NOUS TRACTAMENTS BIOLÒGICS EN L'ASMA BRONQUIAL

XXXI DIADA PNEUMOLÒGICA, Sitges 12 d'Abril de 2013

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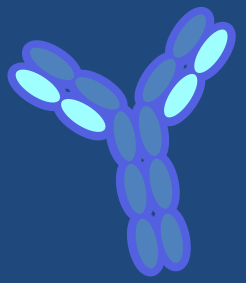
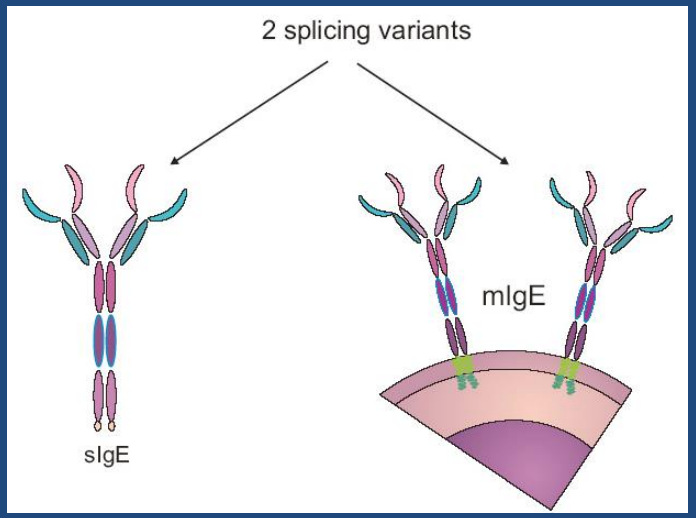
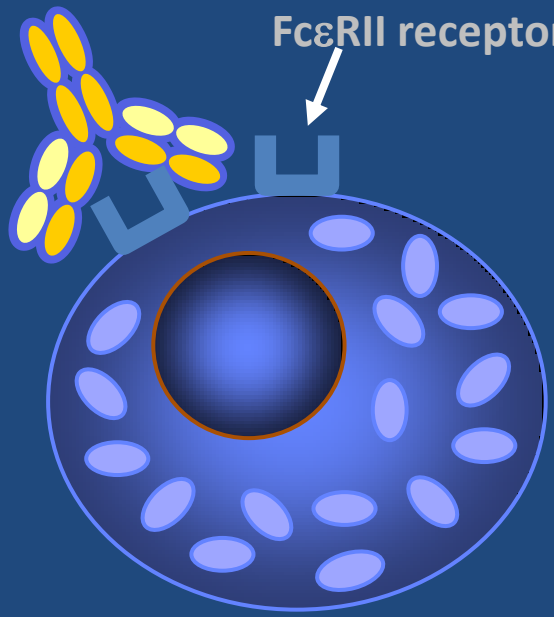
Corporació Sanitària i Universitària Parc Taulí
Sabadell

MECANISMES D'ACTUACIÓ (I)- ANTICOSSOS MONOCLONALS

Ac Anti-IgE

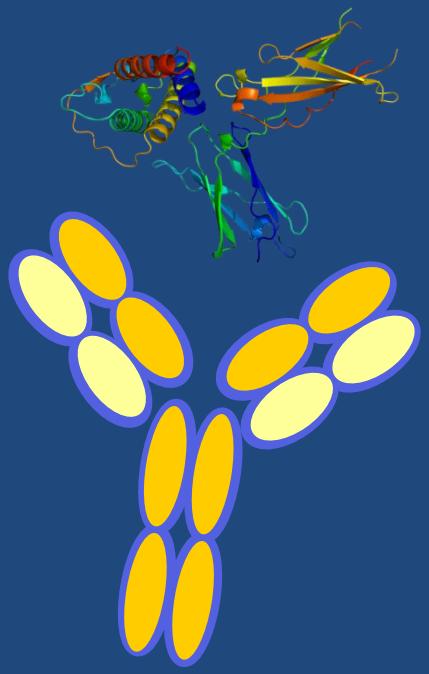






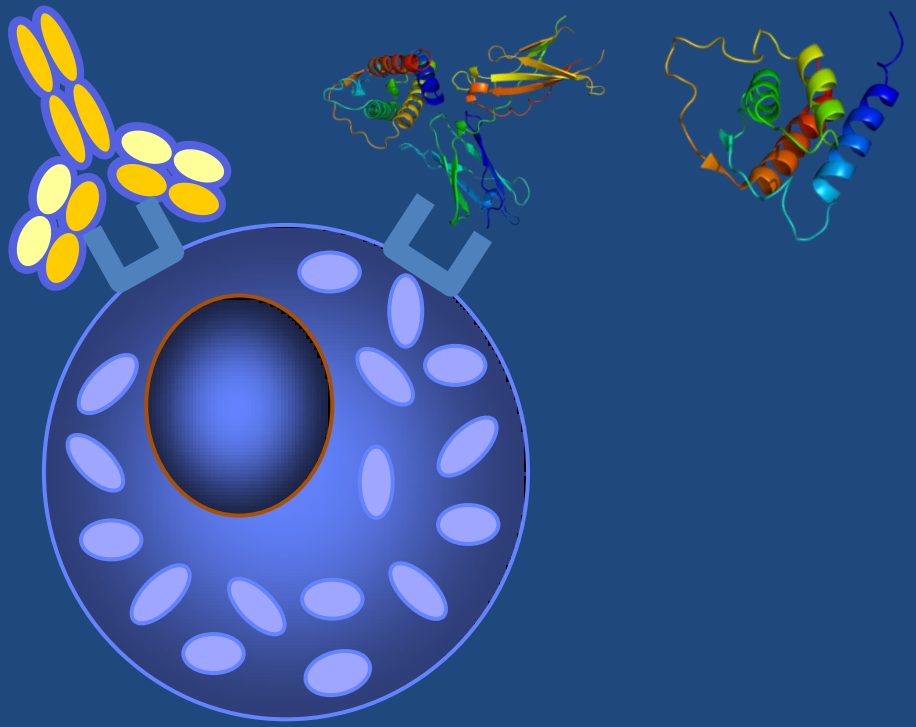
MECANISMES D'ACTUACIÓ (II)-ANTICOSSOS MONOCLONALS

Ac Anti-IL



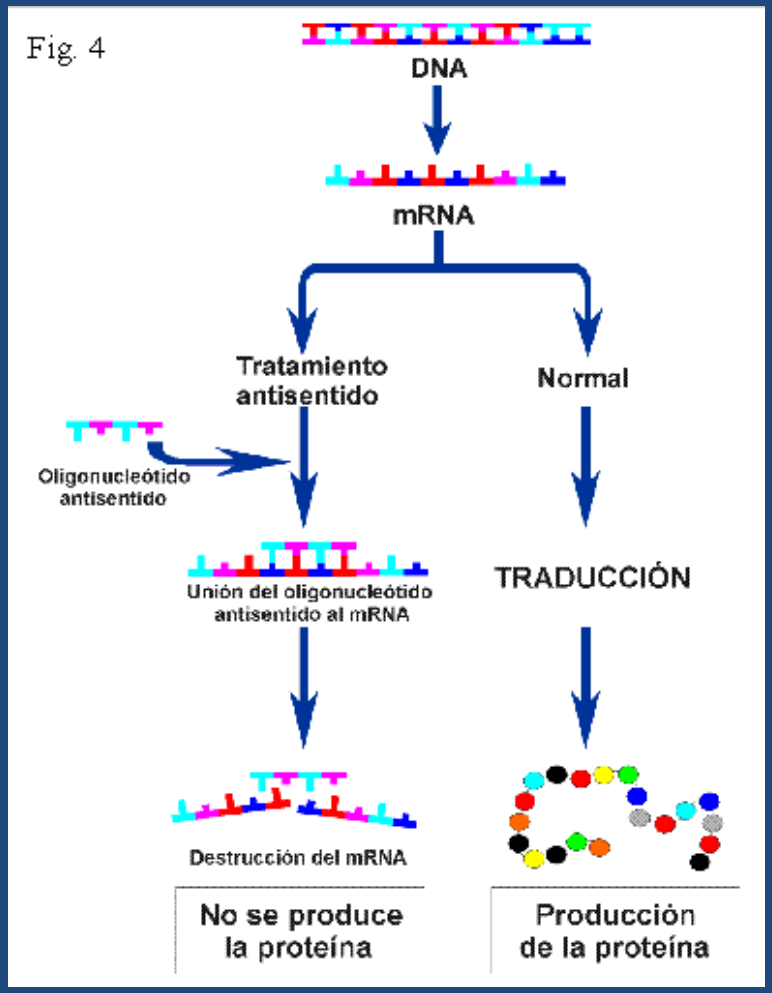
Anti-ILR

Antagonisme competitiu

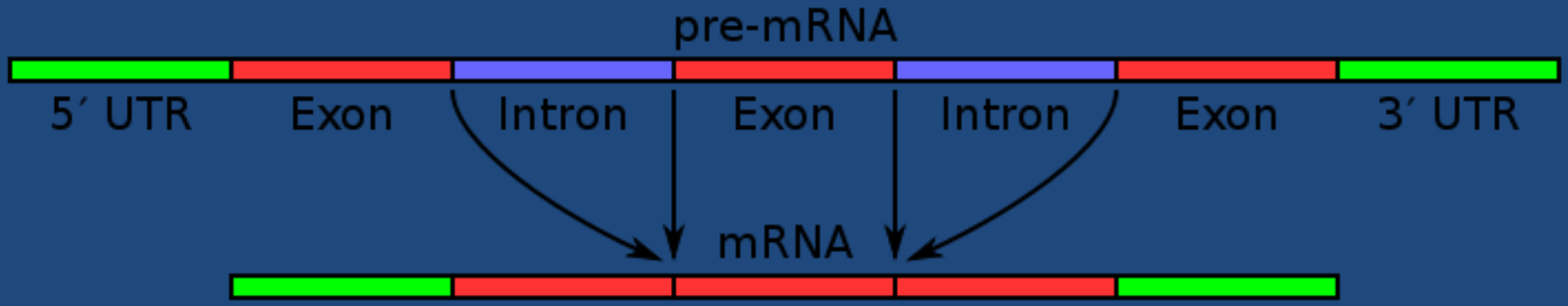


MECANISMES D'ACTUACIÓ (III)- "Anti-sense Therapy"

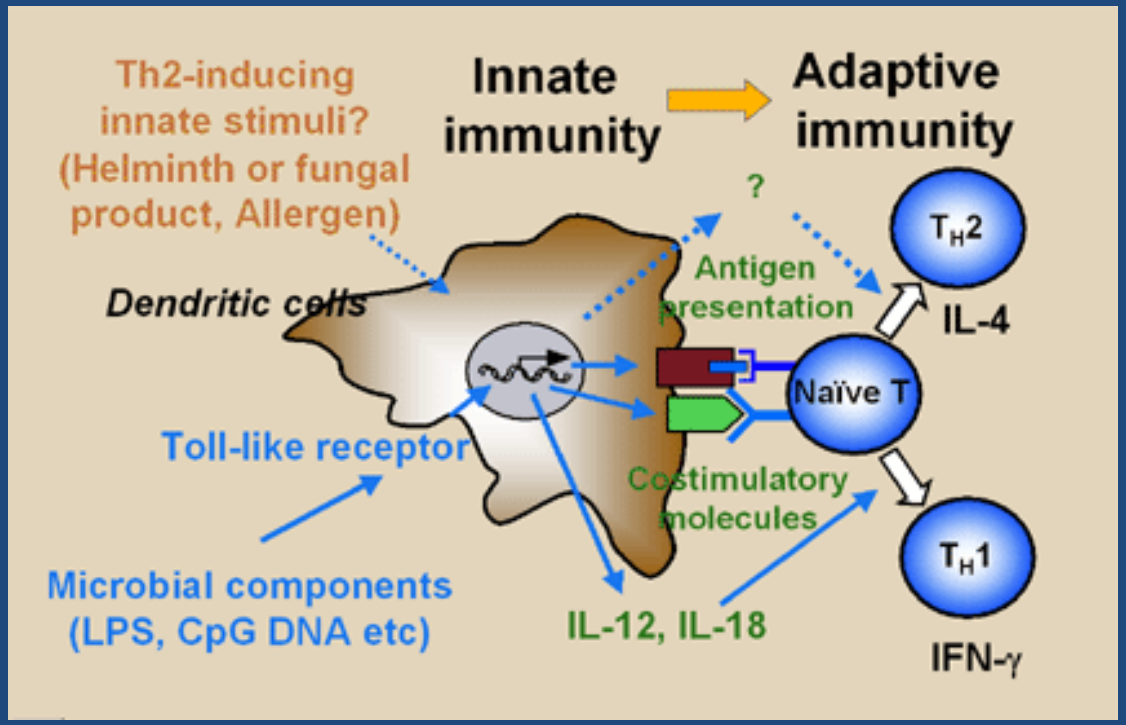
DEFINICIÓ: Se'n diu teràpia anti-sentit per que són un conjunt d'oligonucleòtids que tenen una seqüència de bases complementària a la del mRNA que codifica una proteïna.



