Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

EAACI

Allergy

ORIGINAL ARTICLE EPIDEMIOLOGY AND GENETICS

Chronic rhinosinusitis in Europe – an underestimated disease. A GA²LEN study

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Allergy 2011

→ 10,9%

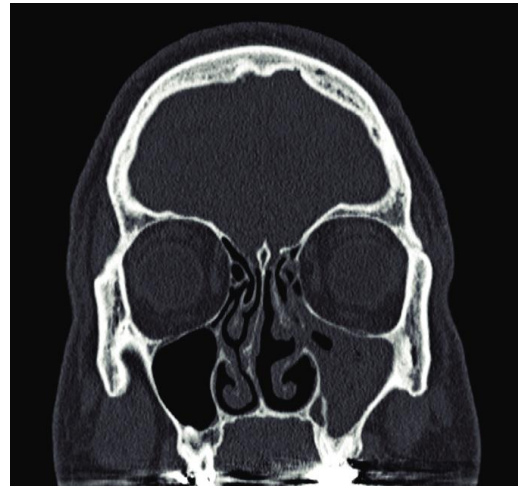
Cronica: >12 settimane o 4 episodi di almeno 10 giorni in assenza di risoluzione + riacutizzazioni

The Laryngoscope
Lippincott Williams & Wilkins, Inc., Philadelphia
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The Accuracy of Computed Tomography in the Diagnosis of Chronic Rhinosinusitis

Neil Bhattacharyya, MD; Marvin P. Fried, MD

→



FENOTIPO

CRSwNP



- CS e ATB
- FESS → Recidiva 20%

CRSsNP



ENDOTIPO

Tipo 2

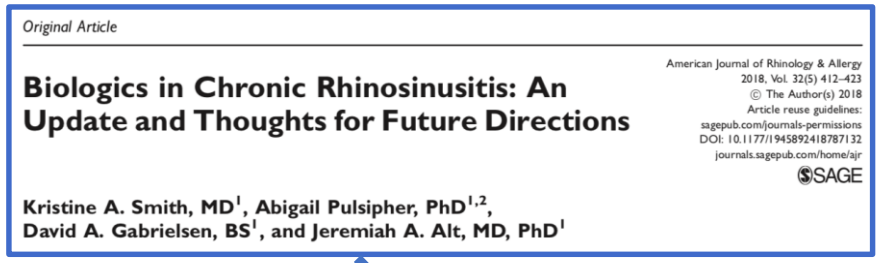
- Citochine tipo 2
- IgE
- Eos
- Cys-Leu

