medication probably reduced symptom severity in the placebo group and decreased the treatment difference between the omalizumab and placebo groups. The proportion of days with rescue antihistamine or concomitant medication use was 43% lower, the rescue antihistamine or concomitant medication use index was 41% lower, and the number of tablets of rescue antihistamines used was 54% lower in those who received 300 mg of omalizumab compared with those who received placebo. Regression analysis of daily nasal symptom severity scores over the entire pollen season confirmed a linear dose-

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response relationship over the dosages of omalizumab evaluated (Figure 2). The linear dose-response is noteworthy when one considers the subjective nature of nasal symptom scoring in more than 500 patients and the inability to control pollen exposure in the ambient environment.

Assessment of quality of life is critical in a study exploring treatment effectiveness in allergic rhinitis because these patients experience poor quality of life.¹² Significant differences in changes from baseline in quality-of-life scores between those taking 300 mg of omalizumab and those taking placebo were shown in 4 of 7 domains and in overall quality-of-life score at the peak of the pollen season. Few published studies have reported quality-of-life changes over the course of a pollen season. However, in a randomized treatment trial that measured quality of life using the RQLQ questionnaire during a ragweed pollen season, patients who received antihistamine, nasal corticosteroid, or both, experienced a deterioration in total RQLQ score between the beginning and height of the ragweed season ($P < .001$).¹⁹ In our study, there was no deterioration in RQLQ scores between baseline and the peak of the pollen season in the 300-mg omalizumab group and in fact, quality of life scores were better at peak season than at study entry.

Pharmacoeconomics outcomes may provide supportive evidence of patient benefit. In this study, patients treated with omalizumab experienced a 75% reduction in days they missed

work, school, or both compared with placebo (0.1 vs 0.4 days, respectively). This result is consistent with the quality-of-life improvements measured by the RQLQ, rhinitis symptom score improvements, and reduction in the use of concomitant rescue medication in the 300-mg omalizumab group.

Patients receiving 300 mg of omalizumab experienced profound reductions in serum free IgE levels after the first dosing interval, when 63% of patients had serum free IgE levels below 10.4 IU/mL. Casale et al²⁵ postulated that suppression of serum free IgE levels lower than 17 IU/mL would correlate with measures of clinical efficacy. In agreement with this hypothesis, this study showed a significant relationship between free IgE level suppression and clinical response.

Overall, the frequency of adverse events was similar in the active treatment and placebo groups and included those commonly prevalent in the study population. There was only 1

withdrawal that was related to omalizumab treatment (for urticaria). There was no evidence of a dose-response relationship with any of the adverse events. Neither adverse events nor laboratory safety analysis data were suggestive of an immune complex-related disorder.

Elevated IgE is characteristic of the immune response during and after parasitic infections, suggesting a theoretical drawback of anti-IgE therapy. However, experimental evidence in animal models indicates a neutral or beneficial effect of low IgE levels on the outcome of parasitic infection and resistance to reinfection.³⁶⁻³⁹

There are several limitations to this study. Despite requiring patients to have a history of significant seasonal allergic rhinitis to ragweed, the subjects in this study were not very symptomatic during the course of the ragweed season. The reason for the low symptom scores is not clear but could be related to the placebo effect of administering

Table 4. Relationship Between Omalizumab Treatment and Median IgE Levels

Treatment	Median IgE Level, IU/mL			
	Omalizumab, mg			Placebo
	300	150	50	
Baseline total IgE level	119	122	121	124
Free IgE level				
Every 4-week schedule				
Week 4	8.8	14.2	27.1	>62.5
Week 8	7.5	10.8	24.6	>62.5
Every 3-week schedule				
Week 3	17.9	28.3	>62.5	>62.5
Week 6	12.9	22.1	55.0	>62.5
Week 9	13.3	21.3	55.0	>62.5

Table 5. Predose Serum Free IgE Levels at Peak of Pollen Season, Average Daily Nasal Symptom Severity (DNSS) Scores, and Rescue Medication Use*

Variable	Nasal Symptom Severity				Rescue Medication Use			
	No. of Patients	DNSS Score, Mean (SD)	Difference (Least Squares Means) vs IgE >62.5 IU/mL (95% CI)	P Value	No. of Patients	Tablets/d, Mean (SD)	Difference vs IgE >62.5 IU/mL (95% CI)	P Value
Predose serum free IgE level, IU/mL*								
≤10.4	112	0.82 (0.49)	-0.19 (-0.33 to -0.05)	.007	112	0.18 (0.40)	-0.22 (-0.34 to -0.10)	<.001
10.4-20.8	119	0.86 (0.50)	-0.14 (-0.28 to -0.00)	.031	120	0.18 (0.34)	-0.22 (-0.34 to -0.10)	<.001
20.9-62.5	148	0.87 (0.51)	-0.13 (-0.25 to -0.01)	.039	150	0.21 (0.35)	-0.18 (-0.28 to -0.08)	<.001
>62.5	139	0.99 (0.58)			141	0.39 (0.60)		

*The free IgE levels correspond to the visit that has the maximum ragweed pollen counts.

