Principali marker dell'infiammazione di tipo 2: IgE, FeNO, eosinofili

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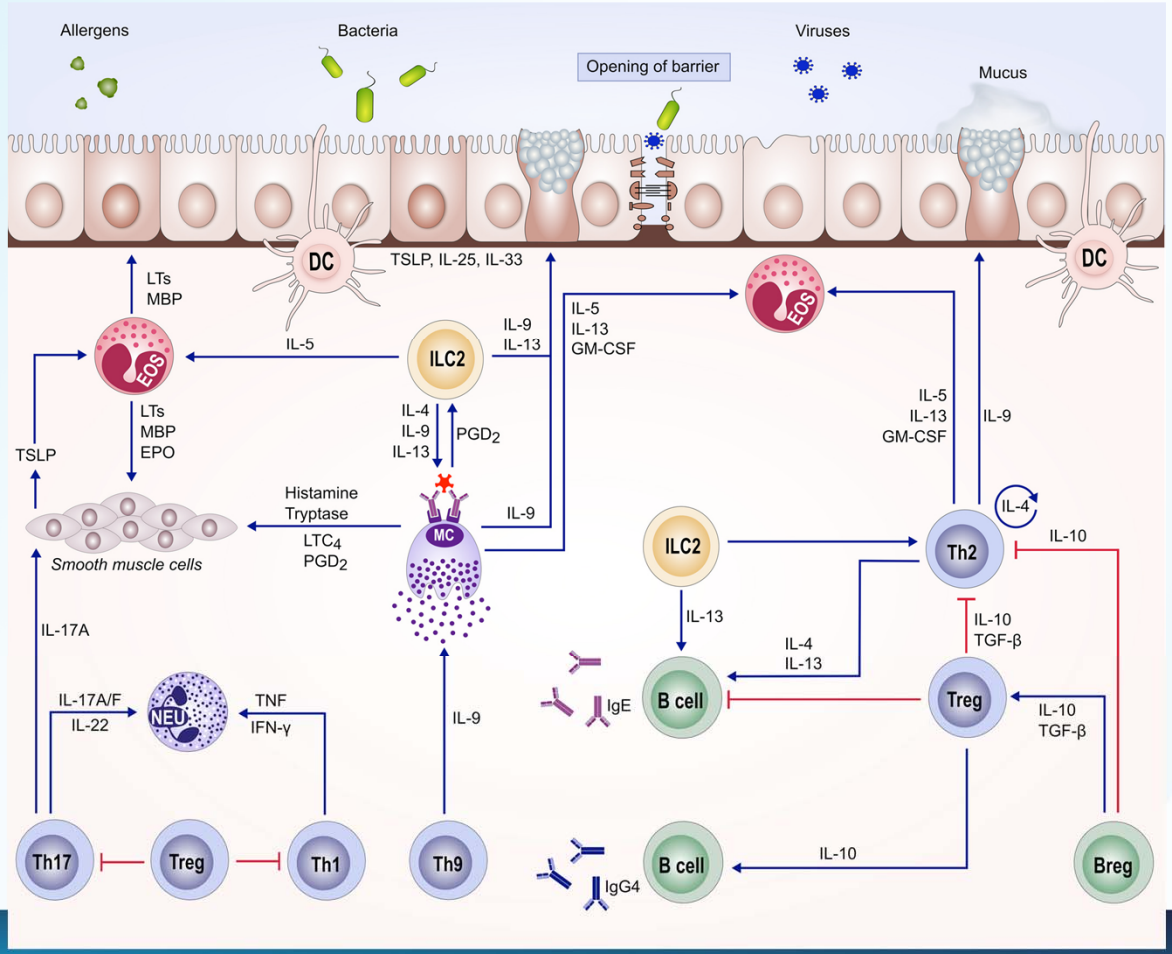
THE COMPLEX PICTURE OF TH2 RESPONSE

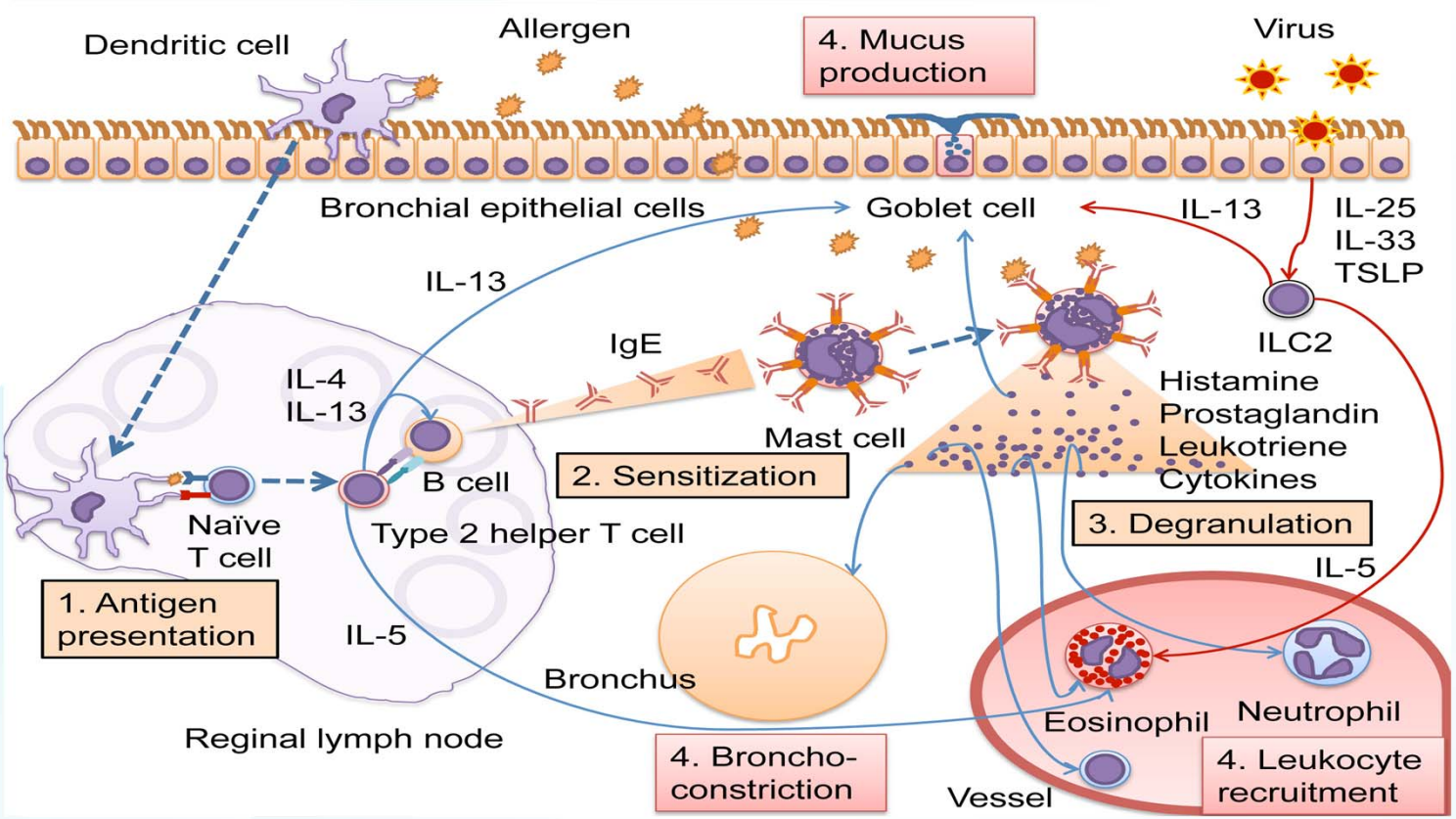
MAIN PLAYERS AND CLINICAL BIOMARKERS



Akdis et al Allergy 2020

THE COMPLEX PICTURE OF TH2 RESPONSE

FOCUS ON IgE



In severe asthma IgEs act as Th2 cytokines, related to epithelial barrier dysfunction
and not to allergic reaction

several cells including mast cells, basophils, and plasmacytoid dendritic cells (pDCs) express FCεRIa

Suraya et al, Resp Invest, 2021
Caminati et al, Expert Rev Clin Immunol, 2019

TARGETING IGEs

UNEXPECTED EVOLUTION..

Case presentation:

→ relapsing nasal polyps (2 polypectomies)