Tipo non-2

- IFN-ɣ
- IL-17
- IL-22
- TNF-α

TERAPIA BIOLOGICA

- Mepolizumab e Reslizumab
- Benralizumab
- Dupilumab
- Omalizumab



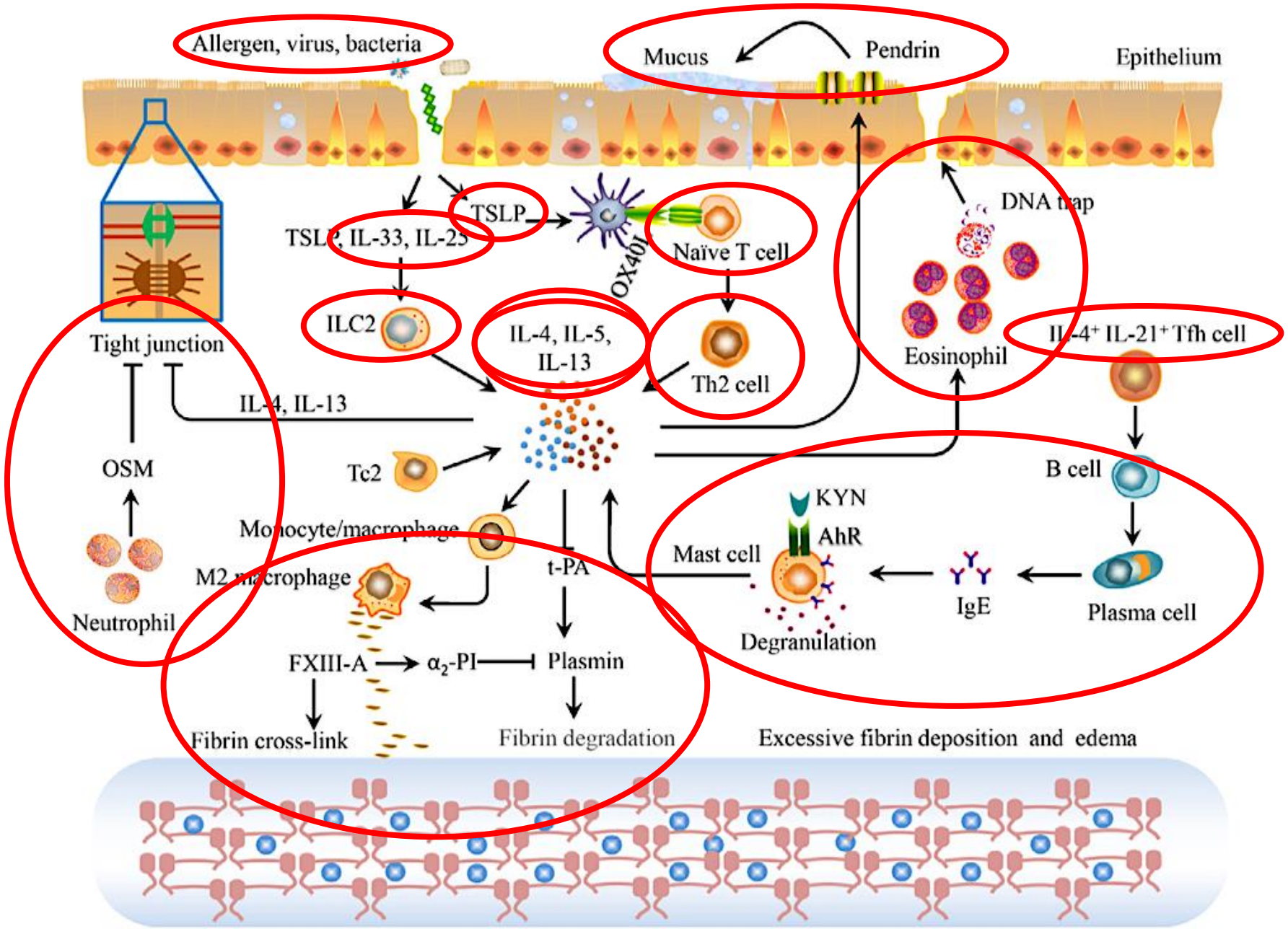
Original Article

Biologics in Chronic Rhinosinusitis: An Update and Thoughts for Future Directions

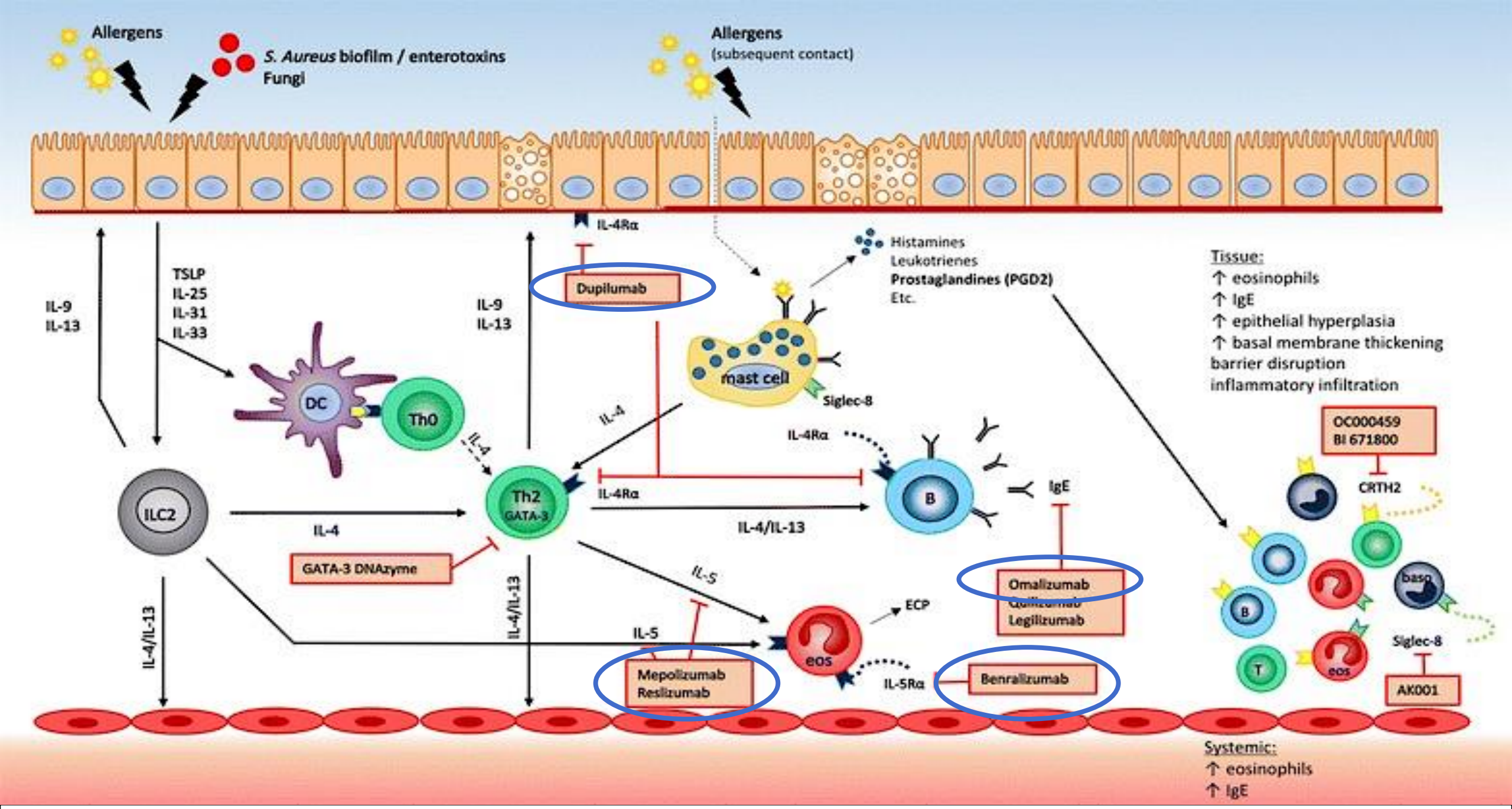
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Kristine A. Smith, MD[1], Abigail Pulsipher, PhD[1,2], David A. Gabrielsen, BS[1], and Jeremiah A. Alt, MD, PhD[1]

- Brodalimumab



Cao et al. Pathophysiologic mechanisms of chronic rhinosinusitis and their roles in emerging disease endotypes. Ann Allergy Asthma Immunol 2019;122(1):33-40.