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Table 6. Frequently Reported Adverse Experiences

Characteristics	No. (%) of Patients			
	Omalizumab, mg			Placebo (n = 136)
	300 (n = 129)	150 (n = 134)	50 (n = 137)	
Body as a whole				
Weight increase	3 (2.3)	4 (3.0)	4 (2.9)	2 (1.5)
Gastrointestinal tract				
Nausea	4 (3.1)	0 (0.0)	2 (1.5)	0 (0.0)
Infections and infestations				
Viral infection	7 (5.4)	11 (8.2)	9 (6.6)	9 (6.6)
Musculoskeletal system				
Arthralgia	2 (1.6)	4 (3.0)	1 (0.7)	3 (2.2)
Back pain	2 (1.6)	6 (4.5)	0 (0.0)	5 (3.7)
Sprains and strains	4 (3.1)	1 (0.7)	2 (1.5)	2 (1.5)
Nervous system				
Headache	15 (11.6)	21 (15.7)	21 (15.3)	22 (16.2)
Respiratory tract				
Coughing	1 (0.8)	4 (3.0)	2 (1.5)	2 (1.5)
Sinus headache	5 (3.9)	3 (3.7)	1 (0.7)	1 (0.7)
Pharyngitis	3 (2.3)	7 (5.2)	3 (2.2)	1 (0.7)
Sinusitis	3 (2.3)	4 (3.0)	5 (3.6)	12 (8.8)
Upper respiratory tract infection	8 (6.2)	11 (8.2)	13 (9.5)	11 (8.1)
Special senses	1 (0.8)	2 (1.5)	0 (0.0)	5 (3.7)

parenteral therapy for a disease traditionally treated with topical and oral medications. There is a considerable placebo effect observed in the study, which decreases the differences observed among treatment groups. However, a placebo effect is not unusual in allergic rhinitis studies. In most allergic rhinitis studies, therapeutic interventions with oral or topical medications result in approximately a 30% to 40% placebo effect.⁴⁰ There is also variability in ragweed exposure across the different sites. For instance, only about two thirds of patients were exposed to the severe pollen season. Lastly, patients entering the study were not completely asymptomatic. This could be a result of carryover from allergic rhinitis symptoms due to the spring allergy season. It would be extremely difficult to find patients who were sensitive to ragweed only, and thus completely asymptomatic during the enrollment and randomization periods.

The majority of clinical pharmacotherapy studies that have evaluated efficacy in allergic rhinitis have randomized symptomatic patients to show that the agent is suitable for the treatment of rhinitis symptoms. Few studies, out-

side of the realm of immunotherapy, report on the outcome of prophylactic treatment, and those that do have failed to show complete prevention of seasonal allergic rhinitis symptoms for the season.^{40,41} In our study, patients treated with omalizumab generally were protected from the seasonal increase in nasal symptoms. It is estimated that only 33% to 50% of patients with seasonal allergic rhinitis are symptom-free with antihistamine therapy.² One study that compared first-line treatments for seasonal allergic rhinitis (nasal corticosteroid spray and second-generation antihistamine) estimated at least 50% of seasonal allergic rhinitis patients needed to take both types of treatment in combination to adequately control symptoms.¹⁹ Despite general agreement that nasal steroids are only minimally bioavailable, the safety of these drugs still remains a concern.^{42,43}

Patients who would most likely benefit from omalizumab would be those who have moderate to severe seasonal allergic rhinitis with evidence of specific IgE antibodies to clinically relevant allergens. In addition, candidates would likely include patients not achieving a satisfactory favorable response to

therapy with antihistamines plus or minus nasal corticosteroids; patients who have intolerable adverse effects from these medications; patients who have difficulty taking daily medications for various compliance reasons; and patients who are unable to tolerate traditional allergy immunotherapy or are unable to comply with the strict regimen of traditional allergy immunotherapy. Others who might benefit are those with comorbid allergic conditions, such as allergic rhinitis and asthma. In recent publications, omalizumab was shown to be effective therapy for moderate to severe asthma, suggesting that omalizumab has the potential to treat multiple comorbid allergic disorders.^{44,45}

In conclusion, in this 12-week study of patients with seasonal ragweed allergic rhinitis, omalizumab therapy decreased serum free IgE levels and provided clinical benefit, improving rhinitis-specific quality of life and reducing rescue medication use. Comparative trials will be necessary to define the exact placement of this agent in the therapeutic armamentarium for seasonal allergic rhinitis.

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Author Contributions: Dr Casale, as principal investigator of omalizumab (rhuMAB-E25) clinical study, had full access to all the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analyses.

Study concept and design: Casale, Nayak, Fowler-Taylor, Fick Gupta.