MECANISMES D'ACTUACIÓ (III) - "Anti-sense Therapy"



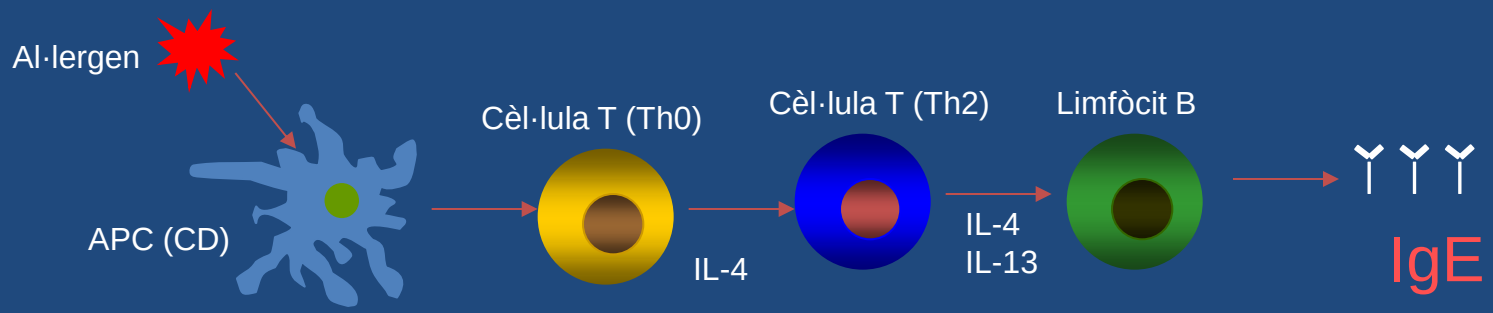
FISIOPATOLOGIA DE LA REACCIÓ AL·LÈRGICA



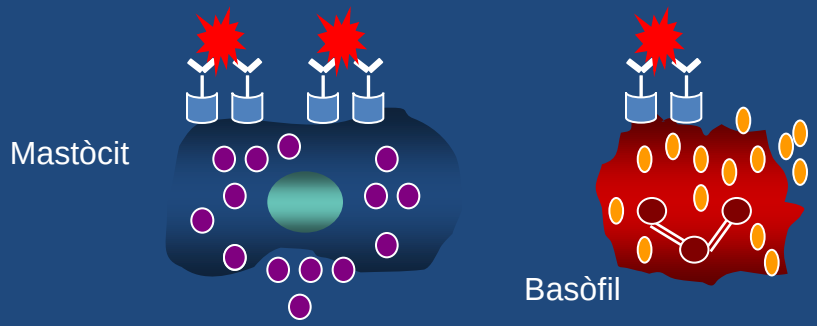
Domingo et al. Recent Patents Inflamm Allergy Drug Discov. 2007; 1: 151-164

FISIOPATOLOGIA DE LA REACCIÓ AL·LÈRGICA

a) Sensibilització



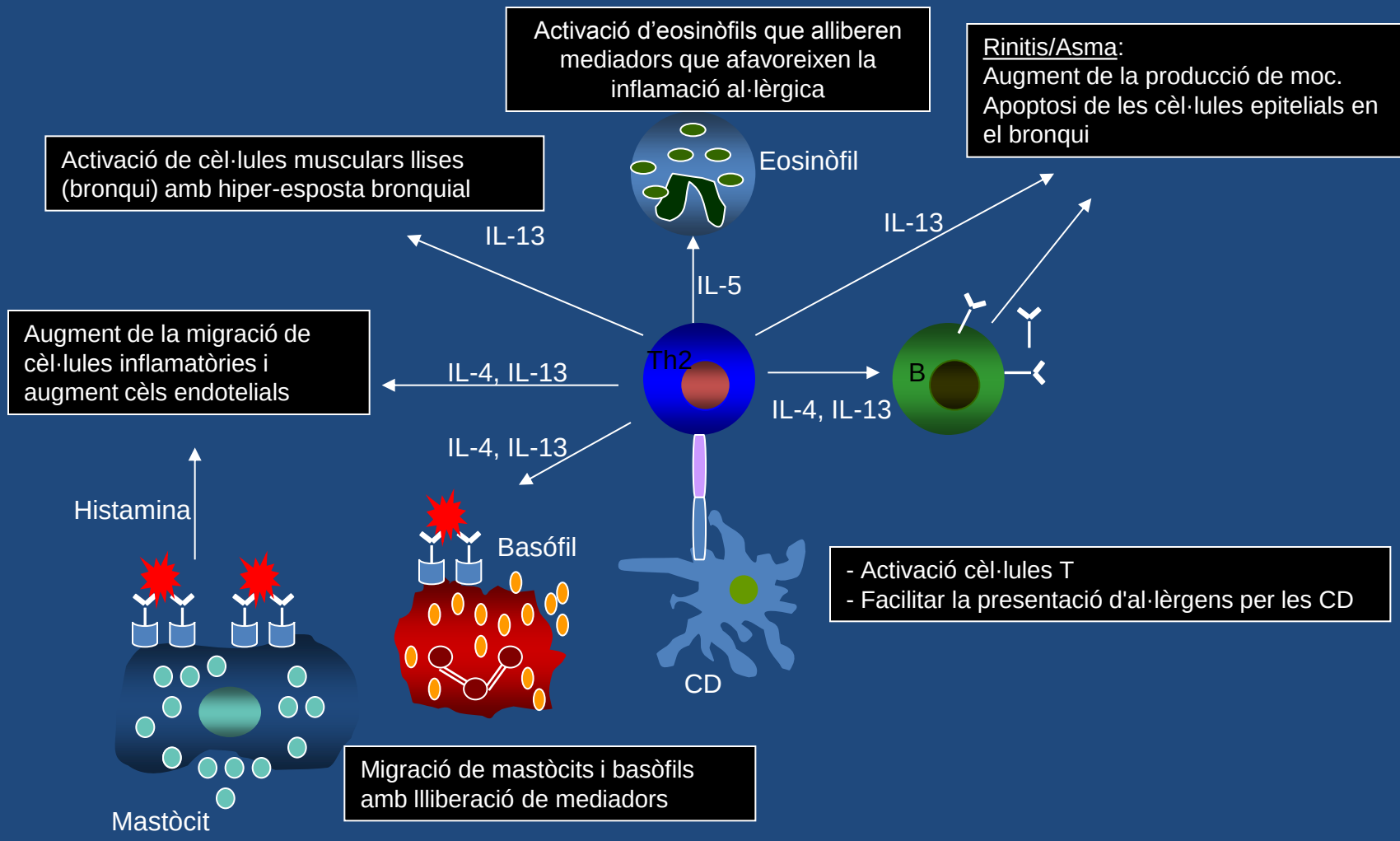
b) Fase immediata: Reacció tipus 1



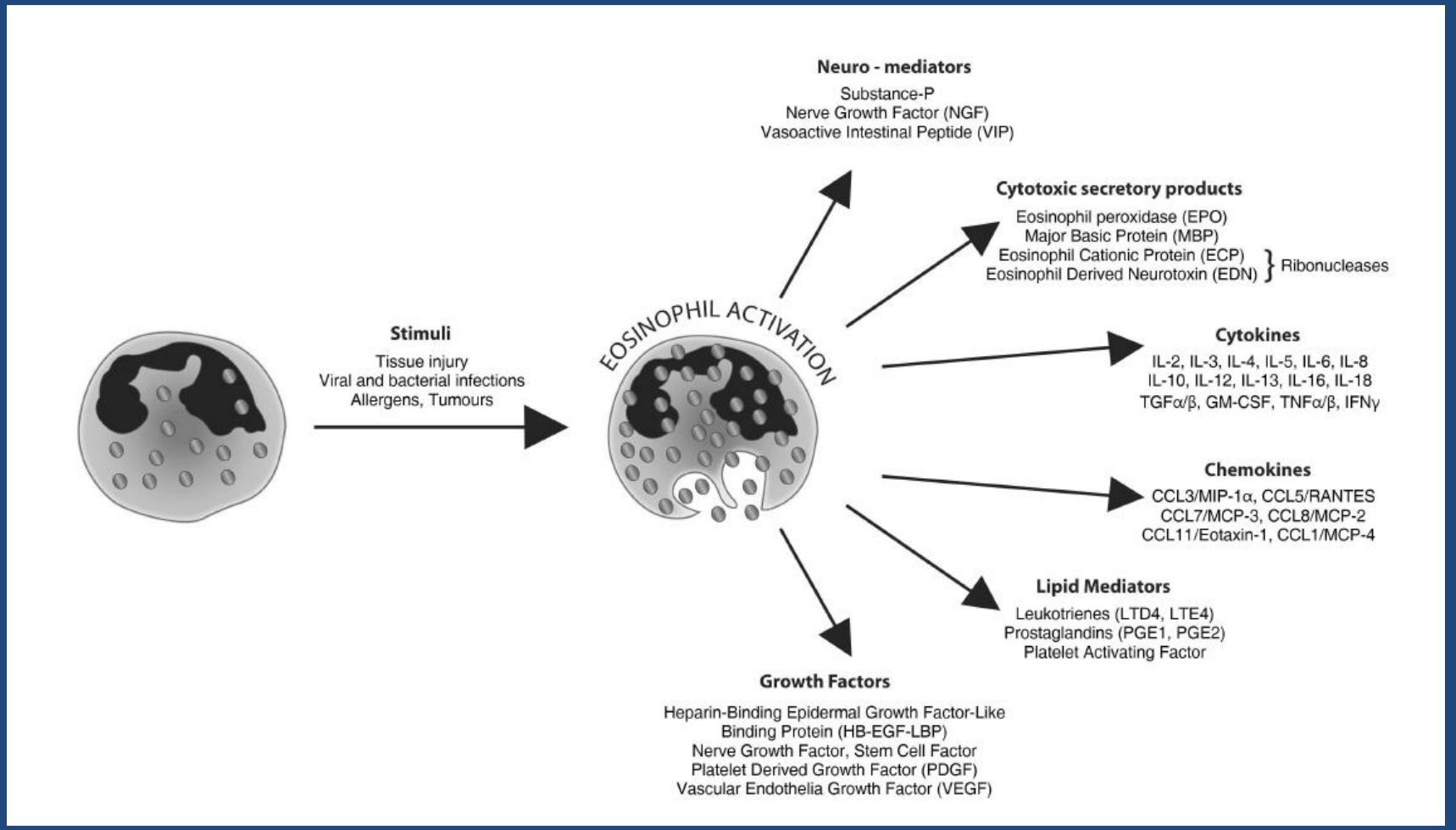
Degranulació:
LLiberació d'histamina, prostaglandines, leucotriens…

FISIOPATOLOGIA DE LA REACCIÓ AL·LÈRGICA

c) Fase tardana: inflamació al·lèrgica



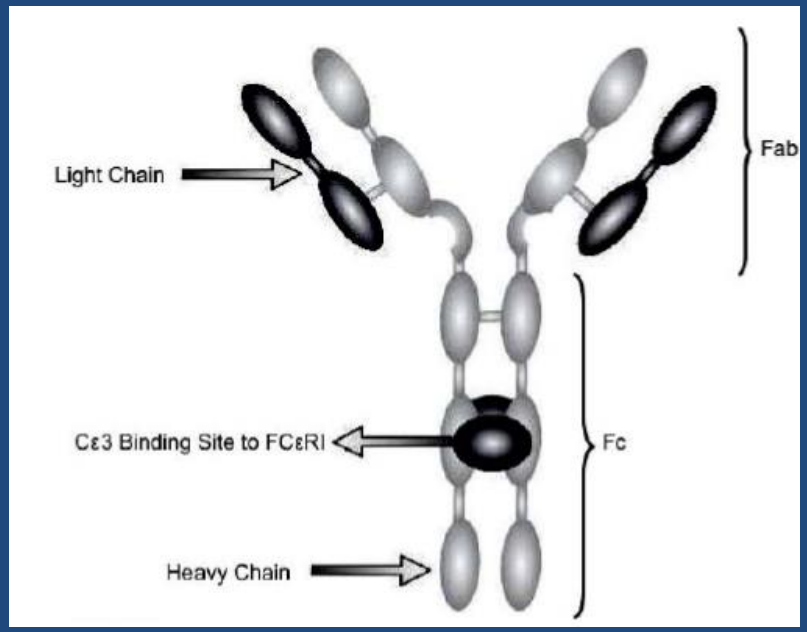
FISIOPATOLOGIA DE LA REACCIÓ AL·LÈRGICA

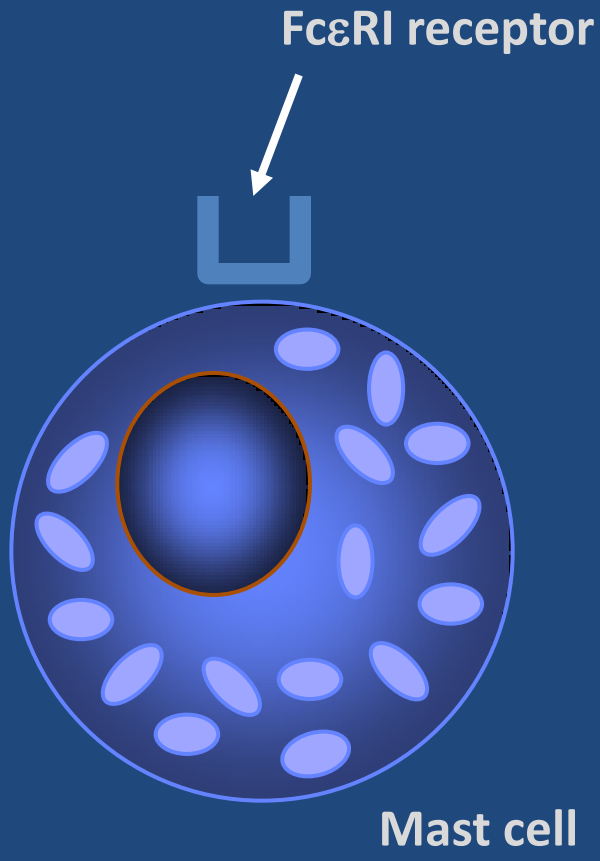


TRACTAMENTS ANTI-IgE

- Bloquejants de la IgE: Omalizumab, Ligelizumab.
- Bloquejants de la producció d'IgE: Quilizumab
- Bloquejant del receptor per la IgE de baixa afinitat FceRII: Lumiliximab