De Greve et al. Endotype-driven treatment in chronic upper airway diseases. Clin Transl Allergy. 2017. Jul 12;7:22.

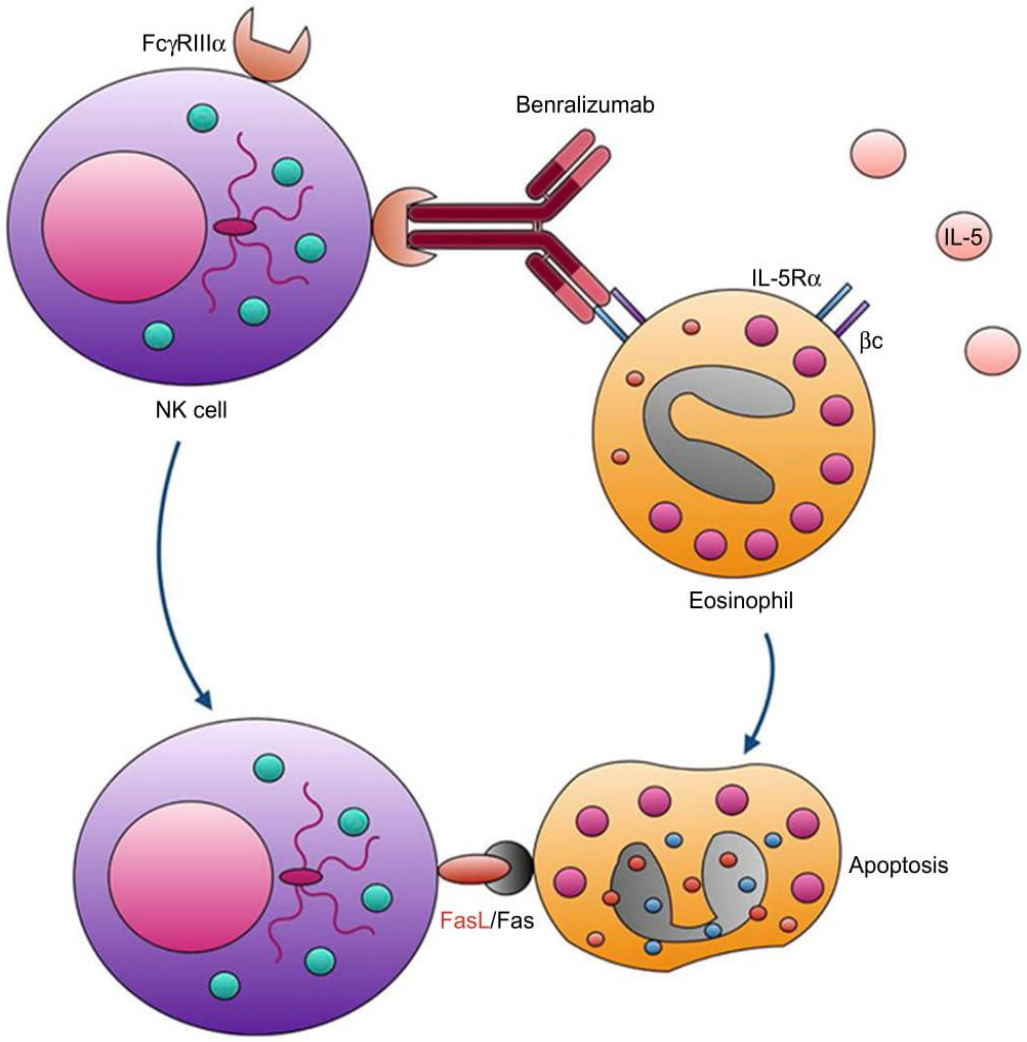
Therapeutic Antibodies for Nasal Polyposis Treatment: Where Are We Headed?