Acquisition of data: Casale, Condemni, LaForce, Nayak, Rowe, Fowler-Taylor, Gupta.

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WO 03/057249 A1

(54) Title: COMBINATION TREATMENTS FOR ALLERGIC DISEASE COMPRISING ADMINISTERING AN ANTI-IGE AN-
TIBODY AND ANTIALLERGIC COMPOUND

(57) Abstract: Pharmaceutical composition comprising an anti-IgE antibody and at least one further antiallergic compound selected
from the group consisting of anti-inflammatory agents, leukotriene modifiers, bronchodilators, antihistamines, interleukin antago-
nists, mast cell inhibitors, and immunotherapeutic agents, such as 33-epichloro, 33-desoxyzascomycin (pimecrolimus), in which
the active ingredients are present in free form or in the form of a pharmaceutically acceptable salt and optionally at least one phar-
maceutically acceptable carrier; for simultaneous, separate or sequential use.

Claims:

1. A pharmaceutical composition comprising as active ingredients an anti-IgE antibody and at least one further antiallergic compound selected from the group consisting of anti-inflammatory agents, leukotriene modifiers, bronchodilators, antihistamines, interleukin antagonists, mast cell inhibitors, and immunotherapeutical agents, in which the active ingredients are present in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.
2. The composition according to claim 1 wherein the anti-IgE antibody and the at least one further antiallergic compound are comprised in a single pharmaceutical formulation.
3. The composition according to claims 1 or 2 wherein the anti-IgE antibody is Omalizumab.
4. The composition according to claim 3, characterized in that Omalizumab is administered in a concentration dependent on the baseline IgE level of the patient to be treated.
5. The composition according to any one of claims 1 to 4, characterized in that the combination comprises a further monoclonal antibody.
6. The composition according to any one of claims 1 to 5, characterized in that the composition comprises at least one immunotherapeutical agent as the further pharmaceutically active compound.
7. The composition according to claim 6, characterized in that the immunotherapeutical agent is a macrolide T-cell immunomodulator or immunosuppressant.
8. The composition according to claim 7, characterized in that the macrolide T-cell immunomodulator or immunosuppressant is a FKBP12-binding calcineurin inhibitor or mitogen-activated kinase modulator or inhibitor.

9. The composition according to claim 8, characterized in that the FKBP12-binding calcineurin inhibitor or mitogen-activated kinase modulator or inhibitor is an asco- or rapamycin.
10. The composition according to claim 9, characterized in that the ascomycin is 33-epichloro,33-desoxyascomycin (pimecrolimus).
11. The composition according to any one of claims 1 to 10, wherein the anti-IgE antibody is Omalizumab and the immunotherapeutical agent is 33-epichloro,33-desoxyascomycin (pimecrolimus).
12. The composition according to any one of claims 1 to 11, wherein the anti-IgE antibody and antiallergic compound are present in respective amounts which are jointly therapeutically effective against allergic disease.
13. The composition according to claim 12 wherein the anti-IgE antibody and antiallergic compound are present in respective amounts which are jointly therapeutically effective against asthma.
14. A method for the prevention, delay of progression or treatment of allergic disease comprising administering to a warm-blooded animal a therapeutically effective amount of a composition according to any one of claims 1 to 13.
15. A method of treatment of allergic disease comprising administering to a warm-blooded animal a therapeutically effective amount of an anti-IgE antibody and an antiallergic compound.
16. A method of treatment of allergic disease according to claim 15, wherein the anti-IgE antibody is Omalizumab.
17. A method of treatment of allergic disease according to claim 15 or 16, wherein the antiallergic compound comprises an immunotherapeutical agent.

18. A method of treatment of allergic disease according to claim 17, wherein the immunotherapeutical agent is a macrolide T-cell immunomodulator or immunosuppressant.
19. A method of treatment of allergic disease according to claim 18 wherein the macrolide T-cell immunomodulator or immunosuppressant is a FKBP12-binding calcineurin inhibitor or mitogen-activated kinase modulator or inhibitor.
20. A method of treatment of allergic disease according to claim 19 wherein the FKBP12-binding calcineurin inhibitor or mitogen-activated kinase modulator or inhibitor is an asco- or rapamycin.
21. A method of treatment of allergic disease according to claim 20 wherein the ascomycin is 33-epichloro,33-desoxyascomycin (pimecrolimus).
22. A method of treatment of allergic disease according to claim 15 wherein the anti-IgE antibody is Omalizumab and the immunotherapeutical agent is 33-epichloro,33-desoxyascomycin (pimecrolimus).
23. A method of treatment of allergic disease wherein an anti-IgE antibody and an antiallergic compound are co-administered.
24. A method of treatment of allergic disease wherein Omalizumab and 33-epichloro,33-desoxyascomycin (pimecrolimus) are co-administered.
25. A method of treatment of allergic disease according to claim 23 wherein Omalizumab is administered before 33-epichloro,33-desoxyascomycin (pimecrolimus).
26. The use of a composition according to any one of claims 1 to 13 in medicine.
27. The use of a composition according to any one of claims 1 to 13 for the manufacture of a medicament for the treatment of a warm-blooded animal having allergic disease.
28. Use of the composition according to any one of claims 1 to 13 for the prevention or treatment of allergic disease.