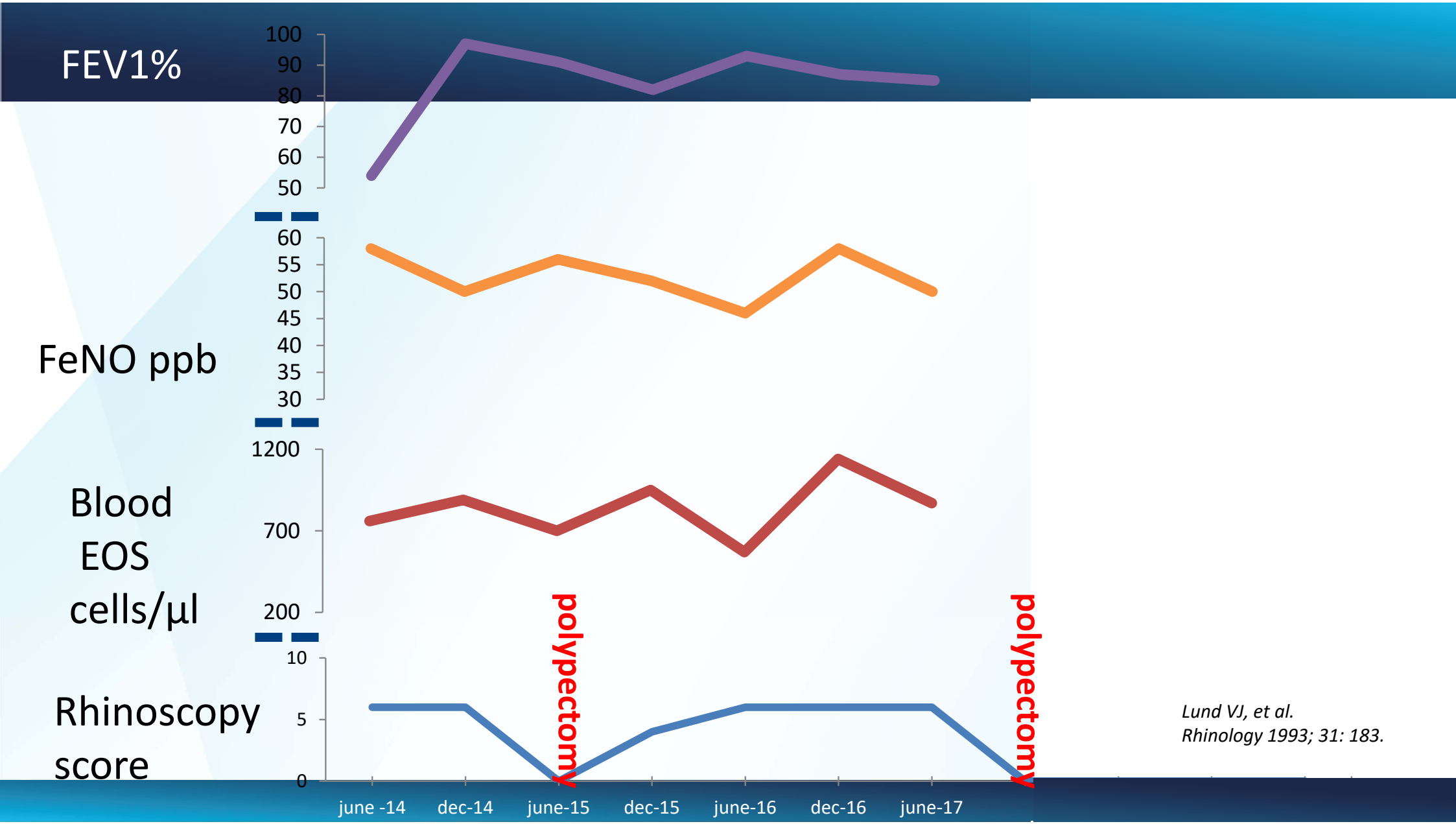
→ Non smoker

→ Sensitization to cat dander (SPT, sIgE 63.2 KUA/l)

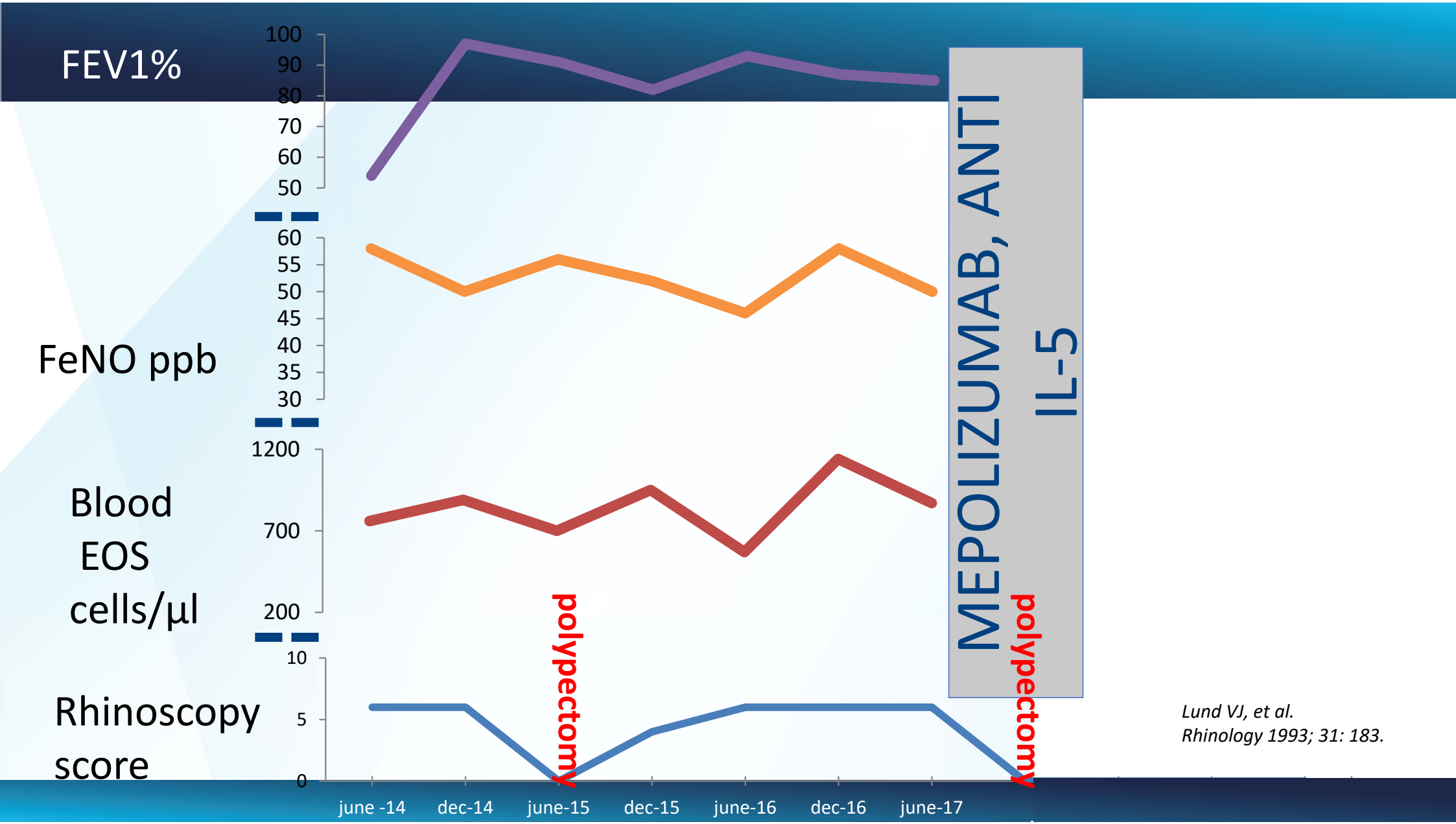
→ Staphylococcal enterotoxin B and C sIgE sensitization (5.26 and 3.12 KUA/l)

→ Blood eosinophilia (800 cells/µL average)

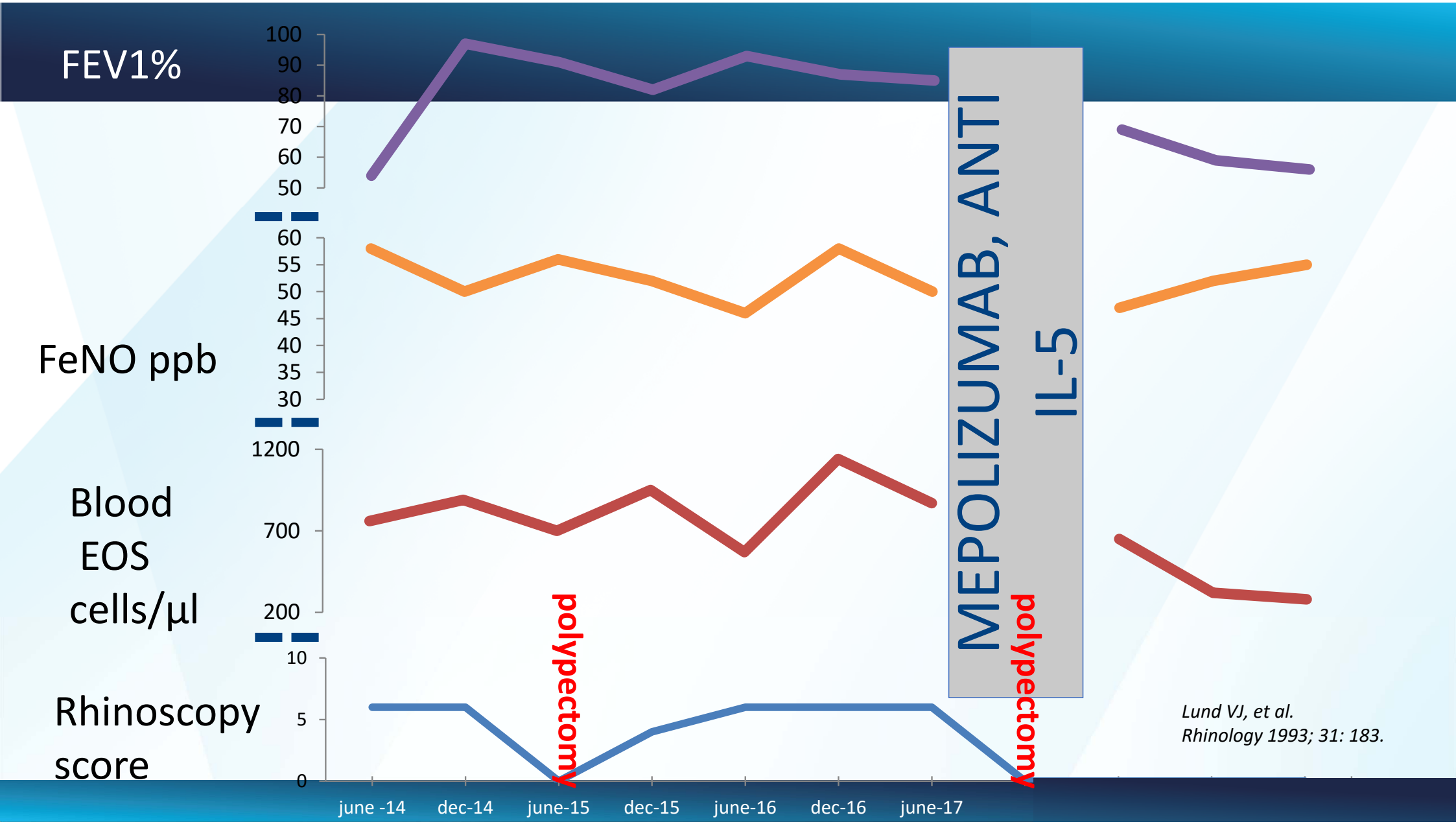
→ Total IgE 393 KUA/l



Lund VJ, et al.
Rhinology 1993; 31: 183.



Lund VJ, et al.
Rhinology 1993; 31: 183.


FEV1%
100
90
80
70
60
50
FeNO ppb
60
55
50
45
40
35
30
Blood EOS cells/µl
1200
700
200
Rhinoscopy score
10
5
0
polypectomy
MEPOLIZUMAB, ANTI IL-5
polypectomy
june -14
dec-14
june-15
dec-15
june-16
dec-16
june-17
Lund VJ, et al.
Rhinology 1993; 31: 183.