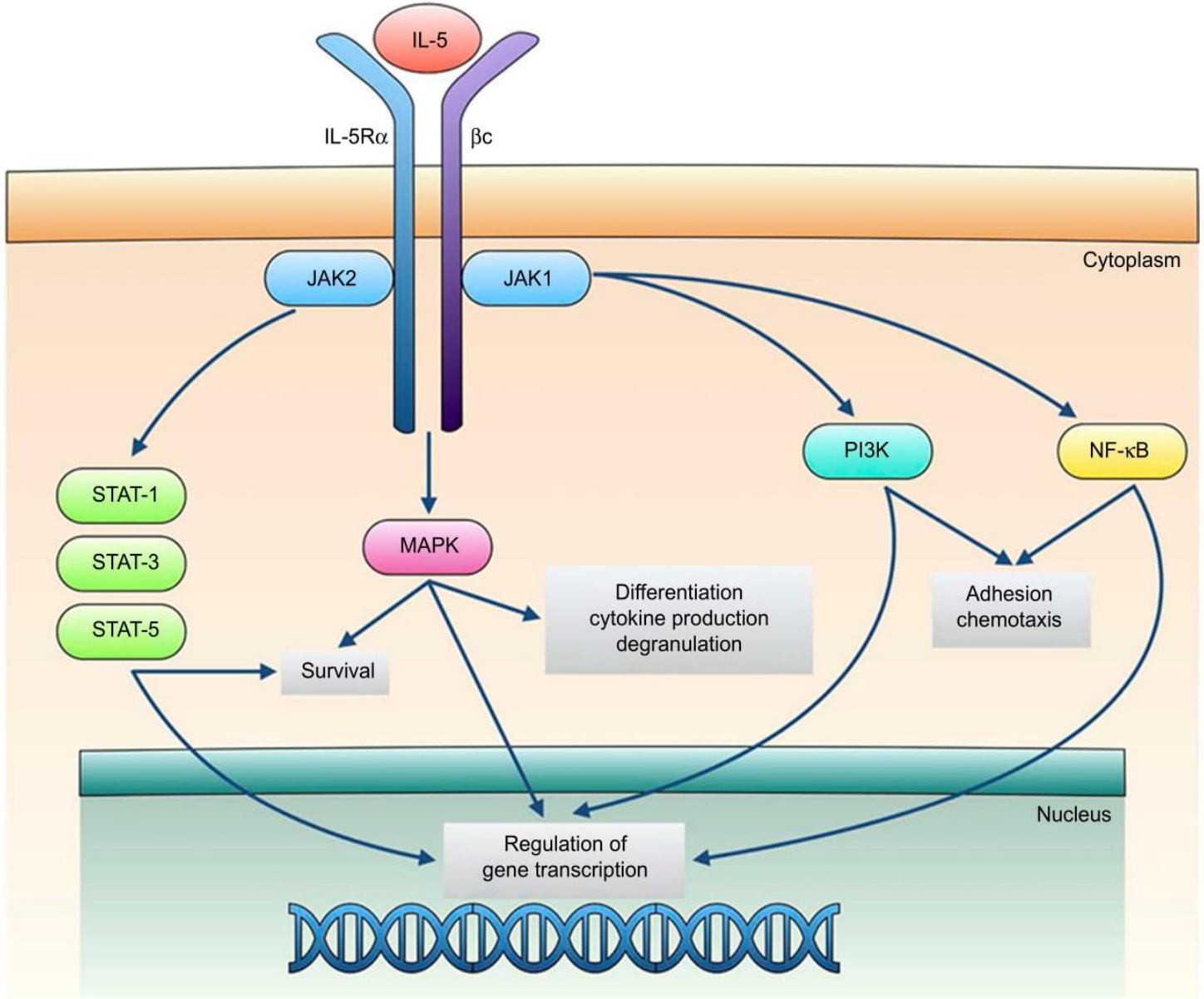
Aarti Agarwal[1] · Derek Spath[1] · David A. Sherris[1] · Hirohito Kita[2] · Jens U. Ponikau[1]

Table 1 Biologics for nasal polyposis

Drug name	Target	Mechanism of action	Randomized double-blind, placebo-controlled clinical trial results				Current status of drug development
			Authors	Dosing	Subjects	Outcome	
Omalizumab	IgE	Humanized monoclonal (IgG1) antibody that binds free-circulating IgE and inhibits the binding of IgE to the high-affinity FcεRI on the Cε3 domain, also decreases IgE receptors on mast cells, basophils, and dendritic cells.	Gevaert, P., et al. 2013. [19]	Weight- and serum IgE–based dosing subcutaneously every 2–4 weeks for 16 weeks, observation for total of 20 weeks	24 adults with CRSwNP and asthma; serum IgE 30 to 700 μg/mL	Improved nasal polyp score at 16 weeks (primary endpoint). Improved Lund-Mackay CT score, decreased nasal congestion, decreased loss of smell, and decreased anterior rhinorrhea Improved SF-36, RSOM-31, and AQLQ scores	Two current phase III trials for the indication of chronic rhinosinusitis with nasal polyposis are active (new 26, new 27), and an open-label extension is currently in recruitment phase (new 28).
Dupilumab	IL-4Rα	Fully human monoclonal antibody to the IL-4 receptor α-subunit which is common to the receptors of both IL-4 and IL-13	Bachert, C. et al. 2016. [20]	600 mg subcutaneous loading dose; 300 mg weekly for 15 additional weeks	60 adults with bilateral, uncontrolled CRSwNP	Improved nasal polyp score at week 16 (primary endpoint); improved Lund-Mackay CT score and SNOT-22 score; improved sense of smell, decreased nasal congestion, and decreased posterior rhinorrhea; decreased maxillary volume occupied by disease; increased morning peak nasal inspiratory flow rate	Active phase III trial for use with background mometasone furoate nasal spray for the indication of nasal polyposis
Reslizumab	IL-5	Humanized monoclonal IL-5 (IgG4κ) antibody that binds IL-5 and prevents it from binding to the IL-5 receptor α-subunit on the surface of eosinophils	Gevaert, P., et al. 2006. [9]	3 mg/kg intravenous or 1 mg/kg intravenous administered as single dose, observation for 36 weeks following dose	24 adults with bilateral nasal polyposis or recurrent nasal polyps after sinus surgery	Phase I trial: not designed for evaluation of efficacy; no difference in the symptom scores or in the nasal peak inspiratory flow values at any time point in either treatment group when compared with placebo; rebound eosinophilia occurred after 24 or 32 weeks	A phase III trial is recruiting for the indication of chronic rhinosinusitis.
Mepolizumab	IL-5	Humanized monoclonal IL-5 (IgG1κ) antibody that binds IL-5 and prevents it from binding to the IL-5 receptor α-subunit on the surface of eosinophils	Bachert, C., et al. 2017. [21]	750 mg intravenous every 4 weeks for 6 doses; observation for total of 25 weeks	105 adults with severe, bilateral nasal polyposis requiring surgery	More patients in the mepolizumab group no longer met the criteria for requiring surgery (30% versus 10% in placebo group) at week 25 (primary endpoint). Improved nasal polyp score and symptom scores for rhinorrhea, nasal obstruction, and sense of smell; no rebound eosinophilia at week 25 (4 weeks after last dose)	Phase III trial currently recruiting participants for use with background mometasone furoate nasal spray for the indication of severe bilateral nasal polyposis
Benralizumab	IL-5Rα	Humanized monoclonal IL-5Rα (IgG1κ) antibody that binds IL-5 receptor α-subunit on eosinophils, preventing binding of IL-5	No published studies in nasal polyposis				Phase III trial currently recruiting participants for use with concomitant mometasone furoate for indication of chronic rhinosinusitis with nasal polyposis