29. The use of Omalizumab and 33-epichloro,33-desoxyascomycin (pimecrolimus).
for the manufacture of a medicament for the treatment of a warm-blooded animal having
allergic disease.
30. The use of an antiallergic compound for the manufacture of a medicament for the
treatment of a patient under treatment with Omalizumab.
31. The use of an antiallergic compound according to claim 30, wherein the antiallergic
compound is an immunotherapeutical agent.
32. The use of an antiallergic compound according to claim 31, wherein the
immunotherapeutical agent is a macrolide T-cell immunomodulator or immunosuppressant.
33. The use of an antiallergic compound according to claim 32, wherein the macrolide T-cell
immunomodulator or immunosuppressant is a FKBP12-binding calcineurin inhibitor or
mitogen-activated kinase modulator or inhibitor.
34. The use of an antiallergic compound according to claim 33, wherein the FKBP12-binding
calcineurin inhibitor or mitogen-activated kinase modulator or inhibitor is an asco- or
rapamycin.
35. The use of an immunotherapeutical agent according to claim 34, wherein the ascomycin
is 33-epichloro,33-desoxyascomycin (pimecrolimus).
36. A kit comprising as active agent a composition according to any one of claims 1 to 13
together with instructions for simultaneous, separate or sequential use thereof in the
prevention, delay of progression or treatment of allergic disease.



US006723833B1

(12) **United States Patent**
Lowman et al.

(10) **Patent No.:** **US 6,723,833 B1**
 (45) **Date of Patent:** ***Apr. 20, 2004**

(54) **THERAPEUTIC COMPOSITIONS
 COMPRISING ANTI-IGE ANTIBODIES AND
 IMMUNOSUPPRESSIVE AGENT**

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(73) Assignee: **Genentech, Inc.**, South San Francisco,
 CA (US)

(*) Notice: Subject to any disclaimer, the term of this
 patent is extended or adjusted under 35
 U.S.C. 154(b) by 99 days.

This patent is subject to a terminal dis-
 claimer.

(21) Appl. No.: **09/716,028**

(22) Filed: **Nov. 17, 2000**

Related U.S. Application Data

(62) Division of application No. 09/109,207, filed on Jun. 30,
 1998, now Pat. No. 6,172,213.

(60) Provisional application No. 60/051,554, filed on Jul. 2,
 1997.

(51) Int. Cl.⁷ **C07K 16/00; C12P 21/08**

(52) U.S. Cl. **530/388.73; 530/387.3;**
536/252.3; 536/23.53; 435/69.6

(58) Field of Search **435/69.6; 536/252.3,**
536/23.53; 530/387.3, 388.73

(56) **References Cited**

U.S. PATENT DOCUMENTS

4,255,519 A	3/1981	Terada et al.
4,275,149 A	6/1981	Litman et al.
4,816,567 A	3/1989	Cabilly et al.
5,534,617 A	7/1996	Cunningham et al.
5,561,053 A	10/1996	Crowley
5,622,700 A *	4/1997	Jardieu et al.
5,705,154 A	1/1998	Dalie et al.
5,750,373 A	5/1998	Garrard et al.
5,821,337 A	10/1998	Carter et al.
5,994,511 A *	11/1999	Lowman et al.

FOREIGN PATENT DOCUMENTS

EP	239400 B1	8/1994
WO	WO 93/04173	3/1993
WO	WO 93/11161	6/1993
WO	WO 93/16185	8/1993
WO	WO 95/24481	9/1995
WO	WO 97/06822	2/1997

OTHER PUBLICATIONS

Amit et al., "Three-Dimensional Structure of an Anti-
 gen-Antibody Complex at 2.8 Å Resolution" *Science*
 233:747-753 (Aug. 1986).

Barbas III et al., "In vitro evolution of a neutralizing human
 antibody to human immunodeficiency virus type 1 to
 enhance affinity and broaden strain cross-reactivity" *Proc.*
Natl. Acad. Sci. USA 91(9):3809-3813 (Apr. 26, 1994).

Brennan et al., "Preparation of bispecific antibodies by
 chemical recombination of monoclonal immunoglobulin G₁
 fragments" *Science* 229:81-83 (Jul. 1985).

Cacia et al., "Isomerization of an aspartic acid residue in the
 complementarity-determining regions of a recombinant
 antibody to human IgE: identification and effect on binding
 affinity" *Biochemistry* 35(6):1897-1903 (Feb. 13, 1996).

Carter et al., "High level *Escherichia coli* expression and
 production of a bivalent humanized antibody fragment"
BioTechnology 10:163-167 (1992).