CASE DISCUSSION

REVISION AND FURTHER CONSIDERATIONS

- Omalizumab was effective on asthma but not on nasal polyps
- Mepolizumab was effective on nasal polyps but not on asthma despite full eligibility of the patient
- A discrepancy between TH2 biomarkers (blood eosinophil count, exhaled FeNO bronchial FeNO) trend and clinical response was observed

Continuing Medical Education examination

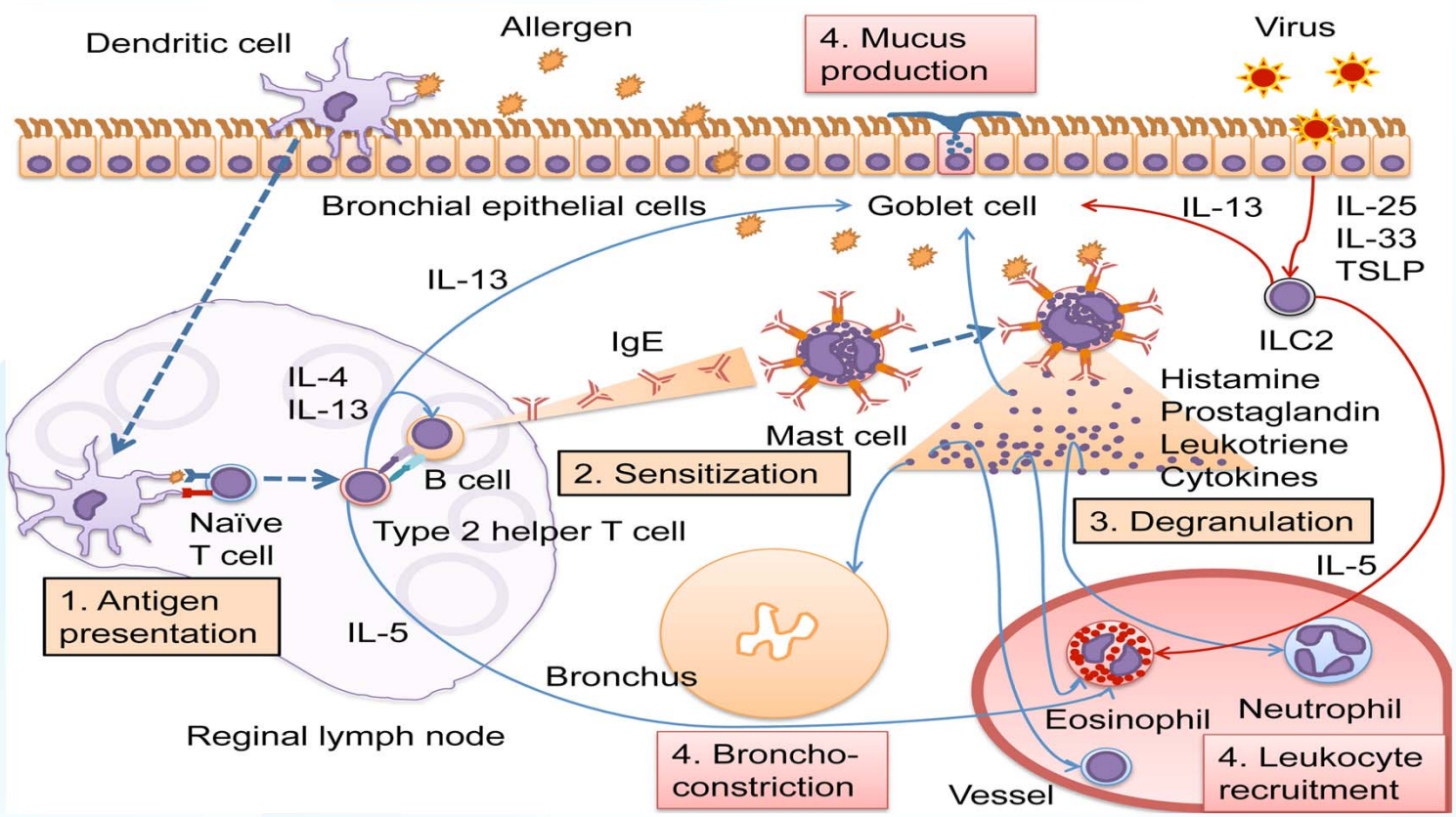
Biologic Therapy in a Patient With Asthma and Nasal Polyps

J ALLERGY CLIN IMMUNOL PRACT
VOLUME 7, NUMBER 5

Caminati & Senna

TARGETING IGEs

(UN)EXPECTED EVOLUTION..

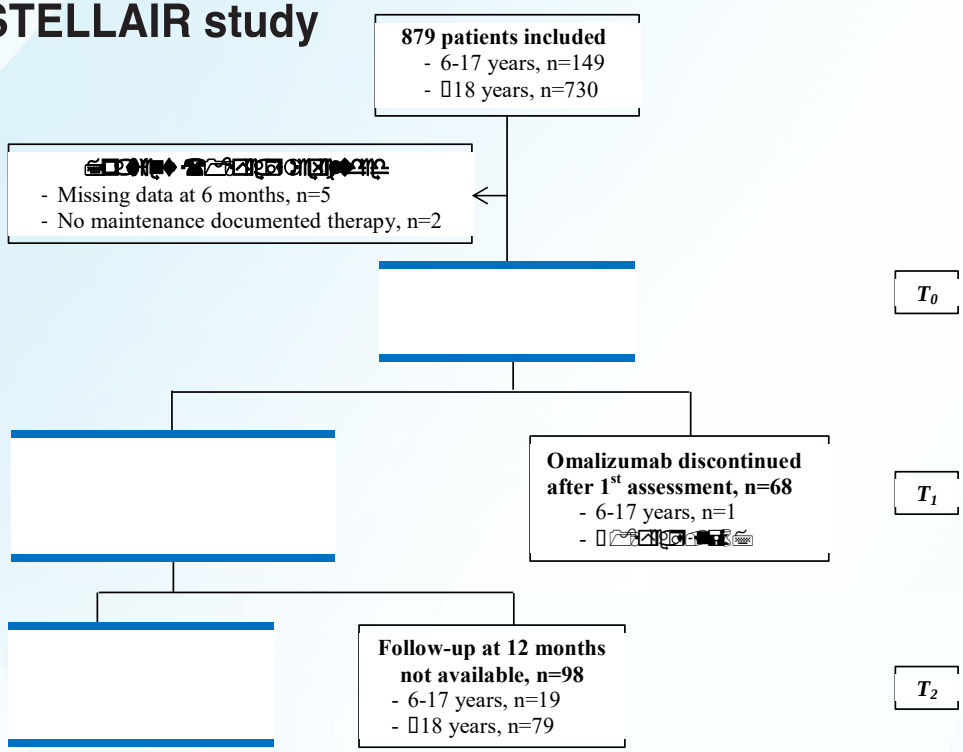


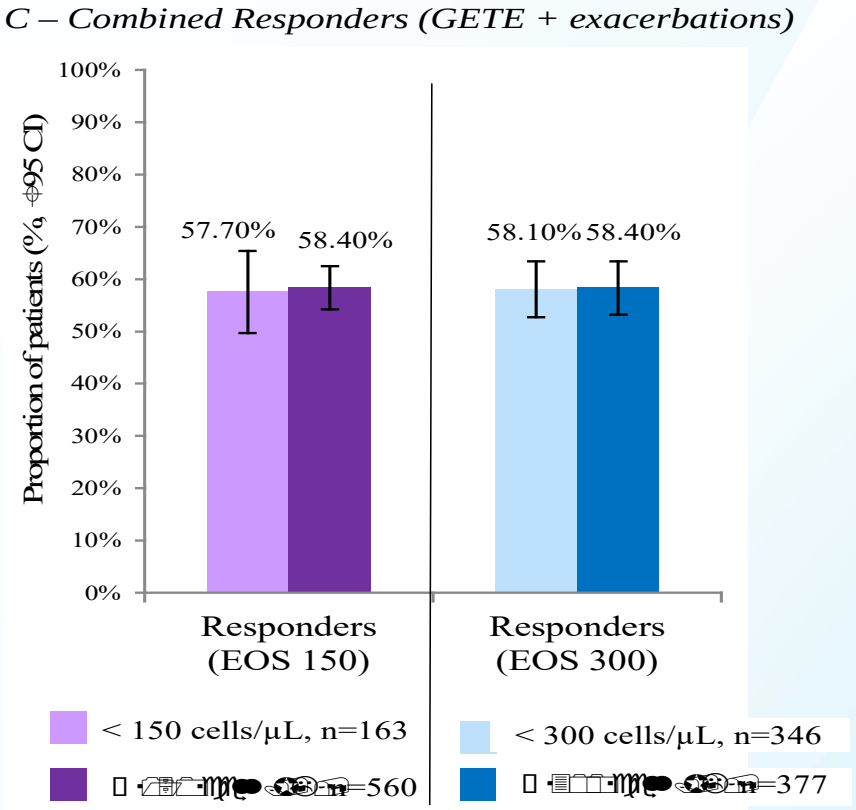
IL-5 an IgE drive different and partially independent "compartments" of Th2 immune response