FISIOPATOLOGIA DE LA REACCIÓ AL·LÈRGICA



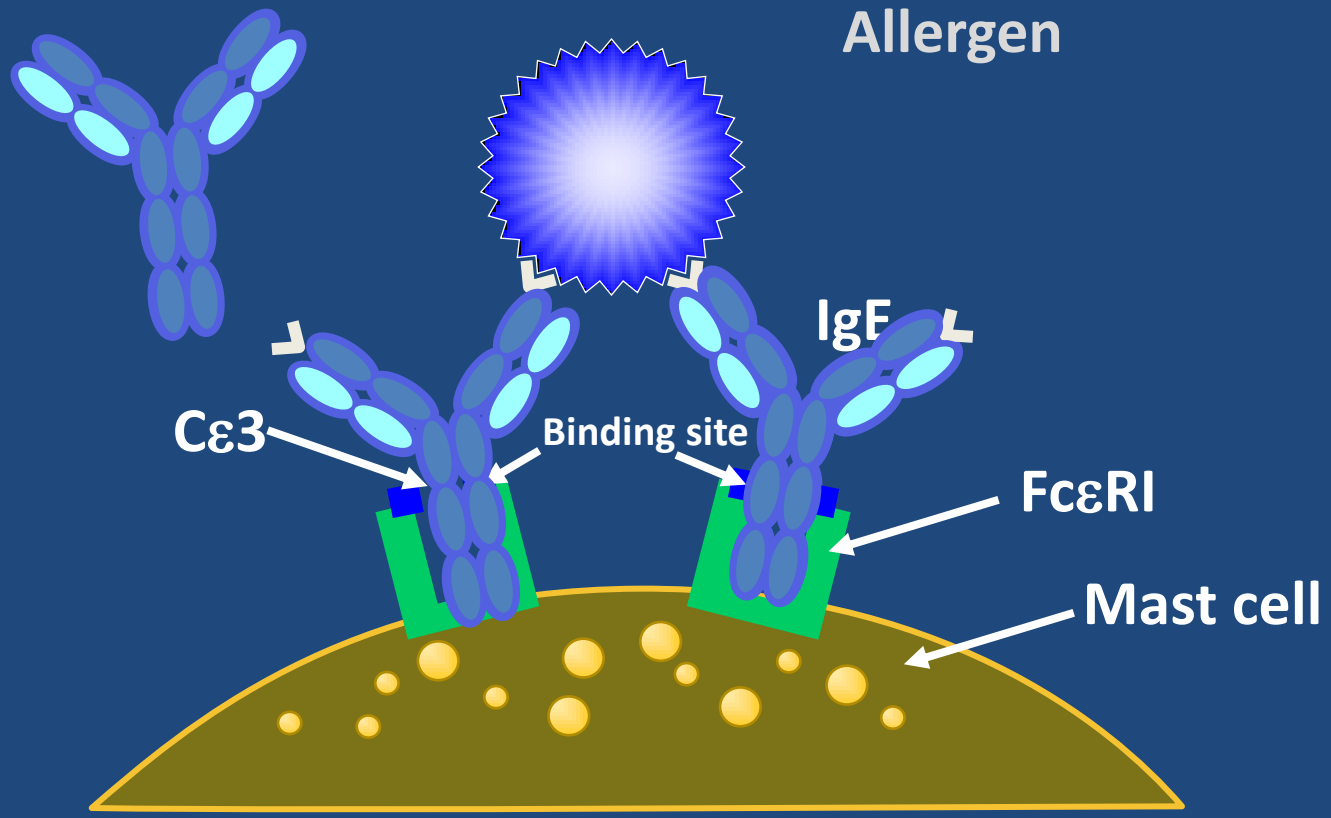


- The Cε3 domain is the portion of the IgE molecule that binds to the membrane receptors.
- The key epitope is the Cε3 domain of human IgE

Domingo et al. Recent Patents Inflamm Allergy Drug Discov. 2007; 1: 151-164

FISIOPATOLOGIA DE LA REACCIÓ AL·LÈRGICA

Allergen and mast cell



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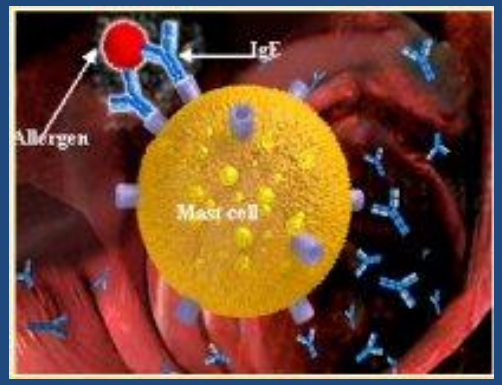

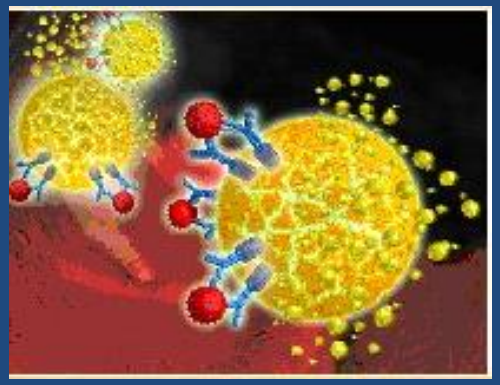

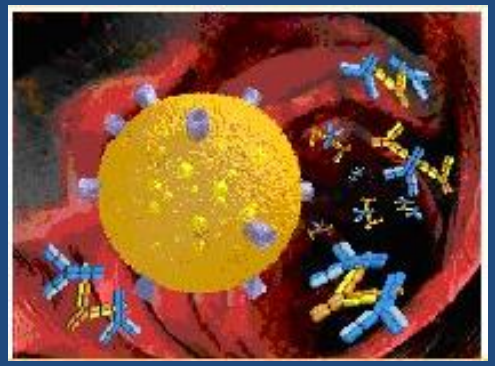

TRACTAMENTS ANTI-IgE

CMRO

Current Medical Research & Opinion Vol. 27, No. 1, 2011, 45–53

0300-7995
doi:10.1185/03007995.2010.536208

Article ST-0018.R1/536208

Original article

Omalizumab in the management of oral corticosteroid-dependent IGE-mediated asthma patients

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Key words:
Asthma – Oral corticosteroids – Omalizumab – Drug tolerance

Abstract

Background:
Several studies have demonstrated the beneficial effects of omalizumab in asthma patients. Here we describe the drug's tolerance and oral corticosteroid sparing capacity in a long-term observational study.

Methods:
Thirty-two patients aged ≥18 years with obstructive airway disease and FEV_1 reversibility ≥12% and 200 mL, with an oral steroid requirement ≥7.5 mg per day of prednisolone during a period of ≥1 year, a positive prick test or in vitro reactivity (RAST) to at least one perennial aeroallergen and a baseline immunoglobulin E level ranking between 30–700 IU/mL were prospectively followed for 17.2 ± 8.5 months. Patients were visited once or twice a month, depending on their schedule for omalizumab administration. Intervention: blood analysis every six months; spirometry and nitric oxide measurement at every visit.

Results:
One patient who dropped out early was excluded. Follow-up period: the treatment benefited 83.9% (26/31) of the cohort; oral corticosteroids were reduced from 7.19 ± 11.1 to 3.29 ± 11.03 mg ($p < 0.002$) and withdrawn in 74.2% of patients. FEV_1 (percent predicted) was 64.4 ± 22.7 at the beginning and 62.9 ± 24.3 at the end. IgE at entry was 322.2 ± 334.2 IU/mL and increased 2.34-fold. Respiratory function and NO did not present statistically significant changes. We identified three groups of patients: the first ($n = 17$) receiving oral steroid at entry in whom the accumulated dose of oral steroids progressively decreased; another ($n = 10$) including patients who had quit oral steroids before starting omalizumab although they had not been instructed to do so and whose oral steroid dose at the end of follow-up was zero; and a third group ($n = 4$) that did not benefit from omalizumab treatment. The only relevant side effect was a flu-like syndrome which required discontinuation of treatment in one patient.

Conclusion:
In our series, a substantial, safe decrease in oral corticosteroid requirements was observed due, at least to some extent, to omalizumab therapy. Oral corticosteroids were withdrawn in three-quarters of the patients. We were unable to identify a factor able to predict which patients would benefit most from omalizumab treatment.

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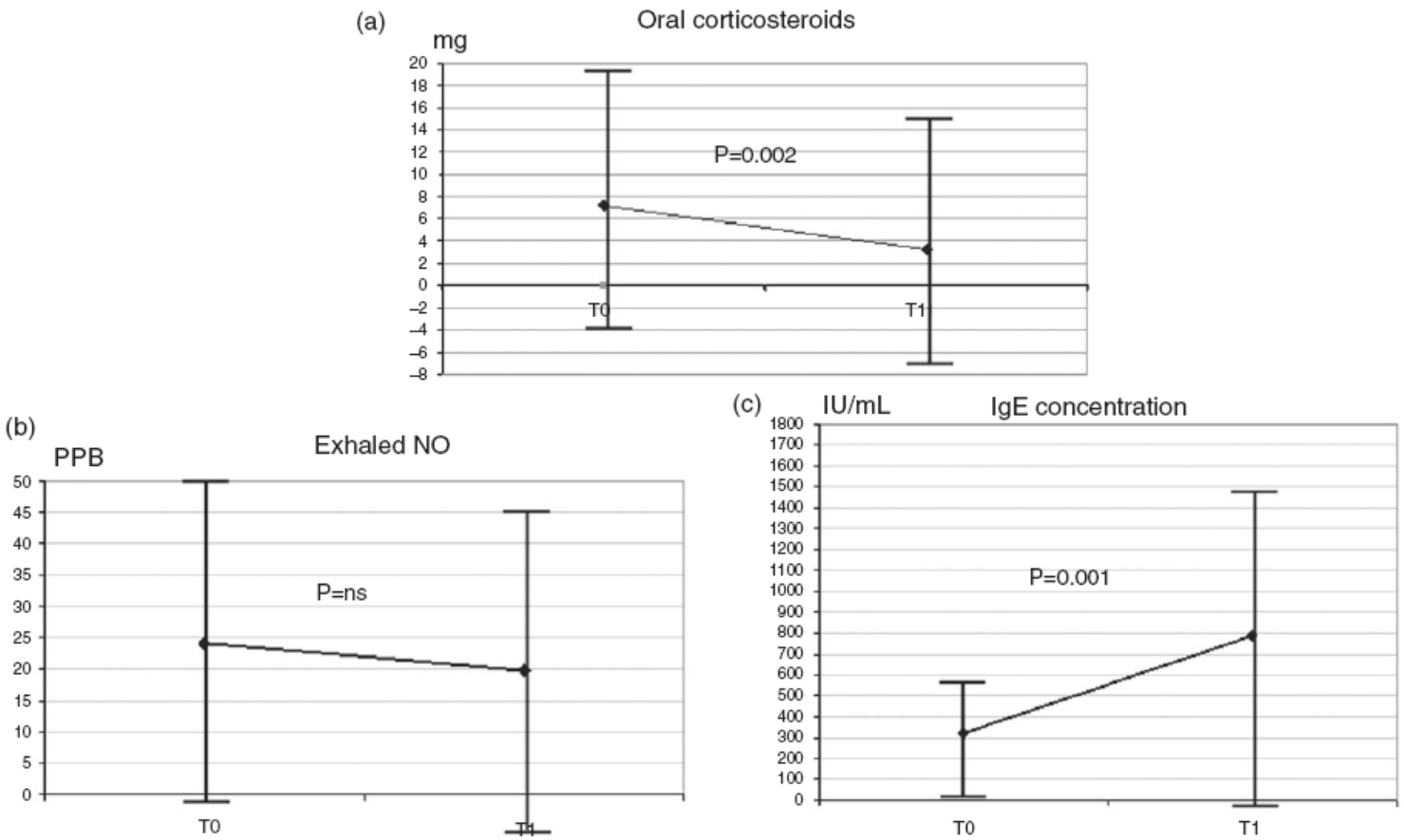

Figure 1. (A) Overall view of initial and end oral corticosteroid intake. (B) Exhaled NO. (C) IgE concentrations. Note the significant decrease of oral corticosteroid intake whilst the exhaled NO remains stable. As a result of the omalizumab treatment, IgE levels notably increased.