Carter et al., "Humanization of an anti-p185^{HER2} antibody
 for human cancer therapy" *Proc. Natl. Acad. Sci.*
 89:4285-4289 (1992).

U.S. patent application Ser. No. 08/146, 206, Carter et al.,
 filed Nov. 17, 1993.

U.S. patent application Ser. No. 08/232,539, Jardieu et al.,
 filed Apr. 21, 1994.

U.S. patent application Ser. No. 08/405,617, Jardieu et al.,
 filed Mar. 15, 1995.

U.S. patent application Ser. No. 08/437,642, Carter et al.
 filed May 9, 1995.

U.S. patent application Ser. No. 08/466,151, Jardieu et al.,
 filed Jun. 6, 1995.

U.S. patent application Ser. No. 08/466,163, Jardieu et al.,
 filed Jun. 6, 1995.

U.S. patent application Ser. No. 09/115,800, Carter et al.,
 filed Jul. 15, 1998.

Champe et al., "Monoclonal antibodies that block the activ-
 ity of leukocyte function-associated antigen 1 recognize
 three discrete epitopes in the inserted domain of CD11a"
Journal of Biological Chemistry 270:1388-1394 (1995).

Chothia and Lesk, "Canonical structures for the hypervari-
 able regions of immunoglobulins" *J. Mol. Biol.*
 196(4):901-917 (1987).

Chothia et al., "Domain Association in Immunoglobulin
 Molecules. The Packing of Variable Domains" *Journal of*
Molecular Biology 186:651-663 (1985).

Chothia, C. et al., "Conformations of immunoglobulin
 hypervariable regions" *Nature* 342(6252):877-883 (1989).

(List continued on next page.)

Primary Examiner—G. R. Ewoldt

(74) *Attorney, Agent, or Firm*—Craig G. Svoboda

(57) **ABSTRACT**

The present invention relates to a method for adjusting the
 affinity of a polypeptide to a target molecule by a combi-
 nation of steps, including: (1) the identification of aspartyl
 residues which are prone to isomerization; (2) the substitu-
 tion of alternative residues and screening the resulting
 mutants for affinity against the target molecule. In a pre-
 ferred embodiment, the method of substituting residues is
 affinity maturation with phage display (AMPD). In a further
 preferred embodiment the polypeptide is an antibody and the
 target molecule is an antigen. In a further preferred
 embodiment, the antibody is anti-IgE and the target mol-
 ecule is IgE. In another embodiment, the invention relates to
 an anti-IgE antibody having improved affinity to IgE.

15 Claims, 19 Drawing Sheets

-continued

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What is claimed is:

1. A composition of an improved anti-IgE antibody or IgE binding fragment thereof in combination with an adjunct immunosuppressive agent, wherein the improved anti-IgE antibody or IgE binding fragment thereof comprises:

- (a) the heavy and light chains of E26 (SEQ ID NOs:15-16);
- (b) the heavy and light chains of E27 (SEQ ID NOs:17-18); or
- (c) antigen binding fragments of (a) or (b).

2. The composition of claim 1, wherein the immunosuppressive agent is selected from the group consisting of: azathioprine, cyclophosphamide, bromocryptine and glutaraldehyde.

3. The composition of claim 1, wherein the immunosuppressive agent is a glucocorticosteroid.

4. The composition of claim 1, wherein the immunosuppressive agent is selected from the group consisting of: cyclosporin A; an anti-CD3 antibody; an anti-CD4 antibody and an anti-CD4a antibody.

5. The composition of claim 1, wherein the immunosuppressive agent is selected from the group consisting of: a soluble peptide containing an I.FA-3 binding domain; strep-

tokinase; TGF- β ; streptodomainase; deoxyspergualin, rapamycin and a T-cell receptor.

6. The composition of claim 1, wherein the improved anti-IgE antibody comprises the heavy and light chain sequences of E26 (SEQ ID NOs:15-16).

7. The composition of claim 1, wherein the improved IgE binding fragment comprises an E26 sequence selected from the group consisting of: an Fab fragment (SEQ ID NOs:19-20; an sFv fragment (SEQ ID NO:22) and an F(ab')₂ fragment (SEQ ID NOs: 24-25).

8. The composition of claim 1, wherein the improved IgE binding fragment comprises an E27 sequence selected from the group consisting of: an Fab fragment (SEQ ID NOs: 19 and 21); an sFv fragment (SEQ ID NO:23) and an F(ab')₂ fragment (SEQ ID NOs: 24 and 26).

9. The composition of claim 1, wherein the improved anti-IgE antibody comprises the heavy and light chains of E27 (SEQ ID NOs: 17-18).

10. The composition of claim 1, wherein the immunosuppressive agent is a 2-amino-5-aryl-substituted pyrimidine.

11. The composition of claim 1, wherein the immunosuppressive agent is an anti-idiotypic antibody which binds MHC antigens or fragments.