Suraya et al, Resp Invest, 2021
Caminati et al, Expert Rev Clin Immunol, 2019

IgEs AND EOS

Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study



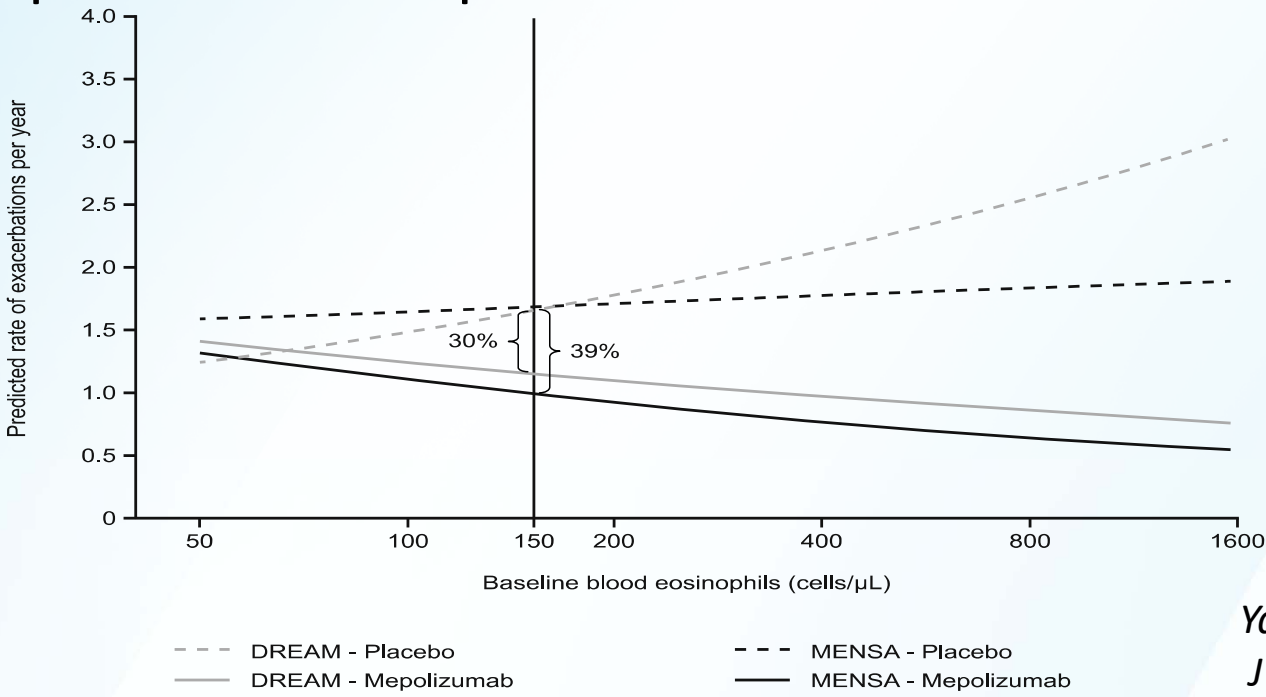


Humbert et al Eur Resp J, 2018

SEVERE ASTHMA & EOSINOPHILS

THE BOX WE LOVE

Biologics for severe asthma work better in patients with high blood eosinophils levels: Mepolizumab

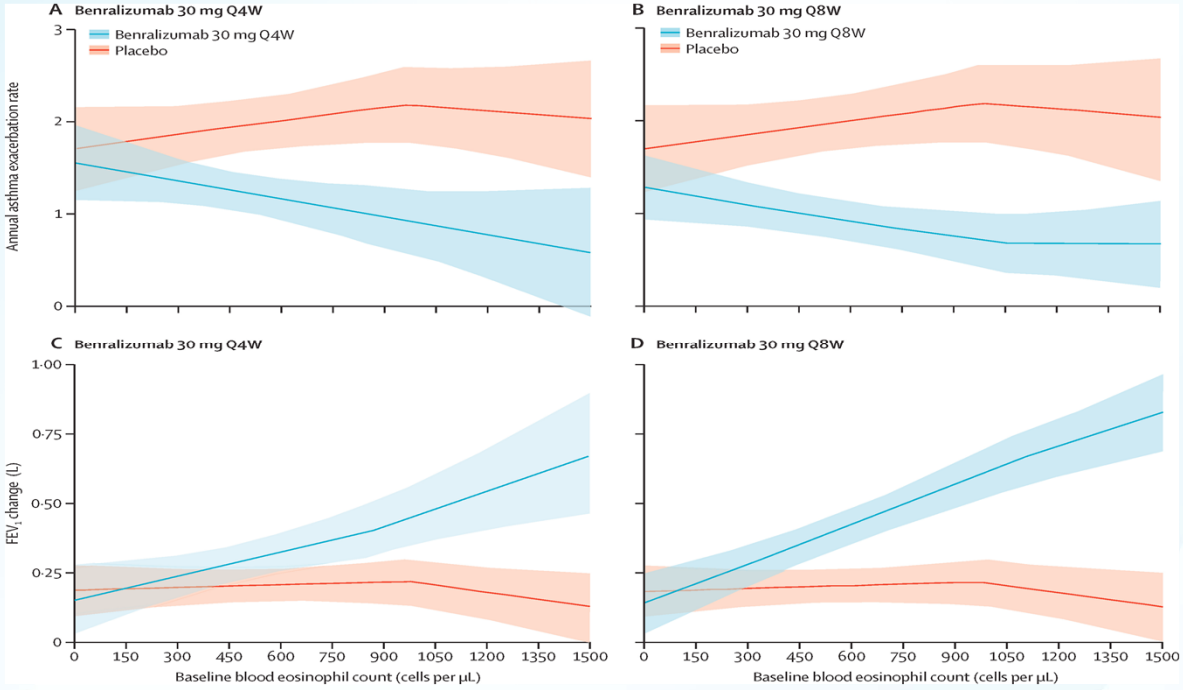


Yancey et al
J Allergy Clin Immunol 2017

SEVERE ASTHMA & EOSINOPHILS

THE BOX WE LOVE

Biologics for severe asthma work better in patients with high blood eosinophils levels: Benralizumab



Fitzgerald et al, Lancet Resp Med 2017

EOSINOPHILS BOX BEYOND TRIALS

A CLINICAL CASE FROM REAL LIFE

Female, 41 years old, caucasian

→ "late onset" asthma, after her second pregnancy (6 years ago) (positive MCH)

→ worsening in the last 2 years difficult to treat asthma despite fluticason 500/ salmeterol 50 BID, then changed into beclometasone formoterol 200/6 3 times/day + montelukast

→ need for OCS almost monthly

→ poor exercise performance

→ fully positive reversibility test, especially during OCS treatment

Caminati et al, J Allergy Clin Immunol IP, in press

EOSINOPHILS BOX BEYOND TRIALS

A CLINICAL CASE FROM REAL LIFE

Clinical frame:

→ CRS WoNP → Nasal steroids on a regular basis

→ Non smoker

→ No sensitization to inhalant allergens (negative SPT and sIgE 24.6)

→ Blood eosinophilia (1400 in OCS wash-out); Total IgE 760 KUA/l

→ ANCA, Aspergillus precipitins and serum antigen, β-glucan, IgG IgA IgM, α1anti-tripsin: negative

→ previous lung CT: no relevant abnormalities

Caminati et al, J Allergy Clin Immunol IP, in press

EOSINOPHILS BOX BEYOND TRIALS

A CLINICAL CASE FROM REAL LIFE

MEPOLIZUMAB

Caminati et al, J Allergy Clin Immunol IP, in press

WHAT'S WRONG WITH THE BOX?

- discrepancy between known Th2 biomarkers and clinical response

WHAT'S WRONG WITH THE EOSINOPHILS BOX?

Low blood eosinophil counts are not always a reliable marker of clinical response to mepolizumab in severe asthma

Iñigo Ojanguren, MD, PhD[a,b], Simone Chaboillez, RT[a], and Catherine Lemiere, MD, MSc[a]

Clinical Implications

- Low blood eosinophil counts do not preclude from the presence of a significant airway eosinophilia. These cases underline the importance of assessing airway inflammation in symptomatic patients treated with anti–IL-5 therapy in spite of low blood eosinophil counts.

J Allergy Clin Immunol Pract, 2018

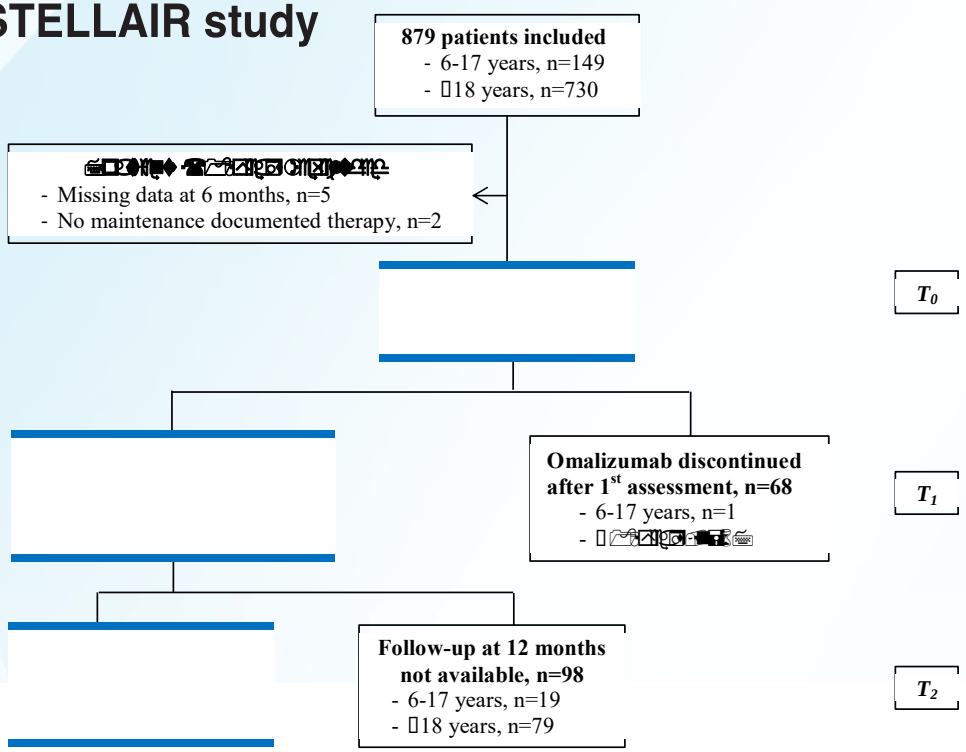
TABLE I. Characteristics of the 3 patients at the time of treatment initiation with mepolizumab and 6 mo or longer after treatment initiation