Clinic Rec Alleg Immunol
Published online: 10 May 2019





Pelaia et al. Benralizumab in the treatment of severe ashtma: design, development and potential place in therapy. Drug, Design, Development and Therapy 2018:12 619-628

Efficacia di Benralizumab (Fasenra®) nel trattamento della rinosinusite cronica con poliposi nasale



MATERIALI E METODI

Uno studio prospettico è stato condotto presso l'UOC di Otorinolaringoiatria dell'Azienda Ospedaliera Universitaria "Mater Domini" di Catanzaro.
Il campione clinico utilizzato è costituito da 10 pazienti (6 M, 4 F), di età compresa tra 43 e 68 anni, affetti da CRSwNP ed asma severo, in trattamento presso l'UOC di Malattie dell' Apparato Respiratorio.



I pazienti sono stati trattati con Benralizumab (Fasenra®), 30 mg/dose s.c.:
- 1 dose ogni 4 settimane per le prime 3 dosi
- 1 dose ogni 8 settimane per le successive

Criteri di inclusione:

- Endoscopic Polyp Score >2;

- Presenza di almeno 2 sintomi tra: ostruzione nasale, rinorrea, senso di pressione/dolore facciale, iposmia/anosmia, ipogeusia/ageusia;

- Eosinofilia periferica> 300 cellule/ml;

- Asma severo, non responsivo alla terapia prevista allo step 5 delle LG GINA.



Criteri di esclusione:

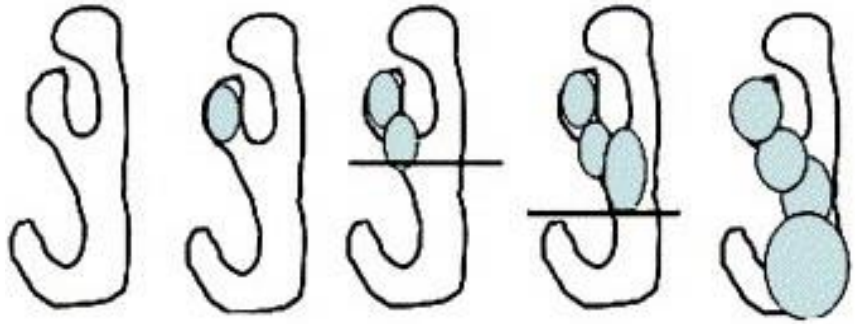
- trattamento con corticosteroidi topici/sistemici, o farmaci immunosoppressivi, o anti-IgE, nei 2 mesi precedenti;

- chirurgia endoscopica funzionale dei seni paranasali nei 6 mesi precedenti;

- chirurgia endoscopica dei seni subita per più di 3 volte.

I pazienti sono stati valutati al tempo 0 e a 24 settimane con:

- Endoscopia nasale mediante fibroscopio OLYMPUS ENF TYPE-GP e definizione dell'Endoscopic Nasal Polyp Score (da 0 a 3 per ciascuna fossa nasale);



- Tomografia Computerizzata (TC) del massiccio facciale e calcolo del Lund-Mackay CT Score;

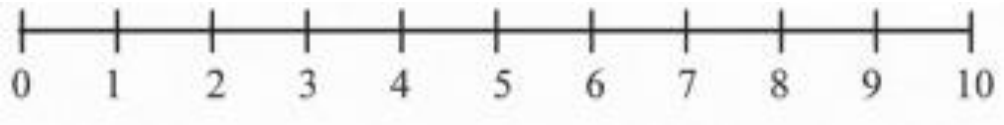
Paranasal sinuses	Right	Left
Maxillary0, 1, 2		
Anterior Ethmoid0, 1, 2		
Posterior Ethmoid0, 1, 2		
Sphenoid0, 1, 2		
Frontal0, 1, 2		
Ostiomeatal complex0* or 2*		
Total points to each side		

0 = no abnormalities; 1 = partial opacification; 2 = total opacification
0* = not occluded and 2* = occluded