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12. The composition of claim 1, wherein the immuno-suppressive agent is a T-cell receptor antibody.

13. The composition of claim 1, wherein the immuno-suppressive agent is a cytokine antagonist or a cytokine receptor antagonist.

14. The composition of claim 13, wherein the immuno-suppressive agent is an antibody selected from the group consisting of: an anti-interferon- γ antibody, an anti-interferon- β antibody, an anti-interferon- α antibody; an anti-

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tumor necrosis factor- α antibody, an anti-tumor necrosis factor- β antibody, an anti-interleukin-2 antibody, anti-IL-2 receptor antibody and an anti-L3T4 antibody.

15. The composition of claim 3, wherein the immuno-suppressive agent is selected from the group consisting of: prednisone, methylprednisone and dexamethasone.

* * * * *

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIRECCIÓN DE NUEVAS CREACIONES

148

2020
Bogotá, D.C.,

Abogado
CARLOS R. OLARTE

ASUNTO

Radicación 07 079 737
Trámite 011
Evento 378
Actuación 519
Oficio
Folios 6. **17502**

Patente de Invención ☒ Patente de Modelo de Utilidad ☐
Vía Nacional ☐
Vía PCT (fase nacional) ☒ Cap. I ☒ Cap. II ☐
No. Solicitud Internacional PCT/EP2006/000911
Fecha de Presentación Internacional 02/Febrero/2006

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

1. Documentos estudiados

Descripción:	Folios 40 a 75	03/Agosto/2007
Reivindicaciones:	Folios 76 a 78	03/Agosto/2007
Oposiciones:	Folios 101 a 147	Lafrancol 28/Agosto/2008
Prioridad	GB0502358	04/Febrero/2005

2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486) y su contenido técnico corresponde con el de la prioridad reivindicada.

3. Objeto de la invención

Título de la solicitud: "Combinación sinérgica de xolair/omalizumab/E25 con agente inmunosupresor"

El problema planteado en esta solicitud consiste en la necesidad de mejorar la medicación actualmente disponible con el objeto de controlar los síntomas y de aminorar los procesos subyacentes de enfermedades alérgicas.

Para resolver este problema técnico la solicitud en estudio proporciona una composición farmacéutica que comprende, como ingredientes activos, un anticuerpo anti-IgE y cuando menos un agente que suprime la respuesta inmune.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): A 61 K 39/395; A 61 P 37/08

4. Excepción a la Patentabilidad (Art 20 D 486 literal d)

El objeto de la reivindicación 12 no es patentable de acuerdo con el Art citado.

5. Reivindicaciones relativas a un uso o a un segundo uso (Art 14 y 21 D 486)

El uso de las reivindicaciones 7 y 13 – 16 no es patentable, de acuerdo con el Art 14.

6. De la Solicitud de Patente

Título

El título no corresponde con el objeto de la solicitud porque la solicitud definida en el capítulo reivindicatorio no indica que el anticuerpo anti-IgE corresponda a xolair/omalizumab/e25, por lo cual se sugiere al Solicitante hacer la corrección necesaria.

Reivindicaciones (Art 30 D 486, Art 22 PCT)

Las Reivindicaciones 1 – 6, 8 – 11 y 17 no son claras porque el **uso** simultaneo, separado o en secuencia no constituye una característica técnica esencial que defina la invención. Se sugiere definirlo exclusivamente por sus características esenciales, estructurales o funcionales; por demás cuando se habla de uso separado o secuencial se hace referencia a un método de tratamiento.

Las reivindicaciones 1 -2 y 3 no son claras cuando se utiliza el término “al menos” “por ejemplo” ya que en este caso el alcance y el ámbito de protección de la reivindicación deja de ser precisa. Se requiere al solicitante eliminar estos términos del alcance del capítulo reivindicatorio.

Las reivindicaciones 1 – 2 y 10 no son claras ni concisas cuando se definen los ingredientes activos como un anticuerpo anti-IgE y un agente inmunosupresor. Se recuerda al solicitante que esta manera de reclamar no es apropiada, porque los activos se están definiendo por su actividad terapéutica, lo cual no define inequívocamente un ingrediente activo como tal. Se requiere al solicitante definir cada uno de los activos por compuestos o activos específicos.

Para la reivindicación 3 se utilizan los nombres comerciales. Estos deben ser eliminados del alcance del pliego reivindicatorio porque le resta claridad a la solicitud.

Las reivindicaciones 1 y 2 no son claras porque no se establecen las dosis de cada activo. Se recuerda al solicitante que el efecto sinérgico de una composición conformada por uno o más activos se basa en las dosis de cada uno de ellos. Se sugiere al solicitante incorporar las dosis (concentraciones de los activos) que hacen parte de la composición.

La reivindicación 9 no es clara porque se caracteriza en que el Omalizumab se administra en una concentración dependiente. Esta manera de caracterizar no es apropiada porque la manera como se administra un activo no es una característica técnica de la composición, sino de un método de tratamiento.