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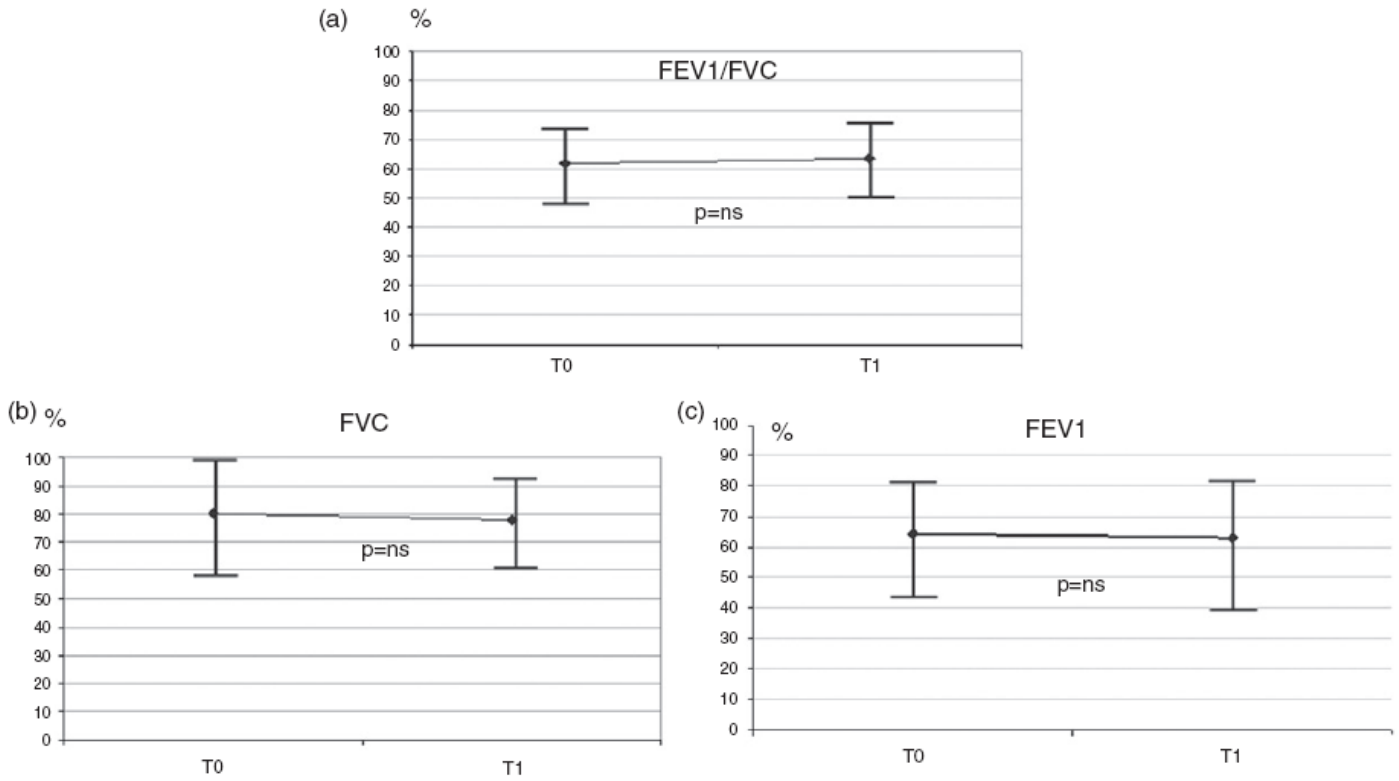

Figure 2. The spirometry results of the cohort of patients are given as a percentage of the predicted results. Note that the FEV_1 values (C) do not fall despite the decrease of oral corticosteroids, whilst the FVC (B) and FEV_1/FVC (A) do not change, ensuring that the airway obstruction does not progress and that there is no subsequent increase in the residual volume.

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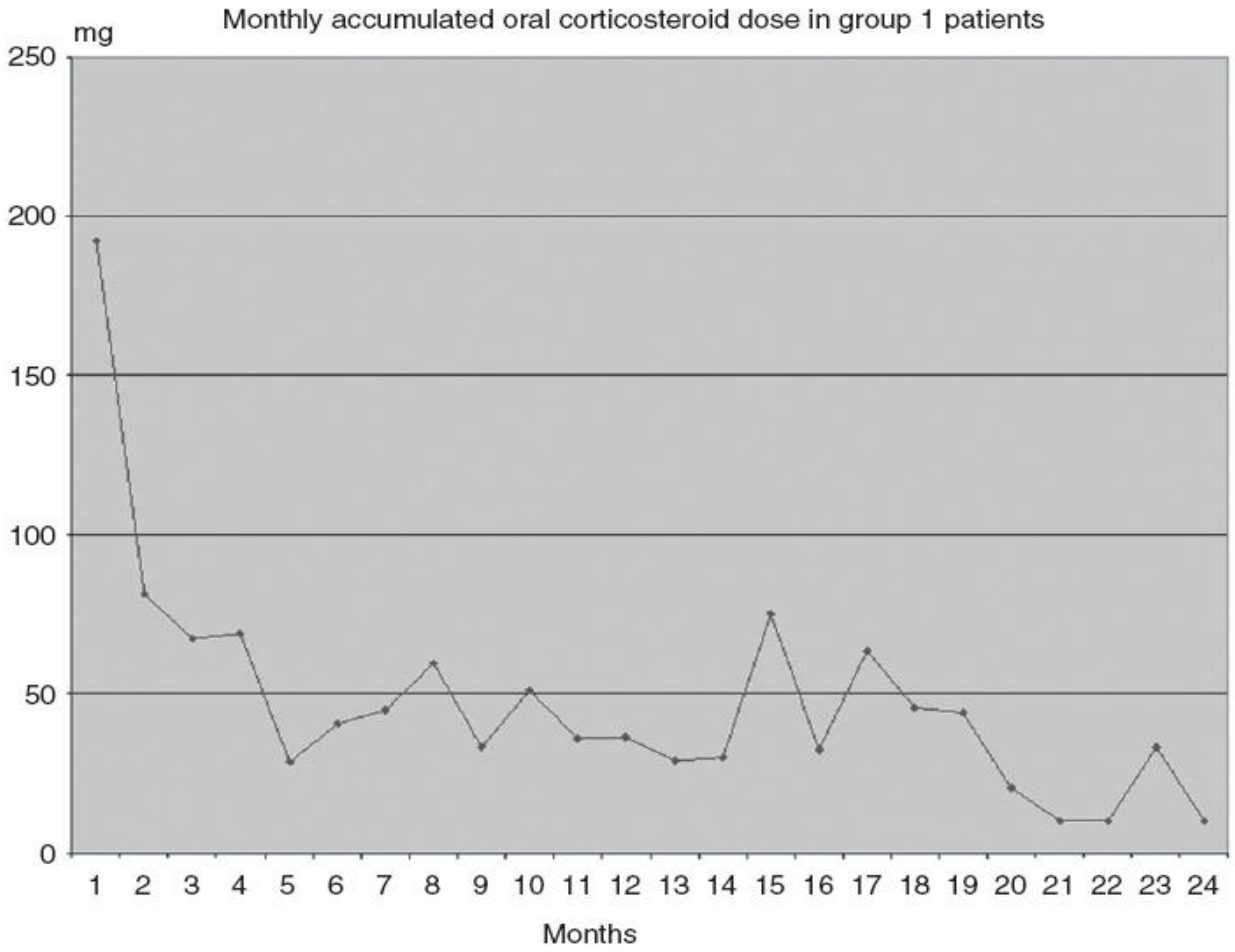

Figure 3. Note the monthly progressive decrease of the accumulated oral corticosteroid dose.

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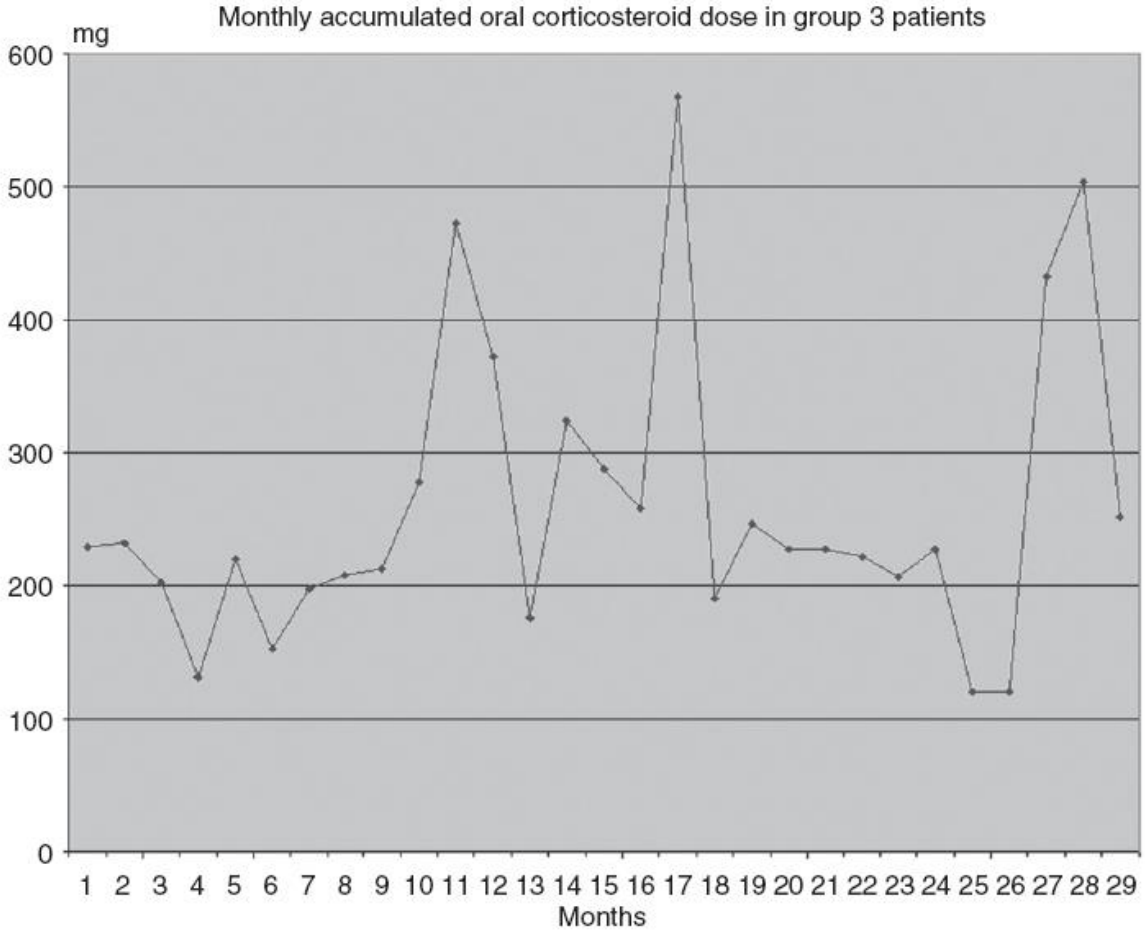


Figure 5. This group is the smallest cohort of patients who did not respond to omalizumab treatment. Their corticosteroid intake was erratic and could not be related to any specific factor.

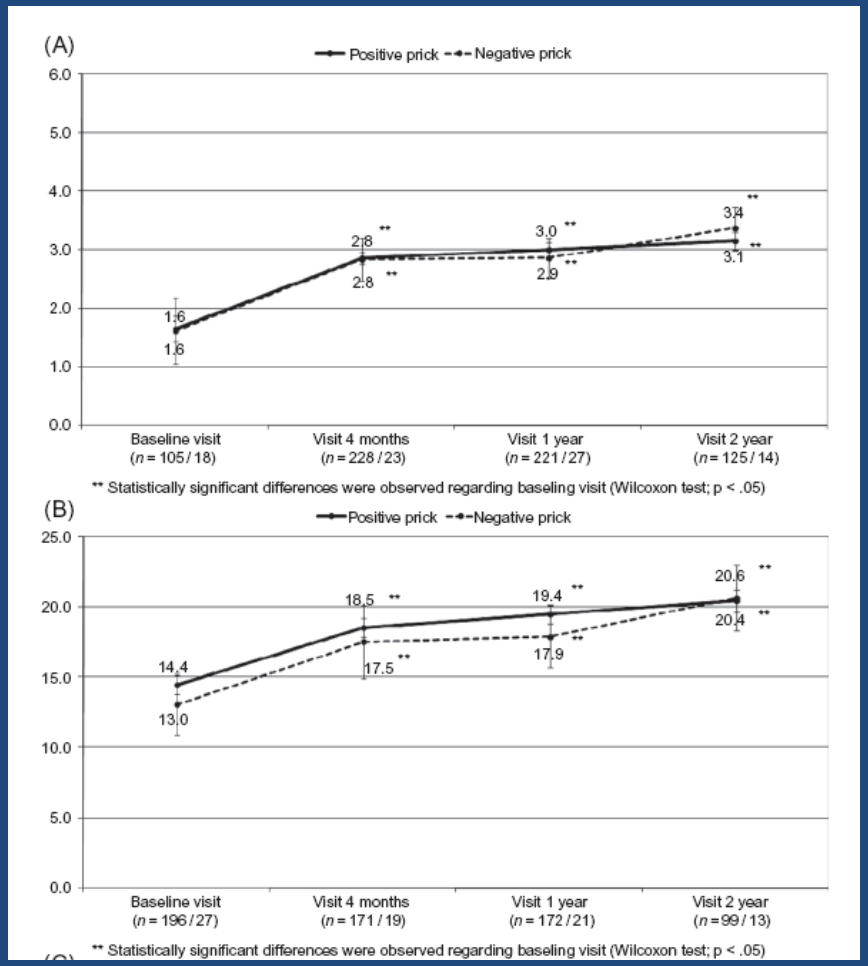
Journal of Asthma, 2013; Early Online: 1–6