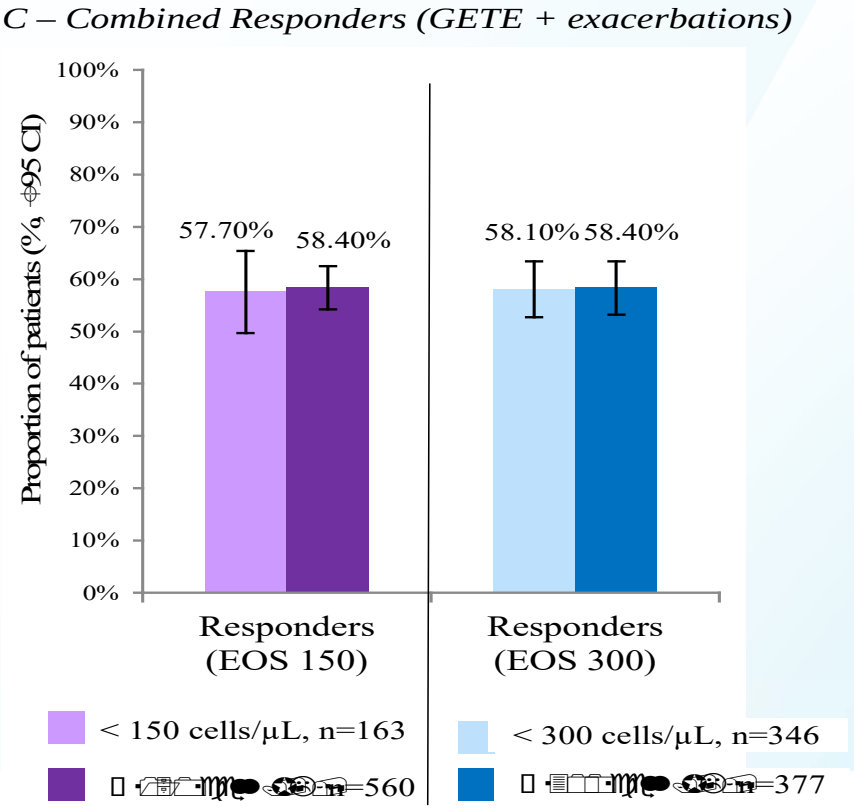
Characteristic	Case 1	Case 2	Case 3
At treatment initiation with mepolizumab			
Sex	Female	Female	Male
Age (y)	59	35	51
Treatment	Budesonide/formoterol 400 µg twice a day Ciclesonide 400 µg twice a day Montelukast 10 mg once a day Salbutamol prn	Fluticasone 500 µg/salmeterol 50 µg twice a day Ciclesonide 400 µg twice a day Tiotropium 18 µg once a day Prednisone 20 mg once a day Montelukast 10 mg once a day Salbutamol prn	Budesonide/formoterol 600 µg twice a day Ciclesonide 400 mg twice a day Tiotropium 18 µg once a day Zafirlukast 20 mg twice a day Salbutamol prn
FEV_1 (L) pre-BDT (% pred)	1.2 (41.0)	1.72 (61.0)	2.0 (59.0)
FEV_1 (L) post-BDT (% pred)	1.7 (59.0)	2.0 (71.4)	2.39 (64.0)
FEV_1/FVC (%) pre- BDT	64.0	74.0	57.0
Blood eosinophil count (10^9 cells/L)	0.7	0.4	0.7
Sputum eosinophil count (%)	72.8	55.8	36.5
Severe asthma exacerbations, in the year preceding mepolizumab initiation (n)	3	2	2
6 mo or longer after treatment initiation			
FEV_1 (L) pre-BDT (% pred)	1.4 (51.3)	1.3 (46.1)	2.1 (61.7)
Blood eosinophil count (10^9 cells/L)	0.1	0.1	0.1
Sputum eosinophil count (%)	42.0	52.0	25.0

BDT, Bronchodilator; *FVC*, forced expiratory volume; *prn*, as needed; *% pred*, percent predicted.

WHAT'S WRONG WITH THE EOSINOPHILS BOX?

Omalizumab effectiveness in patients with severe allergic asthma according to blood eosinophil count: the STELLAIR study





Humbert et al Eur Resp J, 2018

WHAT'S WRONG WITH THE EOSINOPHILS BOX?

Relevance of Th2 markers
in the assessment and therapeutic management
of severe allergic asthma: a real life perspective
Caminati et al JIACI, in press

132 adult patients with severe asthma
(eligible for omalizumab therapy)

	Eosinophil count (mm3)		
	<300	>=300	p-value
DEMOGRAPHIC DATA			
Age - m(sd)	43.7(12.8)	47.1(14.8)	0.16
Gender (%M)	47.8	49.1	0.92
Smoke (%sì)	13.0	1.9	0.10
BMI - m(sd)	25.8(6.4)	25.4(4.5)	0.40
Total IgE - m(sd)	477.0(588.0)	360.6(291.2)	0.19
Perennial sensitizations (%)	91.3	98.1	0.17
History of oral steroids use (%)	52.2	56.6	0.72
LUNG FUNCTION AND PROs			
FEV1% - m(sd)	69.7(18.8)	69.9(17.4)	0.48
FVC% - m(sd)	83.9(13.4)	84.4(15.5)	0.44
Tiffenau - m(sd)	0.7(0.1)	0.7(0.1)	0.25
ACT - m(sd)	14.2(4.3)	14.2(5.6)	0.47
AQLQ - m(sd)	3.7(1.1)	3.7(1.4)	0.47
FeNO - m(sd)	36.3(35.8)	47.8(51.2)	0.16
DIRECT AND INDIRECT COSTS			
Emergency Room admission in the last year - m(sd)	1.1(2.3)	0.9(1.9)	0.35
Hospital Admissions in the last year - m(ds)	0.3(0.8)	0.4(0.7)	0.31
Unscheduled visits - m(ds)	3.2(3.2)	3.5(3.2)	0.35
Lost working days in the last year - m(sd)	13.4(16.8)	24.7(43.0)	0.07
NASAL COMORBIDITIES			
Poliposis (%)	26.1	37.7	0.32
Rhinitis (%)	69.6	86.8	0.07

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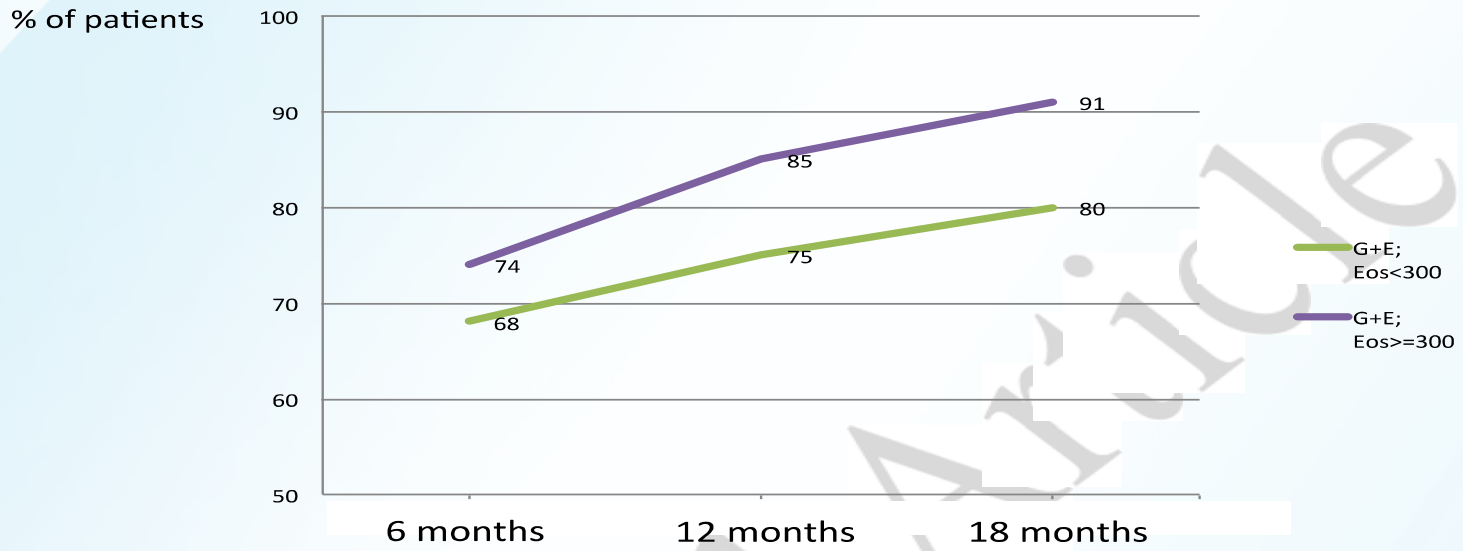
132 adult patients with severe asthma
(eligible for omalizumab therapy)

VARIABLE	Eosinophil count (mm3); FeNO (ppb)					
	<300;<30	<300;>=30	>=300;<30	>=300;>=30	p-value	bartlett's
DEMOGRAPHIC DATA						
Age - m(sd)	42.9(13.7)	42.0(15.1)	46.1(16.9)	46.3(10.3)	0,8385	0,213
Gender (%M)	61,5	50	47,8	50	0,88	--
Smoke (%sì)	38,7	33,3	17,4	15	0,35	--
BMI - m(sd)	27.5/7.4)	21.8(4.2)	25.6(4.2)	24.9(5.3)	0,1836	0,12
Total IgE - m(sd)	347.2(415.2)	613.7(475.2)	441.6(338.7)	311.6(244.7)	0,2447	0,132
Perennial sensitizations (%)	92,3	83,3	95,7	100	0,379	--
History of oral steroids use (%)	46,2	50	60,9	55	0,843	--
LUNG FUNCTION and PROs						
FEV1% - m(sd)	63.7(16.7)	74.7(15.9)	73.7(9.4)	66.0(18.8)	0,1563	0,026
FVC% - m(sd)	78.0(12.9)	91.7(8.7)	87.3(11.1)	84.8(15.9)	0,121	0,271
Tiffenau - m(sd)	0.7(0.1)	0.7(0.1)	0.7(0.1)	0.7(0.1)	0,2269	0,349
ACT - m(sd)	14.9(4.4)	13.2(5.3)	14.9(6.0)	14.7(5.9)	0,9256	0,72
AQLQ - m(sd)	3.7(1.2)	3.3(0.6)	4.0(1.4)	3.4(1.4)	0,5051	0,509
DIRECT AND INDIRECT COSTS						
Emergency Room admission in the last year - m(sd)	1.1(2.9)	1.8(1.6)	1.0(2.5)	1.1(1.6)	0,8671	0,088
Hospital Admissions in the last year - m(ds)	0.25(0.62)	0.67(1.2)	0.35(0.71)	0.55(0.89)	0,6257	0,235
Unscheduled visits - m(ds)	3.5(4.0)	3.8(1.5)	3.0(2.1)	4.1(4.4)	0,7562	0,001
Lost working days in the last year - m(sd)	16.8(19.3)	10.0(7.1)	11.7(16.2)	36.6(50.9)	0,0975	<0.001
COMORBIDITIES'						
Poliposis (%yes)	15,4	50	47,8	35	0,238	--
Rhinitis (%yes)	69,2	100	95,7	90	0,078	--

WHAT'S WRONG WITH THE EOSINOPHILS BOX?