Las reivindicaciones 5 a 6 carecen de claridad, porque se reivindica nuevamente la composición ya reclamada en 1, caracterizándola porque inhibe la activación de las células T. Esta caracterización no aporta ninguna característica técnica esencial adicional a lo ya reclamado anteriormente. Se recuerda al solicitante que la caracterización de una composición se realiza por sus ingredientes activos específicos, excipientes y/o sus proporciones, mas no por su mecanismo de acción.

Las reivindicaciones 10 y 11, no son concisas cuando se habla de "cantidades terapéuticamente efectivas", no se definen ni las cantidades o las dosis de los anticuerpos que hacen parte de la composición.

La reivindicación 17, no es clara cuando se dice " que su uso es simultaneo , secuencial o en secuencia, porque esto hace referencia a un método de tratamiento.

Análisis de Oposiciones

Argumentaciones de Lafranco

1. El oponente presenta los argumentos que demuestran que la solicitud incumple los requisitos de patentabilidad. En primer lugar, el oponente presenta documentos que muestran el uso del omalizumab en transtornos alérgicos, tales como:
 - Omalizumabimproves asthma-related quality o life in patients with severe allergic asthma.
 - Efficacy and tolerability of antiimmunoglobulin E therapy with Omalizumab in patient with poorly controlled (Moderate-to-sever) allergic asthma
 - The anti Ig-E antybody omalizumab reduces exacerbation and steroid requeriment in allergic asthmatics
 - Omalizumab, anti Ig-E rembinated humanized monoclonal antibody, for the treatment of severe allergic asthma
 - Effect of omalizumab on symptoms of seasonal allergyc rinitis

Todos estos documentos muestran el efecto terapéutico del omalizumab sobre transtornos alérgicos, específicamente asma y rinitis. Por esta razón, el opnente dice que una persona medianamente versada en la materia conociendo el mecanismo de acción y la acción terapéutica del anticuerpo, podría llegar fácilmente a la conclusión de que combinando amalizumab con otros agentes inmunosupresores, podría obtenerse un tratamiento efectivo para estos transtornos alérgicos. En la misma via, estos documentos también demuestran donde se muestra que el uso concomitante de omalizumab con corticoesteroides, reduce la cantidad necesaria de dichos agentes inmunosupresores en pacientes asmáticos.

2. Afirma el oponente que esta solicitud la anticipan documentos como la publicación internacional WO 03/057249 (D1) publicada el 17 de julio de 2003 que revela formulaciones farmacéuticas que contiene una combinación entre un anticuerpo anti-IgE -específicamente olamizumab- junto con agentes inmuño supresores útiles para el tratamiento de trastornos alérgicos; a su vez la patente americana US 6,723,833 (D2) publicada el 20 de abril de 2004 que revela formulaciones farmacéuticas que contienen una combinación entreun anticuerpo anti-IgE y diversos agentes inmunosupresores. Por lo cual la solicitud colombiana carece de novedad.

Respuesta del solicitante

El solicitante no realizo pronunciamiento alguno sobre la oposición presentada por Lafrancol

Respuesta del Examinador Técnico

Aunque los primeros documentos presentados por el oponente muestran el efecto del omalizumab sobre trastornos de tipo alérgico, como el asma o la rinitis, estos no muestran una relación clara con una posible combinación de el anticuerpo y los corticoides, poniendo presente que una persona medianamente versada en la materia conoce que el efecto de dos fármacos con una misma actividad, no siempre va a redundar en la suma de los efectos por lo cual estos documentos no desvirtúan los requisitos de patentabilidad de esta solicitud y no se considerarán dentro del examen.

Ahora teniendo en cuenta los documentos WO03/057249 (denominado en adelante D1) y la patente americana US 6,723,833 (denominada en adelante D2) se encuentra que al opositor le asiste la razón porque tal como se encuentra planteada la reivindicación 1 de la actual solicitud sus características técnicas esenciales se encuentran reveladas por los citados documentos, desvirtuando su Novedad. Por tal motivo estos documentos serán tenidos en cuenta dentro del examen de Patentabilidad.

7. Determinación del Estado de la Técnica

El Estado de la Técnica se determinó con base en la

Fecha de Presentación de la Solicitud de Prioridad: 04 de Febrero de 2005

y se encontraron los siguientes documentos que anticipan el objeto de esta solicitud:

Item	Documento	Título	Fecha de Publicación
D1	WO 03/057249	Combination treatments for allergic disease comprising administering an anti-ige antibody and antiallergic compound	17 de julio de 2003
D2	US 6,723,833	Therapeutic compositions comprising anti-IGE antibodies and immunosuppressive agent Therapeutic compositions comprising anti-IGE antibodies and immunosuppressive agent	20 de Abril de 2004

D1 divulga (página 3, renglones 1 – 11) una composición farmacéutica que comprende un anticuerpo anti-IgE y un agente antialérgico, utilizados en el tratamiento de enfermedades alérgicas.