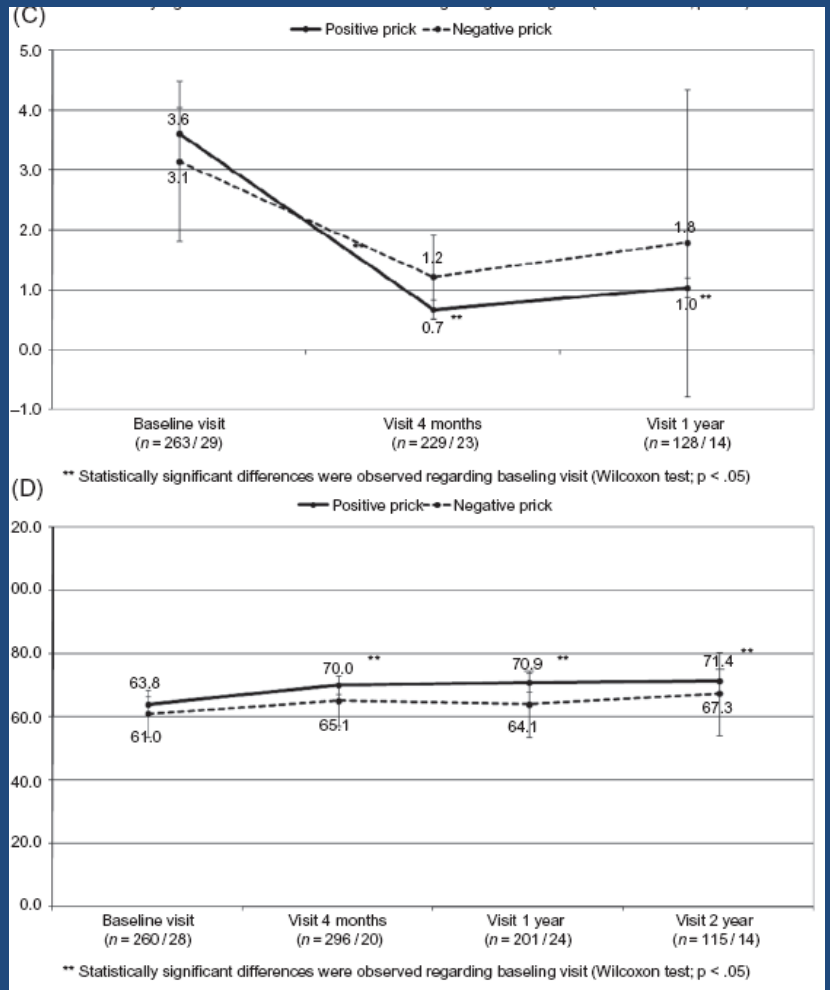
ISSN: 0277-0903 print/1532-4303 online
DOI: 10.3109/02770903.2012.757780

informa
healthcare

Effects of Omalizumab in Non-Atopic Asthma: Results from a Spanish Multicenter Registry

LUIS PÉREZ DE LLANO, M.D., PH.D.,[1] MARÍA DEL CARMEN VENNERA, M.D.,[2,3,4] FRANCISCO J ÁLVAREZ, M.D.,[5] JUAN F. MEDINA, M.D.,[5] LUIS BORDERÍAS, M.D., PH.D.,[6] CONCHA PELLICER, M.D.,[7] HÉCTOR GONZÁLEZ, M.D., PH.D.,[8] JOSÉ A. GULLÓN, M.D., PH.D.,[8] EVA MARTÍNEZ-MORAGÓN, M.D., PH.D.,[9] CARLOS SABADELL, M.D.,[10] SOLEDAD ZAMARRO, M.D.,[11] AND CÉSAR PICADO, M.D., PH.D.[2,3,4]; on behalf of the Spanish Registry





JOURNAL OF BIOLOGICAL REGULATORS & HOMEOSTATIC AGENTS Vol. 27, no. 1, 45-53 (2013)

EFFECTIVENESS OF OMALIZUMAB IN NON-ALLERGIC SEVERE ASTHMA

C. DOMINGO[1,2], X. POMARES[1,2], N. ANGRILL[1,2], N. RUDI[3], M.J. AMENGUAL[2,4] and R.M. MIRAPEIX[5]

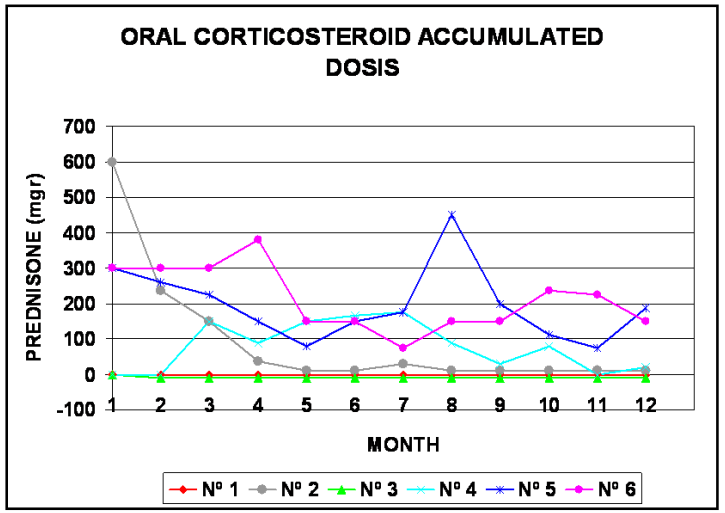


Figure 1

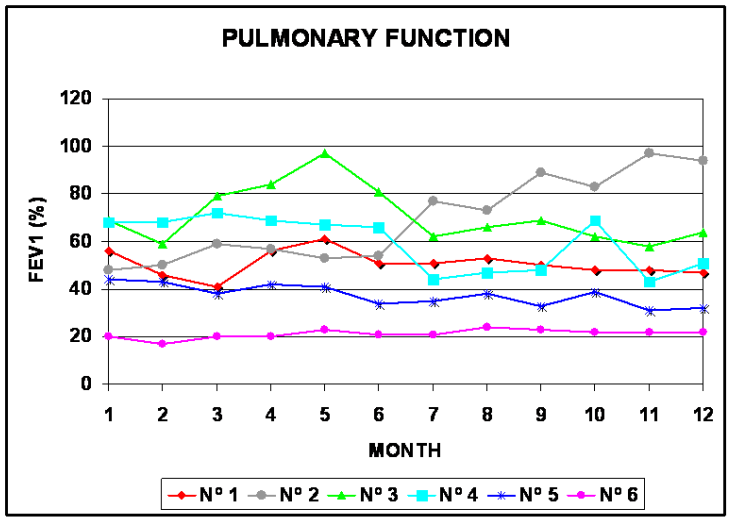


Figure 2

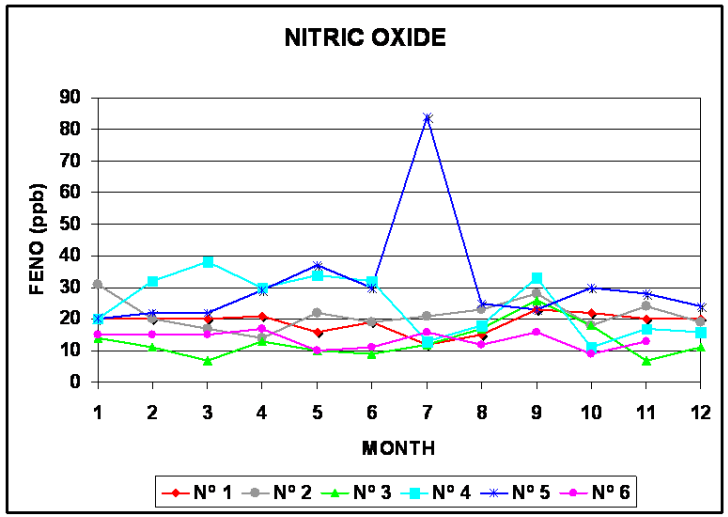
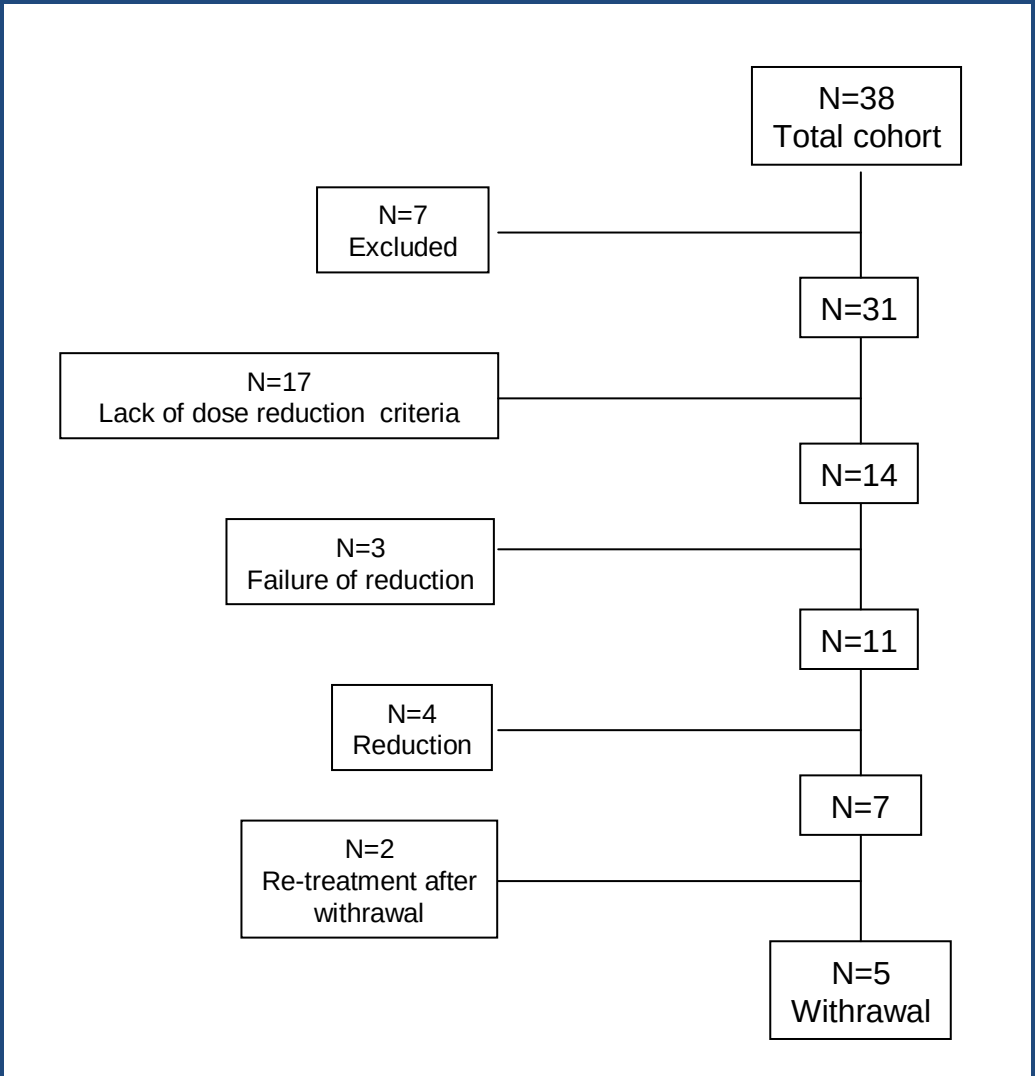


Figure 3

When and how omalizumab can be withdrawn: free IgE as a possible biomonitor.