Figure 1. Trend of responders (defined by GETE questionnaire) in high and low basal eosinophils subgroups



	>=300 (n=23)	<300 (n=53)	Difference	CI95% (referred to the difference)	p-value (referred to the difference)
6 months	74%	68%	6%	-16%;28%	0.3003
12 months	85%	75%	10%	-9%;29%	0.1667
18 months	91%	80%	11%	-5%;27%	0.1186

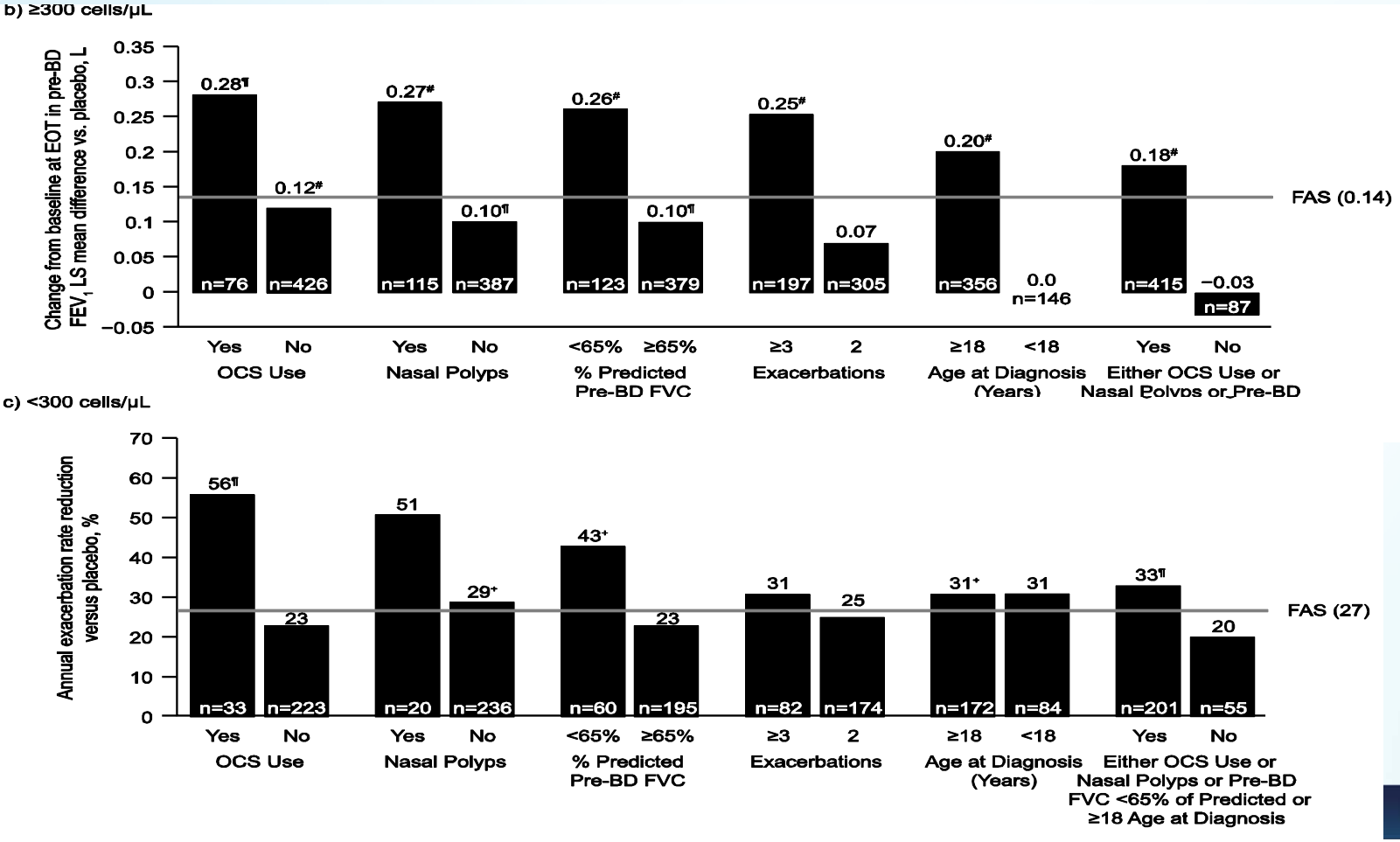
Caminati et al JIACI, in press

Eos: blood eosinophils basal level; G: good responder; E: excellent responder

ERJ 2018

Baseline Patient Factor Impact on the Clinical Efficacy of Benralizumab for Severe Asthma

Eugene R. Bleecker, Michael E. Wechsler, J. Mark FitzGerald, Andrew Menzies-Gow, Yanping Wu, Ian Hirsch, Mitchell Goldman, Paul Newbold, James G. Zangrilli



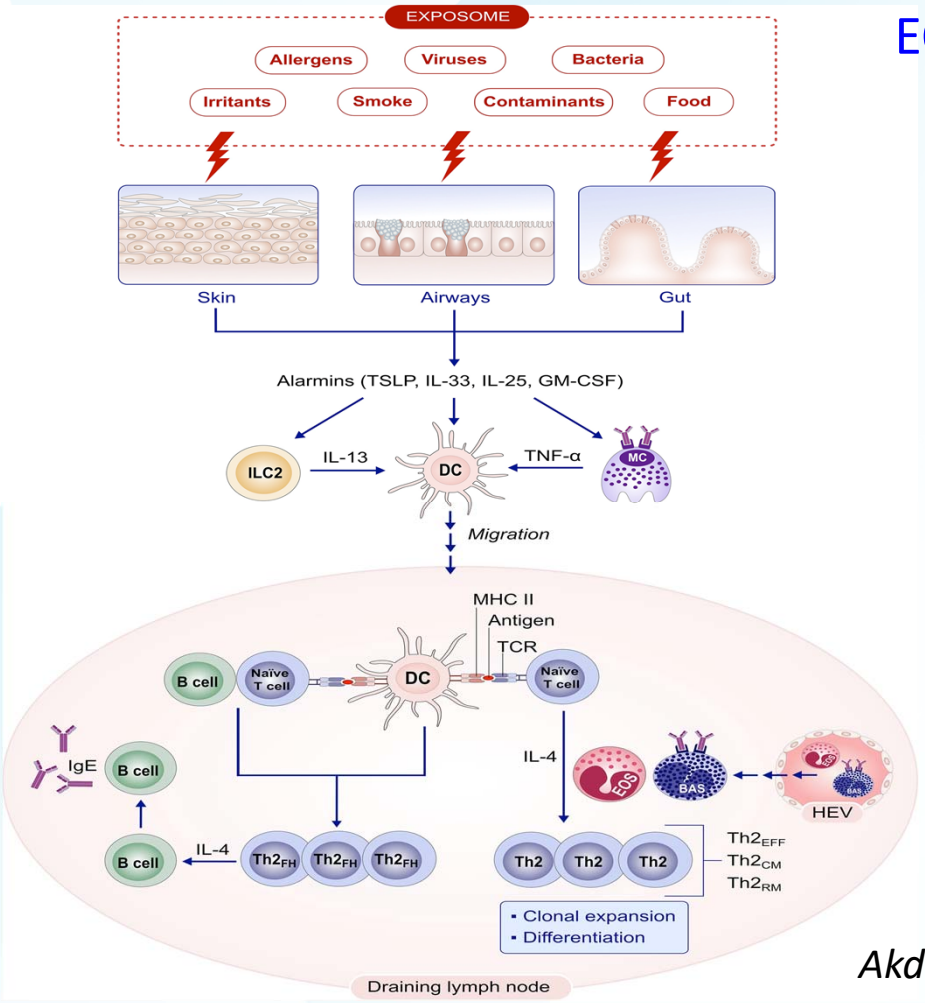
EOSINOPHILS BOX

SHOULD WE CONSIDER SOMETHING BEYOND?

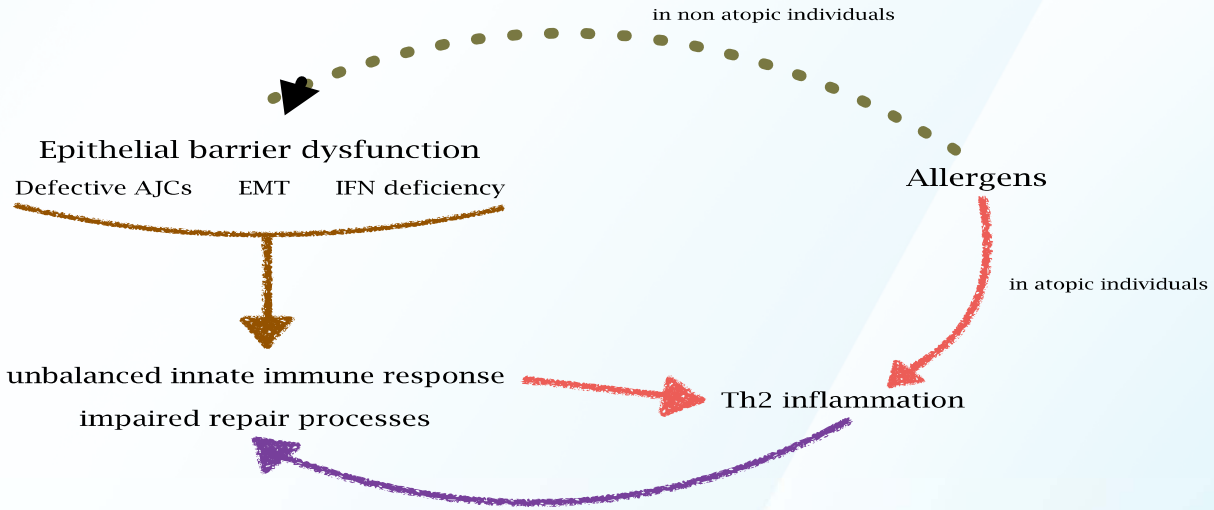
- to what extent peripheral blood eosinophila parallels tissue (bronchial) eosinophilia is not completely known
- the relevance of pathogenetic role played by blood eosinophils is controversial
- bronchial eosinophilia may persist despite peripheral blood eosinophil depletion
- reliable markers of airways eosinophils activation are not currently available