D1 se encuentra disponible en el link http://worldwide.espacenet.com/publicationDetails/biblio?CC=WO&NR=03057249A1&KC=A1&FT=D&date=20030717&DB=EPODOC&locale=en_EP

D2 divulga (Reivindicaxciones 1 – 15) una composición que contiene un anticuerpo anti IgE junto con agente inmunosupresor.

D2 se encuentra disponible en el link http://worldwide.espacenet.com/publicationDetails/biblio?DB=EPODOC&II=0&adjacent=true&locale=en_EP&FT=D&date=20040420&CC=US&NR=6723833B1&KC=B1

8. Examen de Patentabilidad (Art 14 D486)

Novedad (Art 16 D486)

La reivindicación 1 consiste en una composición farmacéutica que comprende un anticuerpo anti-IgE y cuando menos un agente inmunosupresor, en donde los ingredientes activos están presentes en cada caso en forma libre o en la forma de una sal farmacéuticamente aceptable, y opcionalmente cuando menos un vehículo farmacéuticamente aceptable; para su uso simultáneo, separado, o en secuencia.

Comparación de las características técnicas **esenciales** de la reivindicación 1, con las del Estado de la Técnica:

Características esenciales	D1
Composición farmacéutica	Composición farmacéutica (pagina 25, reivindicación 1)
Anticuerpo anti-IgE	Anticuerpo anti-IgE (pagina 25, reivindicación 1)
Al menos un agente inmunosupresor	Agente inmunosupresor de células T (pagina 25, reivindicación 7)
Activos están presentes en cada caso en forma libre o en la forma de una sal farmacéuticamente aceptable	Activos presentes en forma libre o en forma de una sal farmacéuticamente aceptable (pagina 25, reivindicación 1)
Opcionalmente un vehículo farmacéuticamente aceptable	Opcionalmente un vehículo farmacéuticamente aceptable (pagina 25, reivindicación 1)

Las características **esenciales** de la composición de la reivindicación 1 habían sido divulgadas previamente en D1, el cual revela, composición farmacéutica que comprende un anticuerpo anti-IgE y cuando menos un agente antialérgico (inmunoterapeutico, supresor o modulador) en donde los ingredientes activos están presentes en forma libre o en forma de una sal farmacéuticamente aceptable, y opcionalmente un vehículo farmacéuticamente aceptable; para su uso simultáneo, separado, o en secuencia (página 25, reivindicaciones 1 – 7)

En consecuencia, la reivindicación 1 carece de novedad, según lo divulgado en el documento D1.

Las reivindicaciones dependientes 2 – 6, 8 – 11 no mencionan alguna característica que haga nueva a la composición de la reivindicación 1, por lo cual se considera que no son nuevas.

Comparación de las características técnicas **esenciales** de la reivindicación 1, con las del Estado de la Técnica:

Características esenciales	D2
Composición farmacéutica	Composición farmacéutica (Columna 131, reivindicación 1)
Anticuerpo anti-IgE	Anticuerpo anti-IgE (Columna 131, reivindicación 1)
Al menos un agente inmunosupresor	Agente inmunosupresor (Columnas 131 – 134, reivindicaciones 2 - 15)
Activos están presentes en cada caso en forma libre o en la forma de una sal	Activos presentes en forma libre (pagina 25, reivindicación 1)

farmacéuticamente aceptable	
Opcionalmente un vehículo farmacéuticamente aceptable	Opcionalmente un vehículo (Columna 58, renglones 62 – 67; columna 59, renglones 1 – 2)

Las características **esenciales** de la composición de la reivindicación 1 habían sido divulgadas previamente en D2, el cual revela, composición que comprende un anticuerpo anti-IgE (Columna 131, Reivindicación 1) y cuando menos un agente inmunosupresor (Columna 131 - 134, reivindicaciones 2 – 15) en donde los ingredientes activos están presentes en forma libre y opcionalmente un vehículo (Columna 58, renglones 62 – 67; columna 59, renglones 1 – 2)

En consecuencia, la reivindicación 1 carece de novedad, según lo divulgado en el documento D1.

Las reivindicaciones dependientes 2 – 6, 8 – 11 no mencionan alguna característica que haga nueva a la composición de la reivindicación 1, por lo cual se considera que no son nuevas.

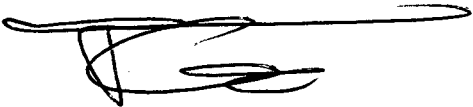
9. Conclusión

Los requisitos de Patentabilidad de la presente Solicitud están afectados así:

Item	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	WO 03/057249	1 – 6, 8 – 11	Novedad
D2	US 6,723,833	1 – 6, 8 – 11	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



JOSÉ LUIS SALAZAR LÓPEZ
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha 17-0 NOV. 2011

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Revisado por : Jacqueline Alfonso. *OK / JA*