1. Considering how severe the problem is when you experience it and how often it happens, please rate each item below on how "bad" it is by circling the number that corresponds with how you feel using this scale: →	No Problem	Very Mild Problem	Mild or slight Problem	Moderate Problem	Severe Problem	Problem as bad as it can be		5 Most Important Items
1. Need to blow nose	**0**	**1**	**2**	**3**	**4**	**5**		○
2. Nasal Blockage	**0**	**1**	**2**	**3**	**4**	**5**		○
3. Sneezing	**0**	**1**	**2**	**3**	**4**	**5**		○
4. Runny nose	**0**	**1**	**2**	**3**	**4**	**5**		○
5. Cough	**0**	**1**	**2**	**3**	**4**	**5**		○
6. Post-nasal discharge	**0**	**1**	**2**	**3**	**4**	**5**		○
7. Thick nasal discharge	**0**	**1**	**2**	**3**	**4**	**5**		○
8. Ear fullness	**0**	**1**	**2**	**3**	**4**	**5**		○
9. Dizziness	**0**	**1**	**2**	**3**	**4**	**5**		○
10. Ear pain	**0**	**1**	**2**	**3**	**4**	**5**		○
11. Facial pain/pressure	**0**	**1**	**2**	**3**	**4**	**5**		○
12. Decreased Sense of Smell/Taste	**0**	**1**	**2**	**3**	**4**	**5**		○
13. Difficulty falling asleep	**0**	**1**	**2**	**3**	**4**	**5**		○
14. Wake up at night	**0**	**1**	**2**	**3**	**4**	**5**		○
15. Lack of a good night's sleep	**0**	**1**	**2**	**3**	**4**	**5**		○
16. Wake up tired	**0**	**1**	**2**	**3**	**4**	**5**		○
17. Fatigue	**0**	**1**	**2**	**3**	**4**	**5**		○
18. Reduced productivity	**0**	**1**	**2**	**3**	**4**	**5**		○
19. Reduced concentration	**0**	**1**	**2**	**3**	**4**	**5**		○
20. Frustrated/restless/irritable	**0**	**1**	**2**	**3**	**4**	**5**		○
21. Sad	**0**	**1**	**2**	**3**	**4**	**5**		○
22. Embarrassed	**0**	**1**	**2**	**3**	**4**	**5**		○

- Stima dell'impatto sulla QoL attraverso Sino Nasal Outcome Test (SNOT-22) – Washington University – St. Louis, Missouri. Punteggio da 0 a 5 per ciascun item. Punteggio totale da 0 a 110;

- Impatto generale della malattia mediante scala di valutazione numerica (NRS= numeric rating scale);



- Eosinofilia periferica espressa come numero assoluto di cellule/ml.