Mukherjee et al, Lancet Resp Med 2015
Caminati et al, Curr Med Res Opin, 2018
Caminati et al, JIACI, in press

TH2 (INFLAMMATION) IMMUNITY



EOSINOPHILS AND BEYOND

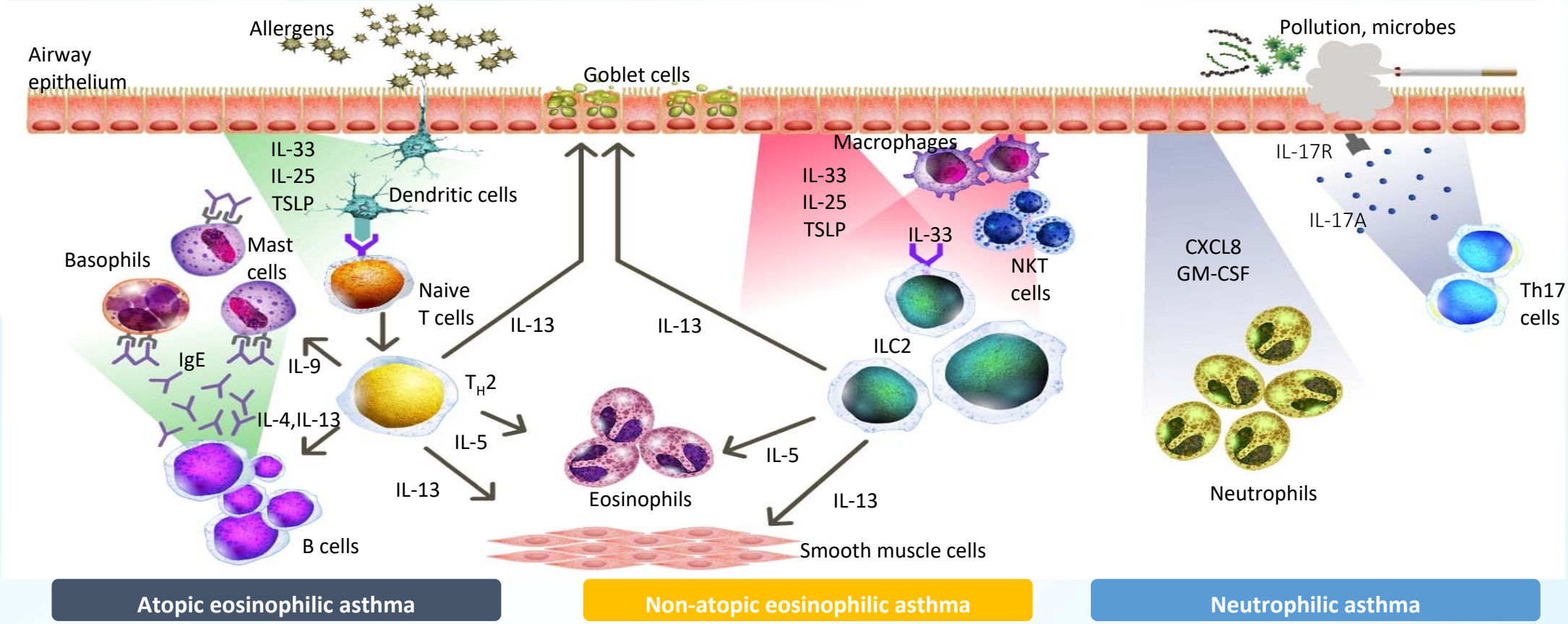


Akdis et al Allergy 2020

Caminati et al, World Allergy Organ j 2018

IL-5 INDEPENDENT EOSINOPHILIC INFLAMMATION

THE CASE OF EPITHELIAL CYTOKINES



Brusselle G et al. *Ann Am Thorac Soc.* 2014:11;S322–S328.

Graphic Source: Brusselle GG et al, Eosinophilic airway inflammation in nonallergic asthma, 2013: p978,B

IL-5 INDEPENDENT EOSINOPHILIC INFLAMMATION

THE CASE OF EPITHELIAL CYTOKINES

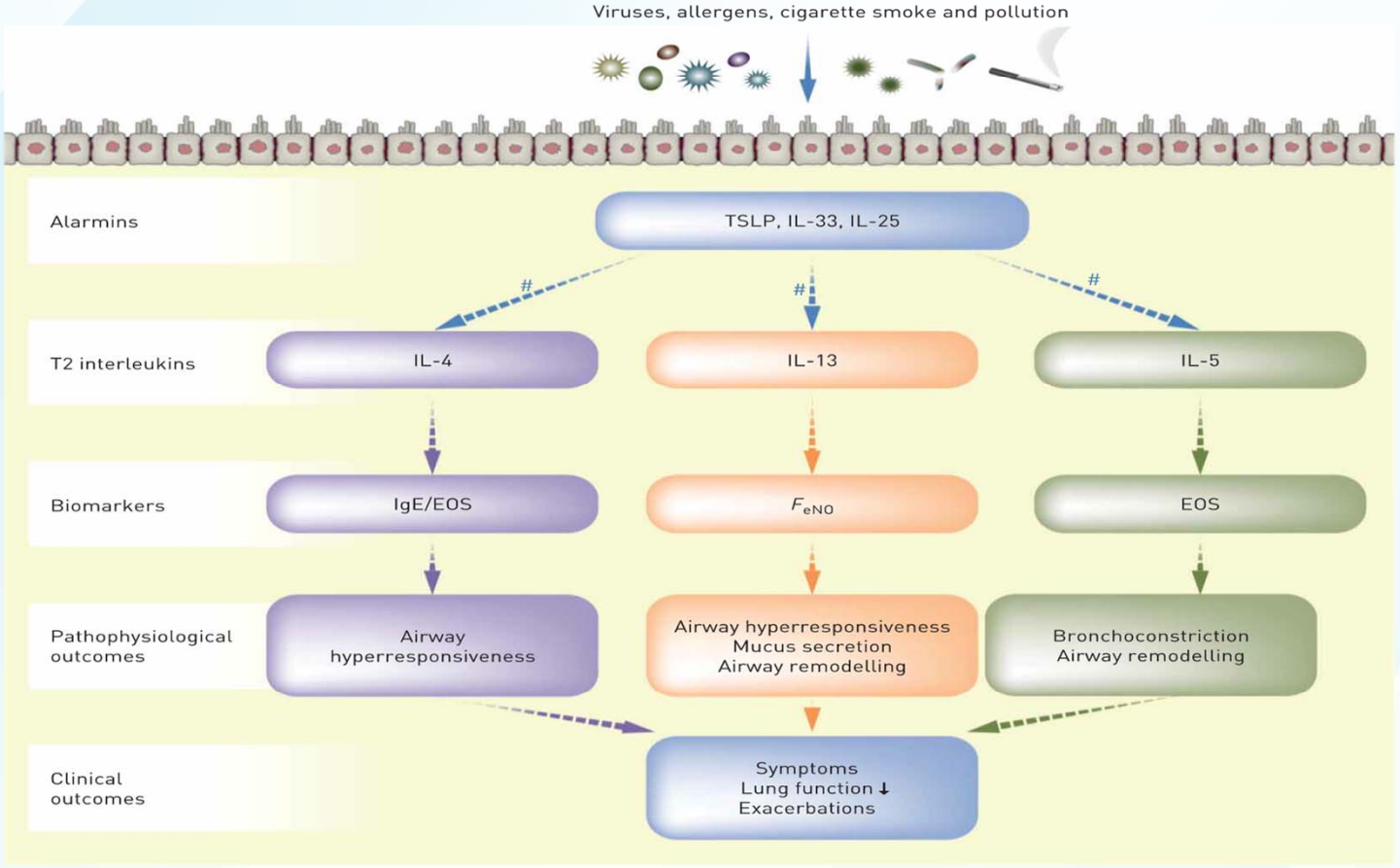


FIGURE 1 Role of the alarmins in driving type 2 inflammation, biomarkers and clinical outcomes in asthma. EOS: eosinophils; F_{eNO}: fractional exhaled nitric oxide; IgE: immunoglobulin E; IL: interleukin; ILC2: type 2 innate lymphoid cell; Th2: type 2 T helper cell; TSLP: thymic stromal lymphopoietin. #: Released from Th2 cells and ILC2s.

Porsbjergl et al
Eur Resp J, 2020

IL-5 INDEPENDENT Th2/EOSINOPHILIC INFLAMMATION

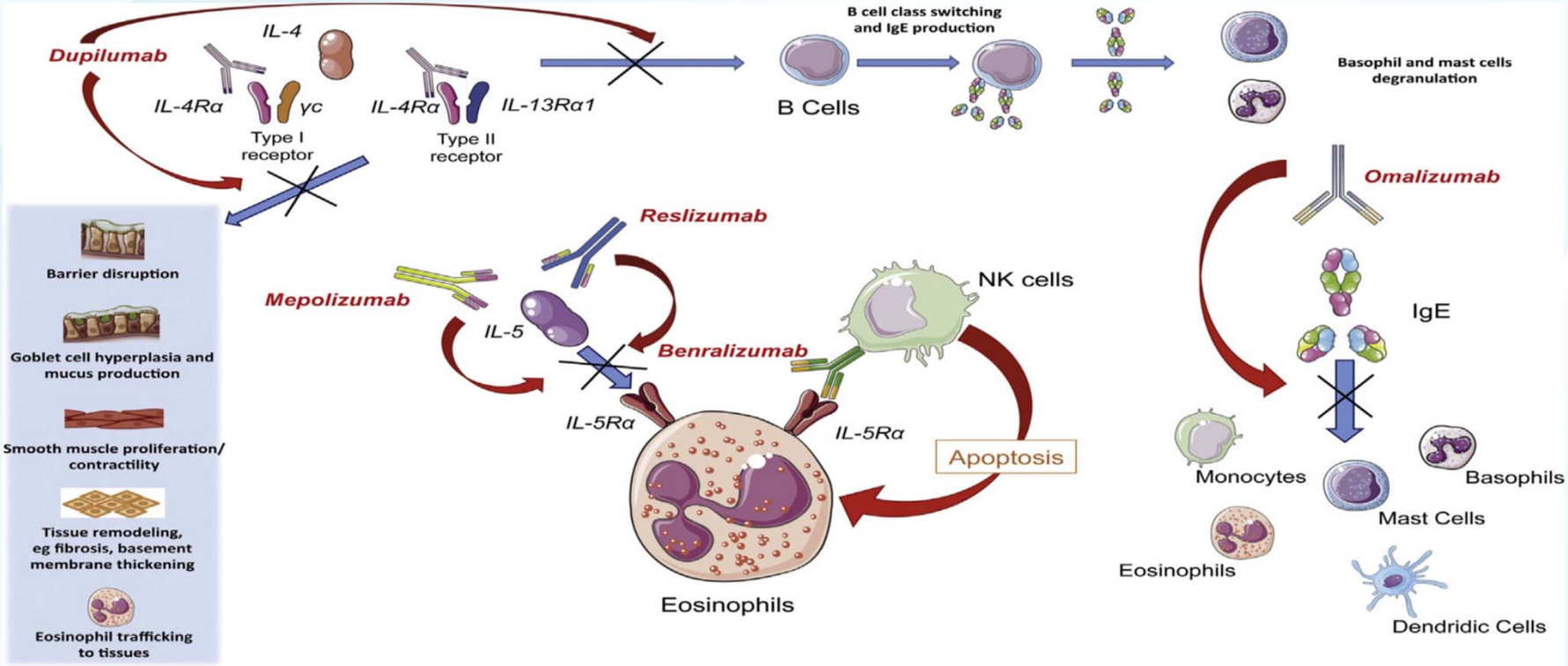
FeNO and THE EPITHELIAL BARRIER DYSFUNCTION CONCEPT