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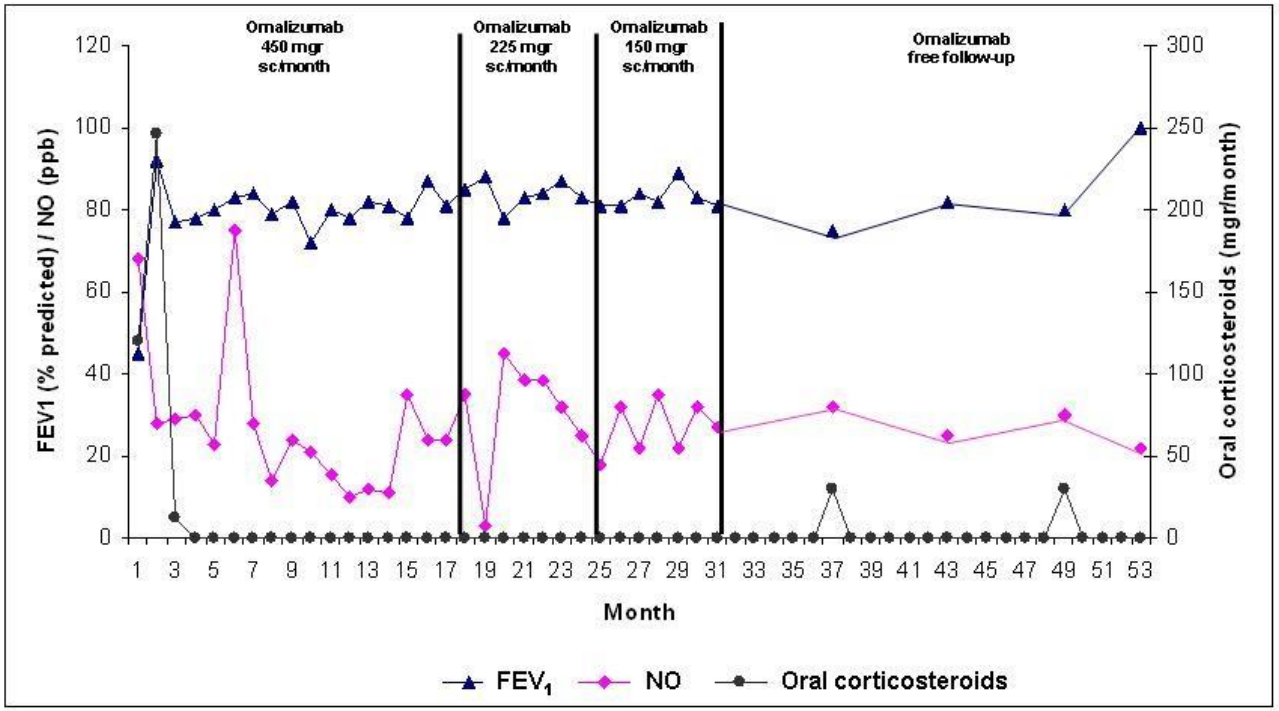
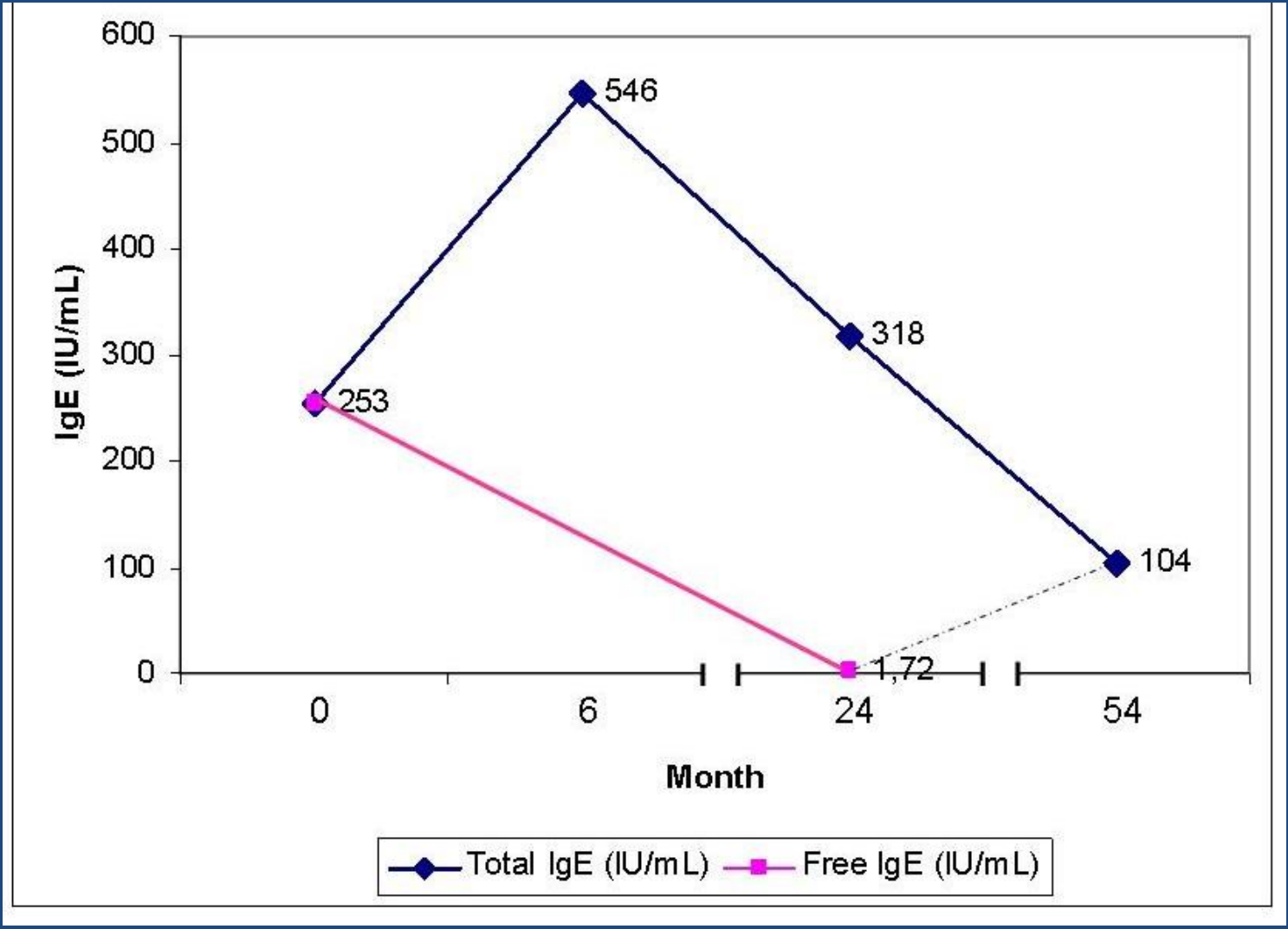


When and how omalizumab can be withdrawn: free IgE as a possible biomonitor.



Monitoring free serum IgE in severe asthma patients treated with omalizumab

Stephanie Korn [a,*], Ina Haasler [a], Florian Fliedner [a], Gunther Becher [b], Pavel Strohner [c], Antonia Staatz [c], Christian Taube [a], Roland Buhl [a]

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Respiratory Medicine (2012)

CHEST Correspondence

Can Omalizumab Be Effective in Chronic Eosinophilic Pneumonia?

[AQ1]

To the Editor:

We have recently read with interest the article by Kaya et al[1] in *CHEST* (August 2012) reporting on a patient suffering from chronic eosinophilic pneumonia (CEP) who responded successfully to omalizumab.

Five years ago, we attended a 43-year-old nonsmoking man who complained of cough, fever, dyspnea, and wheezing. On the basis of his clinical presentation, peripheral blood and BAL eosinophilia, and the presence of bilateral peripheral infiltrates on the chest radiograph, the diagnosis of CEP was made. As in the Kaya et al[1] case, oral corticosteroids (OCs) were started with an initial successful response. After 3 months of therapy, the dose of OC was progressively tapered. When the dose reached 10 mg prednisolone, a relapse occurred that forced us to increase the dose of OC. The patient improved and bronchospasm and chest infiltrates disappeared. During the process of OC tapering, a new relapse occurred, bronchospasm being the most relevant clinical symptom that forced us to increase again the dose of OC. A skin prick test was performed that was positive for mite dust. Total blood IgE level was 253 IU/mL. Omalizumab treatment was started at the dose calculated according to the patient's weight and IgE concentration. The patient progressively improved and

More recently, Noga et al [4] demonstrated an increase in eosinophil apoptosis and a decrease in granulocyte-macrophage colony-stimulating factor. All this information can help to explain the benefits of omalizumab in CEP.

In their report, Kaya et al[1] communicate that their patient remains free of symptoms 15 months after omalizumab treatment began, but they do not state future treatment options. We believe some of these patients can benefit from a decreasing dose protocol.[2]

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Xavier Pomares, MD
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DOI: 10.1378/chest.12-2035

TRACTAMENTS ANTI-IgE

Antibodies specific for a segment of human membrane IgE deplete IgE-producing B cells in humanized mice

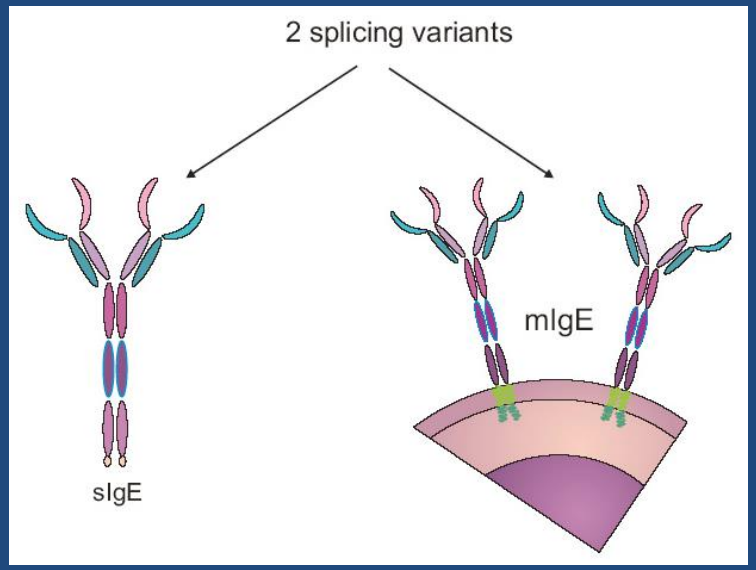
Hans D. Brightbill,[1] Surinder Jeet,[1] Zhonghua Lin,[1] Donghong Yan,[1] Meijuan Zhou,[1] Martha Tan,[2] Allen Nguyen,[2] Sherry Yeh,[2] Donnie Delarosa,[2] Steven R. Leong,[1] Terence Wong,[3] Yvonne Chen,[3] Mark Ultsch,[4] Elizabeth Luis,[5] Sree Ranjani Ramani,[5] Janet Jackman,[1] Lino Gonzalez,[5] Mark S. Dennis,[3] Anan Chuntharapai,[3] Laura DeForge,[2] Y. Gloria Meng,[2] Min Xu,[1] Charles Eigenbrot,[4] Wyne P. Lee,[1] Canio J. Refino,[1] Mercedesz Balazs,[1] and Lawren C. Wu[1]

[1]Department of Immunology, [2]Department of Assay and Automation Technology, [3]Department of Antibody Engineering, [4]Department of Protein Engineering, and [5]Department of Protein Chemistry, Genentech Inc., South San Francisco, California, USA.

The Journal of Clinical Investigation http://www.jci.org Volume 120 Number 6 June 2010

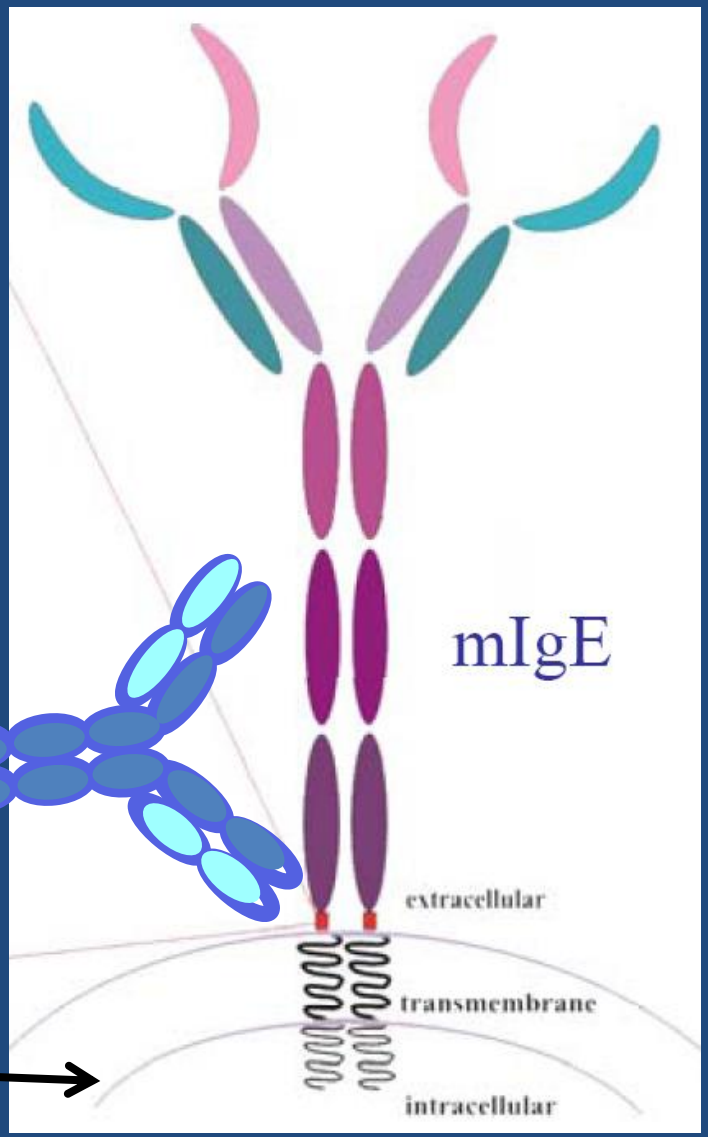
QUILIZUMAB

.- Ac humanitzat
.- S'uneix al segment M' de la IgE expressada per la Cél·lula B
.- Afavoreix l'apoptosi de les Cel·lules B diferenciades (expressen IgE de membrana)
.- Disminueixen les IgE plasmàtiques en disminuir la seva producció.