ANALISI STATISTICA

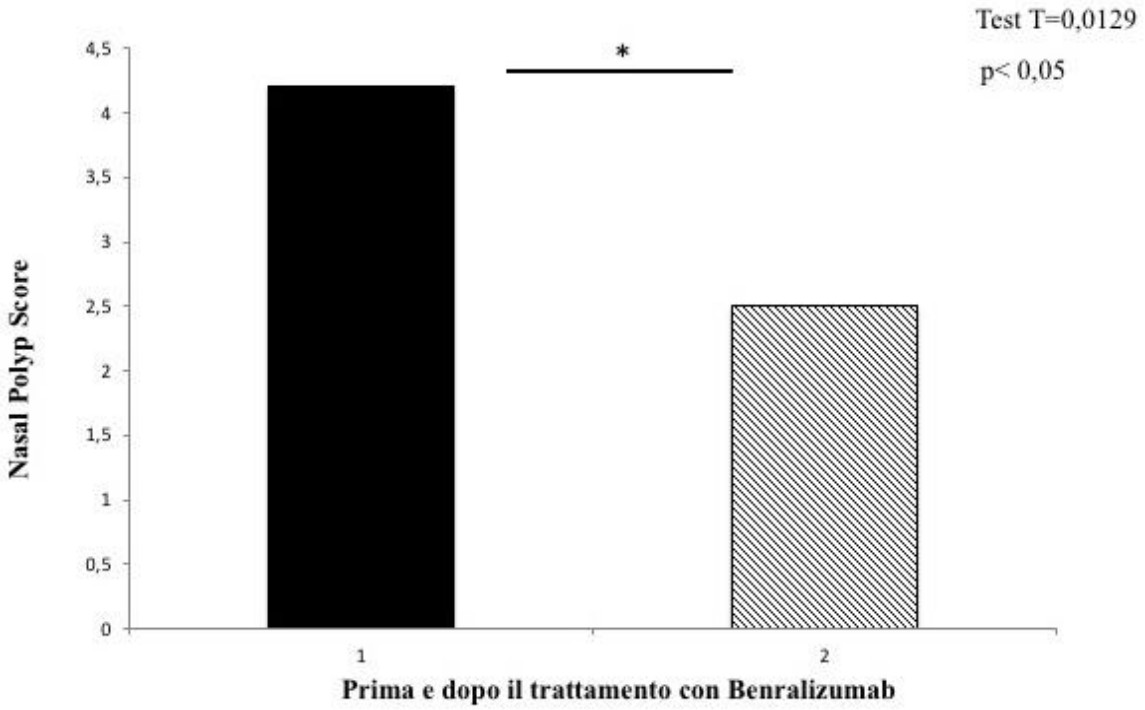
- Microsoft Excel

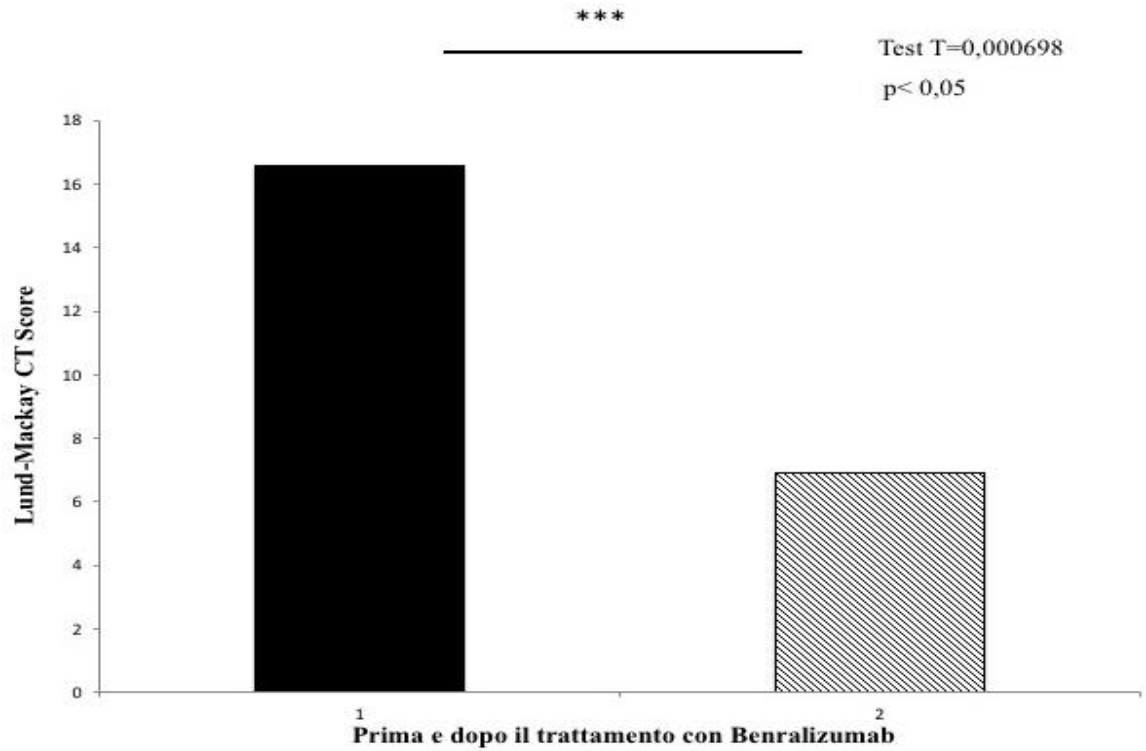
- t-test pre e post trattamento

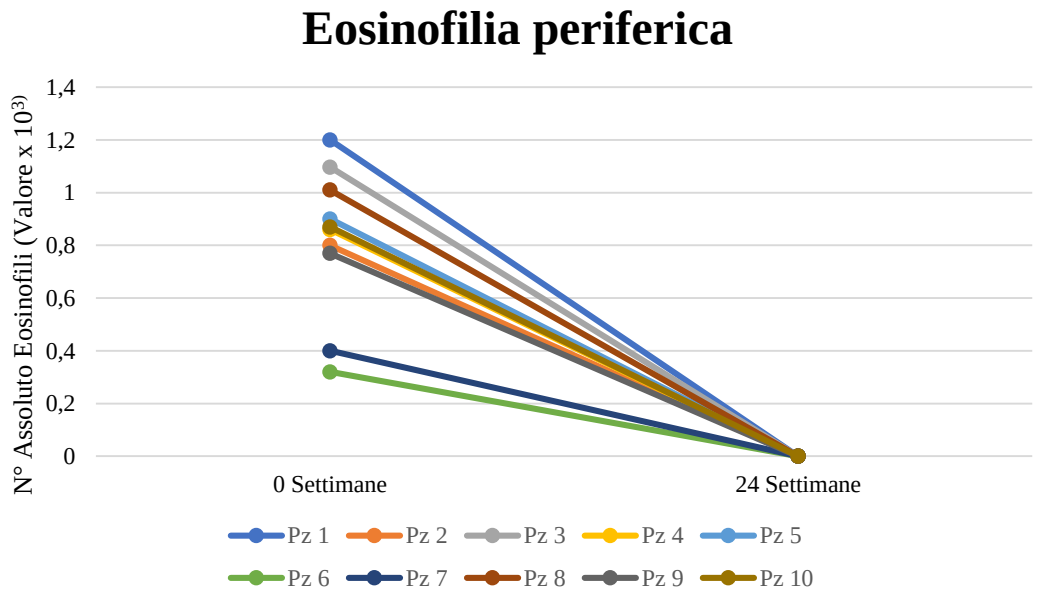
- $p<0,05$

RISULTATI

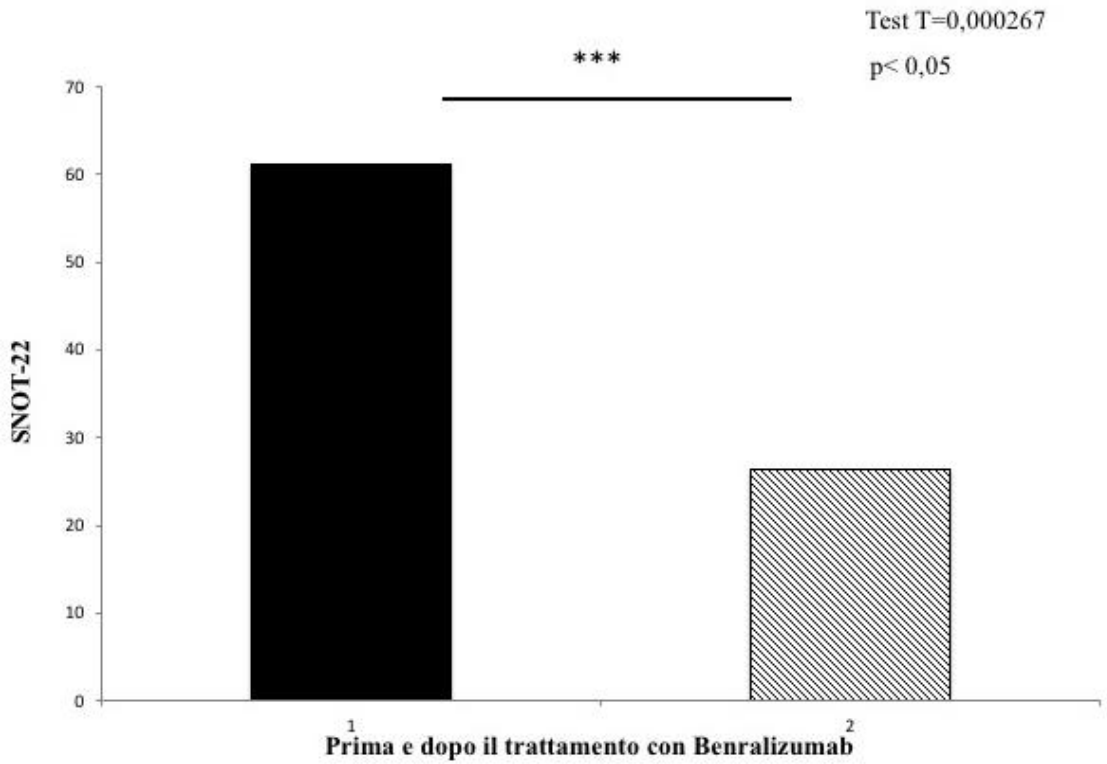
In tutti i pazienti si è ottenuto un miglioramento statisticamente significativo dei parametri valutativi scelti per lo studio

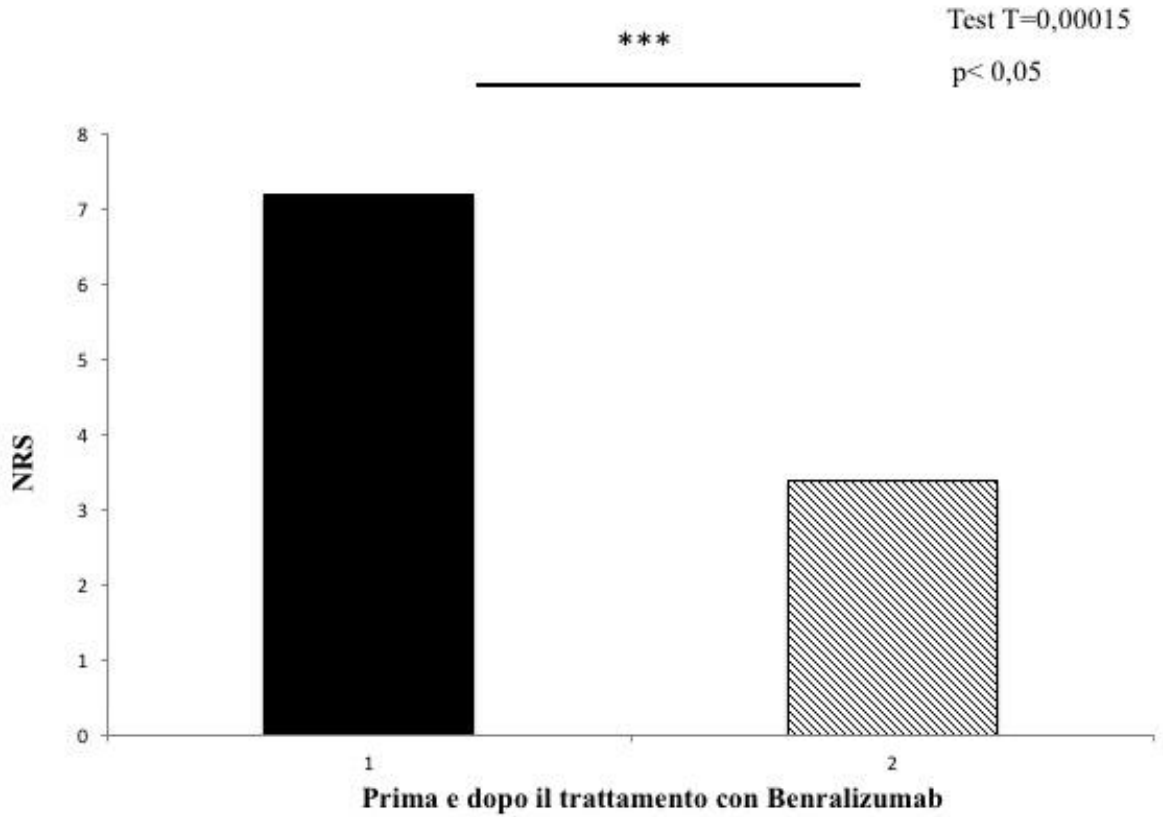






RISULTATI


Test T=0,000267
p< 0,05
***
SNOT-22
70
60
50
40
30
20
10
0
1
2
Prima e dopo il trattamento con Benralizumab


Test T=0,00015
p< 0,05
***
NRS
8
7
6
5
4
3
2
1
0
1
2
Prima e dopo il trattamento con Benralizumab

CONCLUSIONI

- Benralizumab è efficace nel trattamento della CRSwNP già dopo 24 settimane.





- Occorrono studi per definirne i pazienti candidabili a tale terapia e validarne l'efficacia a lungo termine.

- Il futuro delle CRS dovrà prendere in considerazione:

- biomarcatori