	Infiammazione eosinofila delle vie aeree	Risposta a steroide inalatorio	In paziente con sintomi asmatiformi	In paziente senza sintomi asmatiformi
FeNO <25 ppb	Poco probabile	Poco probabile	Valutare diagnosi alternative	Aderenza ottimale a steroide inalatorio Valutare *step down*
FeNO 25-50 ppb	Possibile (da valutare nel contesto clinico)	Possibile (da valutare nel contesto clinico)	Aderenza non ottimale o dosaggio terapeutico inadeguato Possibile steroido-resistenza Esposizione allergenica	Aderenza ottimale e adeguato dosaggio terapeutico Proseguire monitoraggio del FeNO
FeNO >50 ppb	Probabile	Probabile	Aderenza non ottimale o dosaggio terapeutico inadeguato Rivedere tecnica inalatoria Possibile steroido-resistenza Esposizione allergenica Aumentato rischio di riacutizzazioni	Aderenza non ottimale o dosaggio terapeutico inadeguato Rivedere tecnica inalatoria

TARGETING TH2 INFLAMMATION

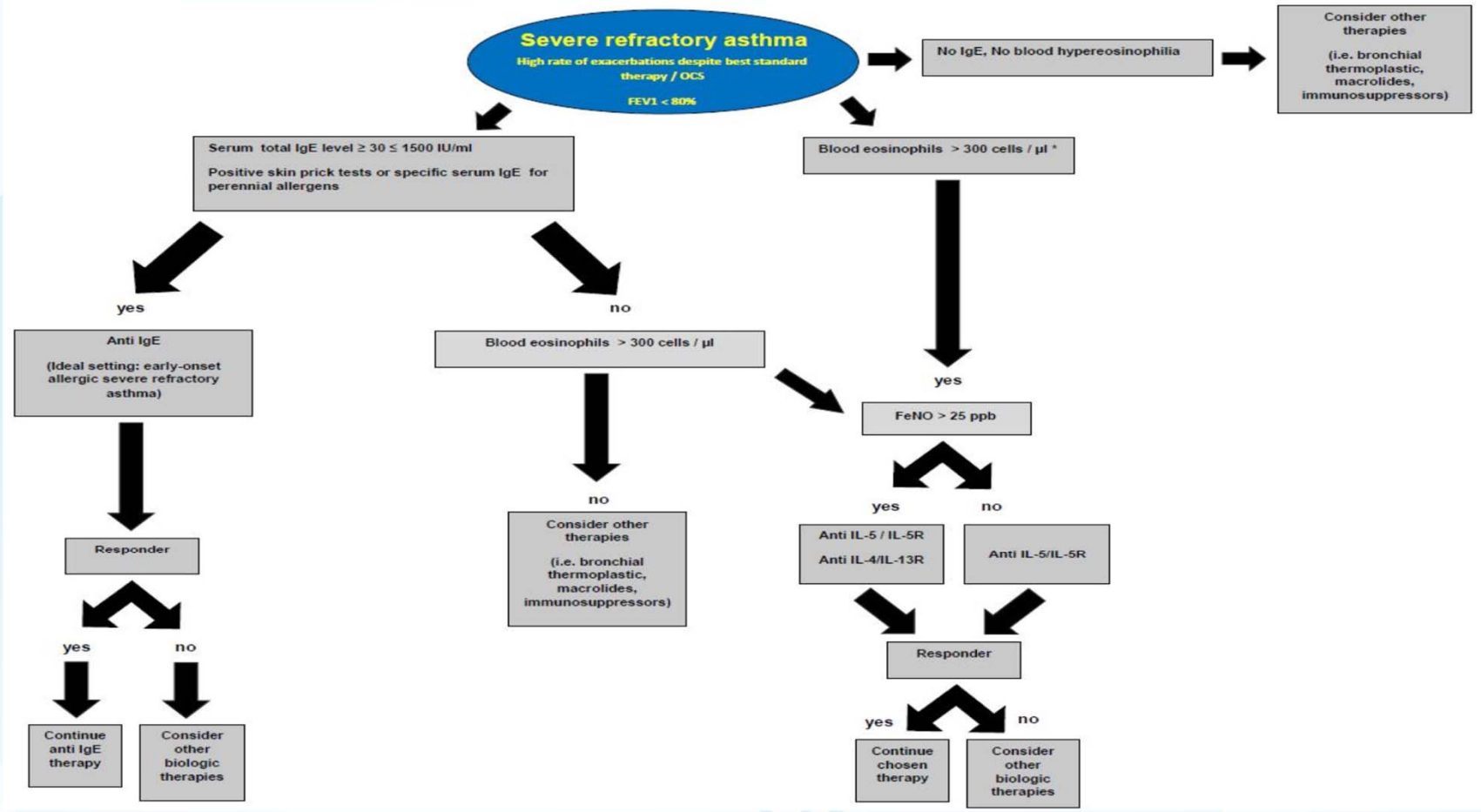
WHAT WE NEED TO KNOW TODAY

- Different potential targets for “personalized” treatments



Caminati e al, Immunol Allergy Clin N Am 2020

BIOMARKER - BASED DECISION TREE

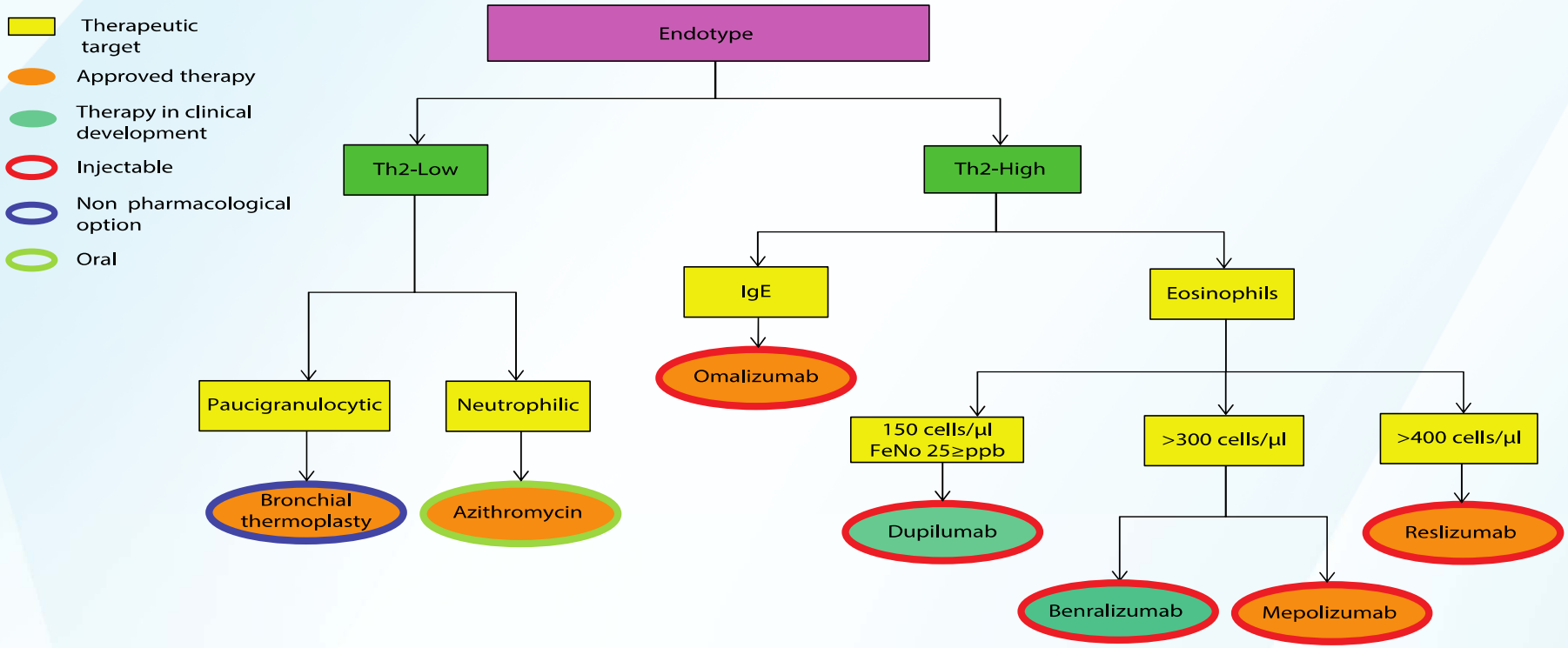


Bagnasco, Caminati et al, Expert Review Resp Med 2019

..BACK TO ASTHMA TO GO BEYOND..

PRACTICALLY APPROACHING A PATIENT..

Figure 2. Severe asthma endotype serving for the correct therapeutic choice.



IgE, immunoglobulin E; Th2, T helper 2.

Menzella, Caminati et al, Drugs in Context 2019