TRACTAMENTS ANTI-IgE

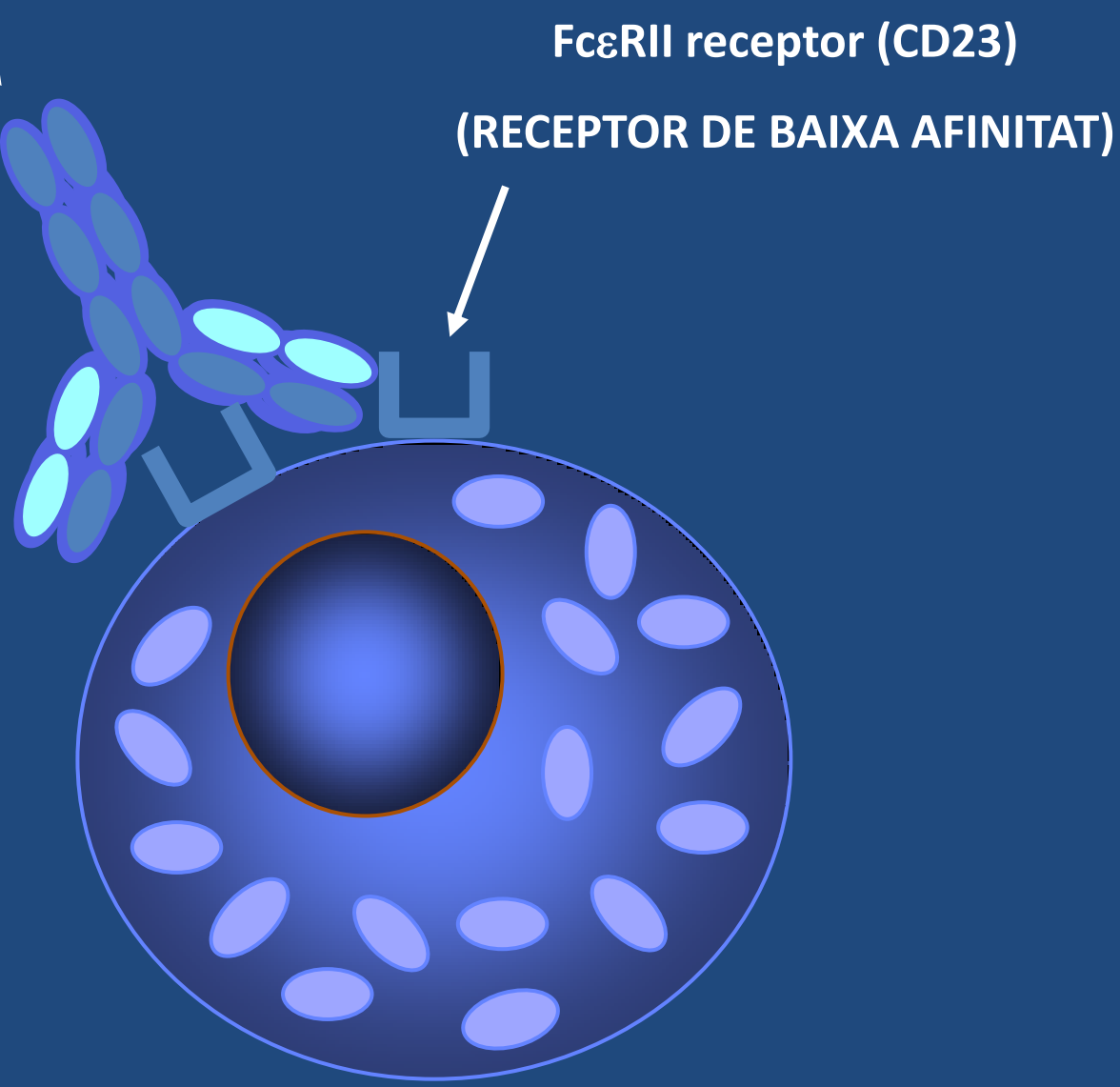
QUILIZUMAB



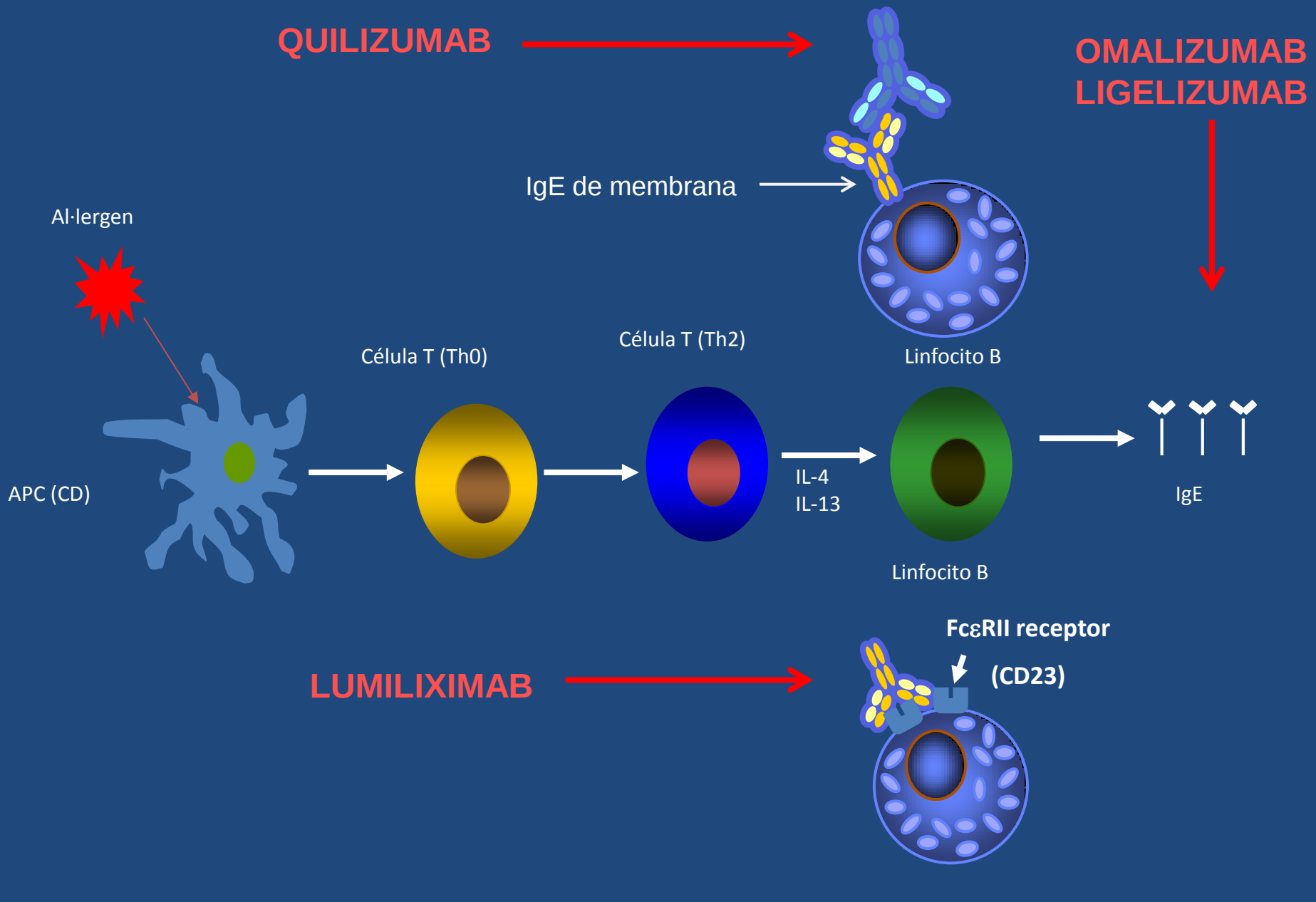
B cell

TRACTAMENTS ANTI-IgE

LUMILIXIMAB



TRACTAMENTS ANTI-IgE



ALTRES TRACTAMENTS (I)

TRACTAMENTS ANTI-IL5

- MEPOLIZUMAB
- RESLIZUMAB

TRACTAMENTS ANTI-RECEPTORS DE L'IL5

- BENRALIZUMAB

TRACTAMENTS ANTI-IL-5. MEPOLIZUMAB

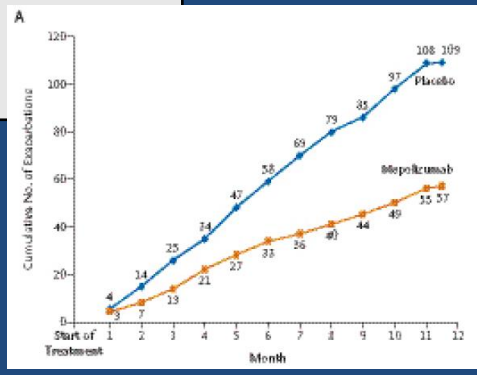
Autor	Corticoides	Efecte
Lecki (2000)	No	↓ Eosinòfils en sang
Flood-Page (2003)	No	↓ 100% Eosinòfils en sang, 52% medul·la i 54% a via aèria
Menzies-Gow 2003	No	↓ Eosinòfils a medul·la i mucosa bronquial
Flood-Page (2007)	Si	↓ Eosinòfils en sang i esput Absència de millora en exacerbacions, FEV1 o medicació de rescat

HIPÒTESIS:

- ❑ Eosinòfils de la via aèria tenen menys receptors de membrana per l'IL5
- ❑ Persistència d'eosinòfils a la via aèria
- ❑ Els malalts van ser escollits en funció del fenotip i no de l'endotip

TRACTAMENTS ANTI-IL-5. MEPOLIZUMAB

Autor	Corticoides	Efecte
Nair (2009)	Si	↓ Eosinòfils en sang i esput ↓ Nº d'exacerbacions i temps d'aparició Efecte estalviador de corticoides Milloria significativa del FEV1 Milloria en qualitat de vida
Haldar (2009)	Si	↓Eosinòfils en sang i esput ↓Nº d'exacerbacions i temps d'aparició Absència d'efecte estalviador de corticoides Absència de milloria del FEV1 Milloria en qualitat de vida



HIPÒTESI:

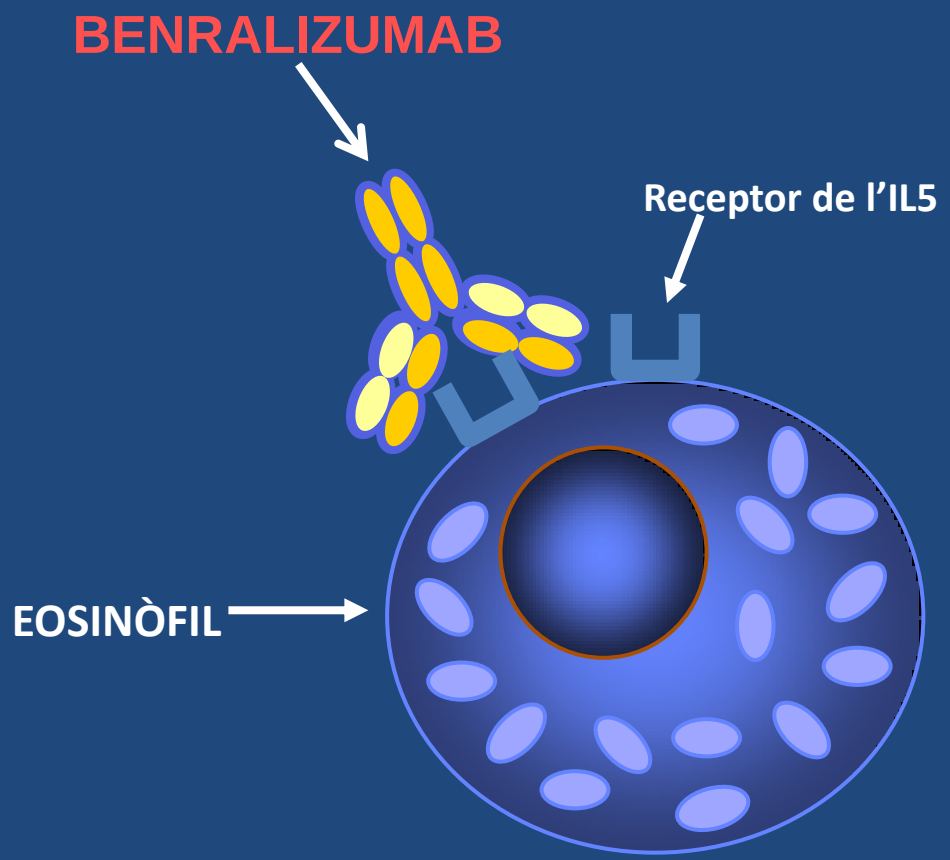
Mepolizumab podria ser eficaç solament en malalts amb:

- Asma refractària
- Asma amb perfil eosinofílic

TRACTAMENTS ANTI-IL-5. RESLIZUMAB

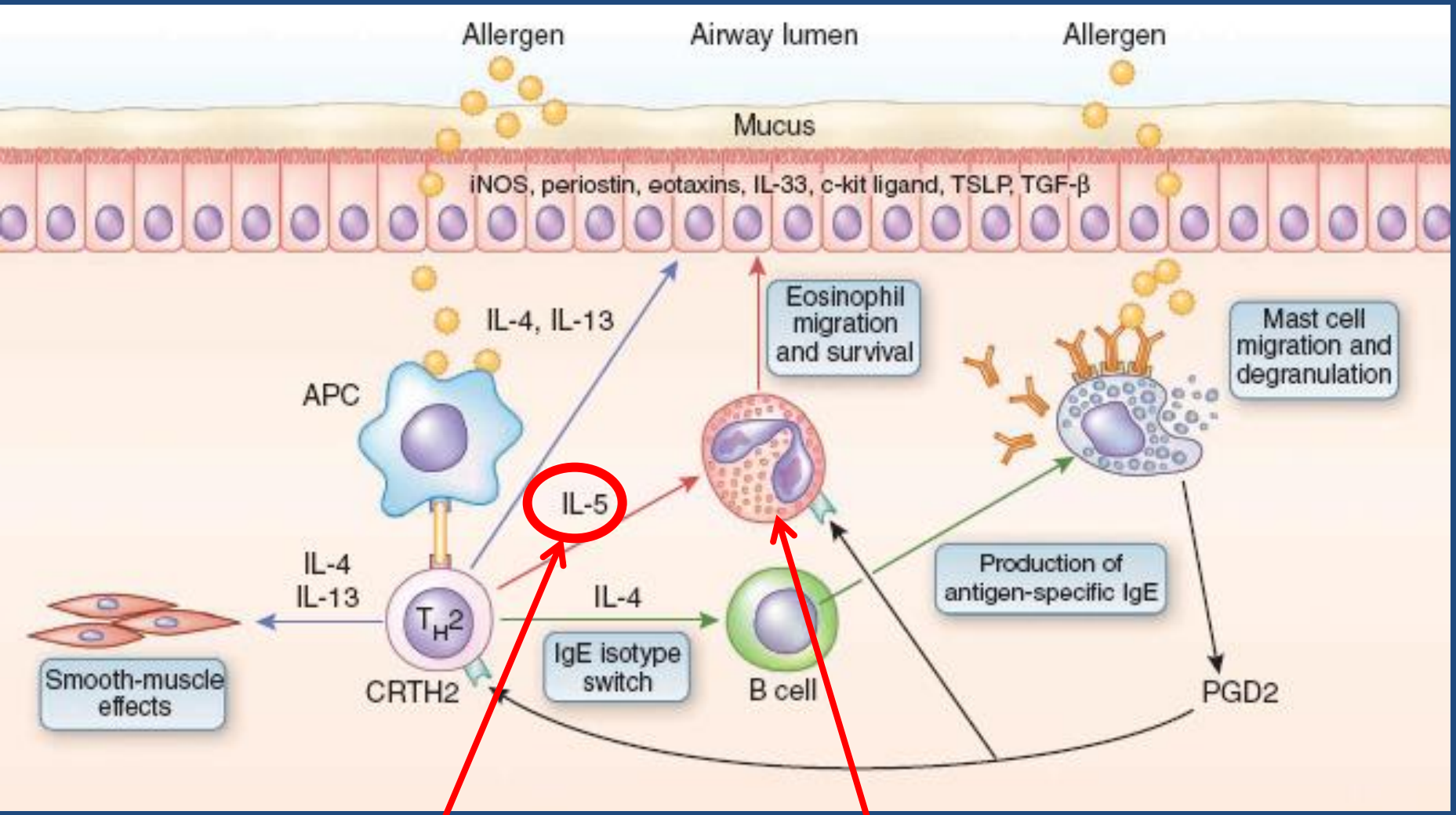
Autor	Corticoides	Efecte
Kips 2003	Si (inh. + orals)	↓ Eosinòfils en sang Milloria significativa del FEV1 Absència de milloria en qualitat de vida
Castro 2011	Si	↓ Eosinòfils en sang i esput Milloria significativa del FEV1 No ↓ Exacerbacions Absència de milloria en qualitat de vida

TRACTAMENTS ANTI-RECEPTORS DE IL-5. BENRALIZUMAB



EFECTES:

- Neutralitza l'efecte de l'IL-5
- Afavoreix l'apoptosi



MEPOLIZUMAB
RESLIZUMAB

BENRALIZUMAB

ALTRES TRACTAMENTS (II)

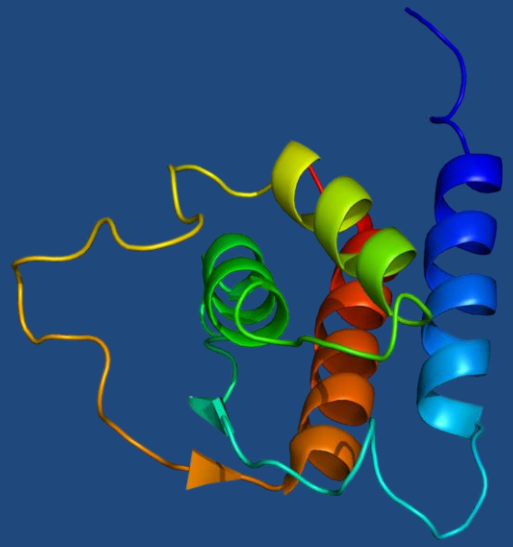
TRACTAMENTS ANTI-IL-13

- LEBRIKIZUMAB

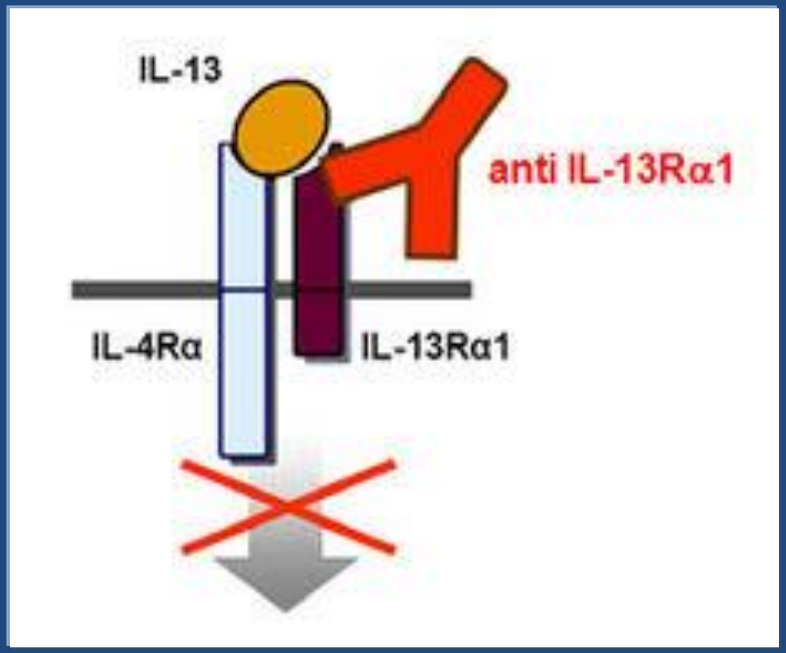
TRACTAMENTS ANTI- IL-4 + IL-13

– DUPILUMAB

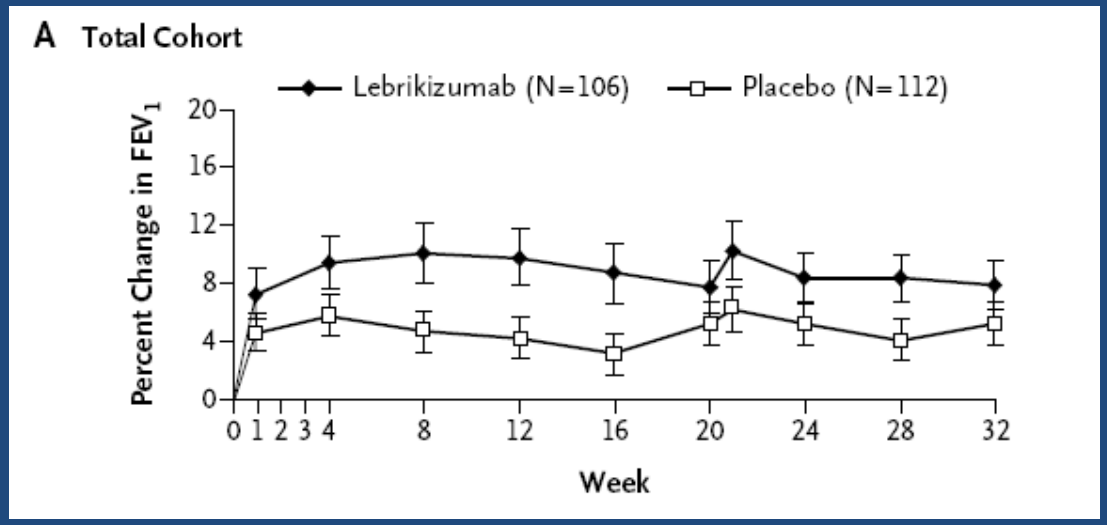
TRACTAMENTS ANTI-IL-13.

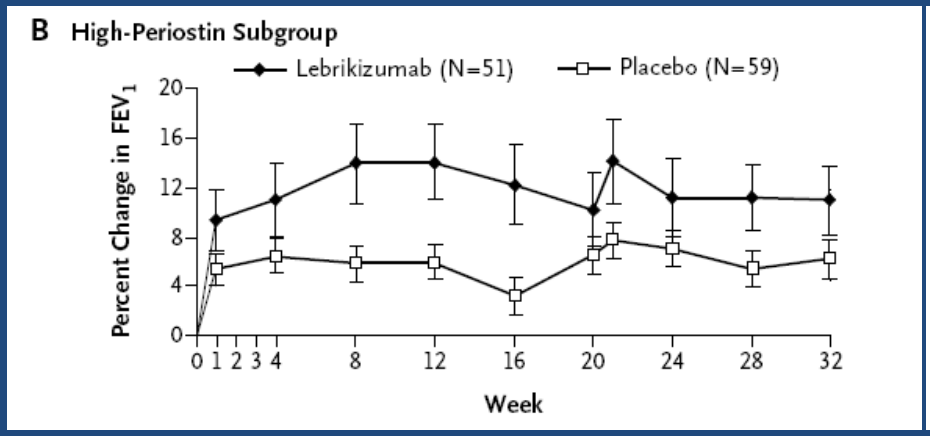


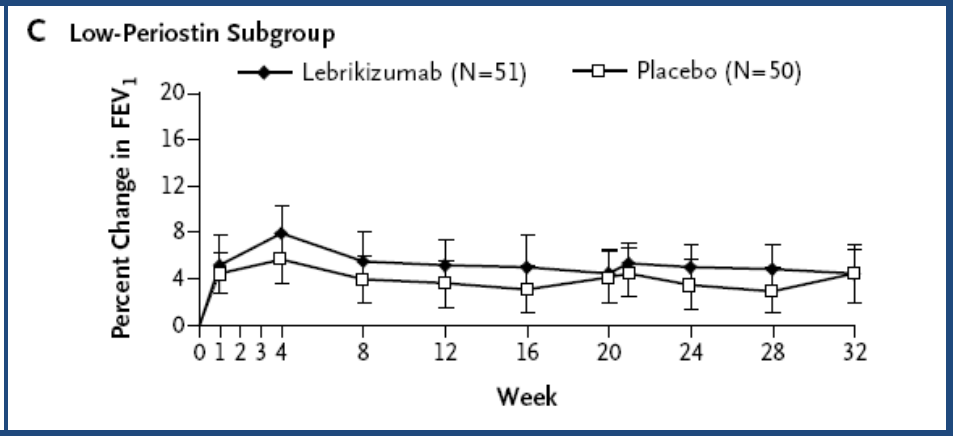
IL-13



TRACTAMENTS ANTI-IL-13: LEBRIKIZUMAB

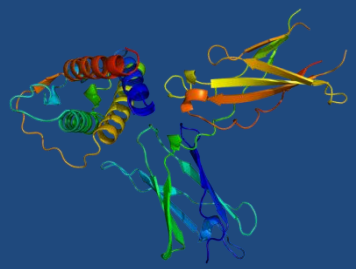




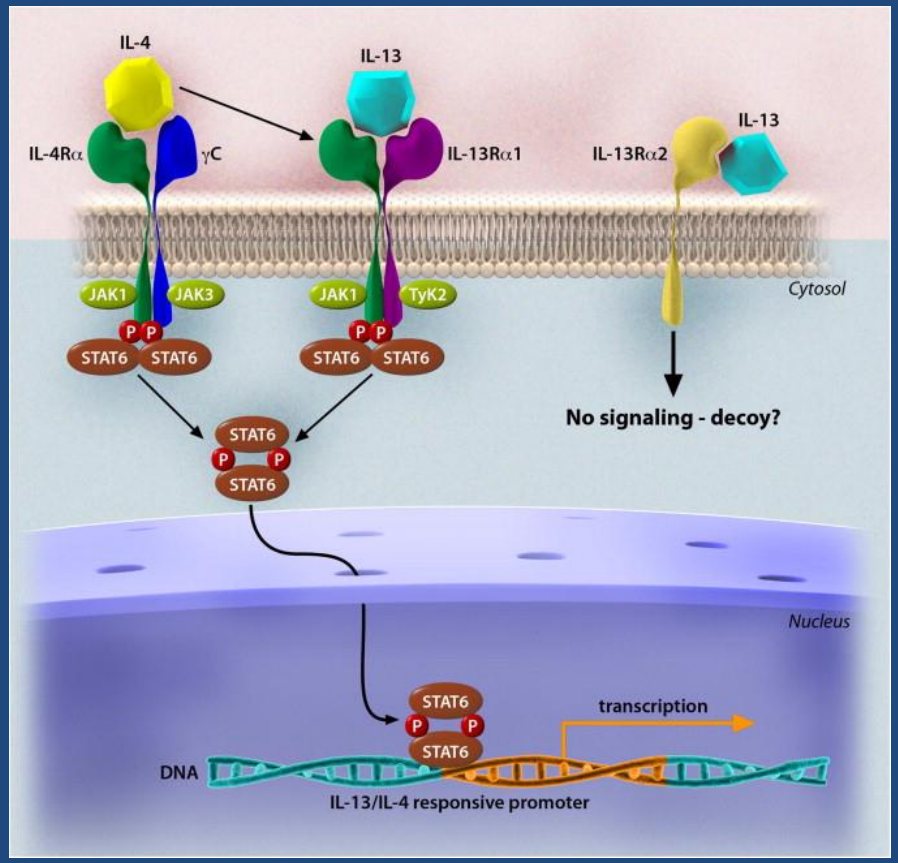


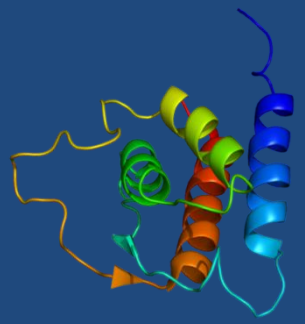
Ac monoclonal humanitzat tipus IgG4
Marcadors de resposta: FENO i Periostina

TRACTAMENTS ANTI-IL-4 + IL-13: DUPILUMAB



IL-4





IL-13

TRACTAMENTS ANTI-IL-4 + IL-13

PITRAKINRA: es una variant de la IL-4 humana que es comporta com un inhibidor competitiu del receptor IL-4alfa (IL-4Ra) de manera que interfereix en l'acció tan de l'IL-4 com de l'IL-13.