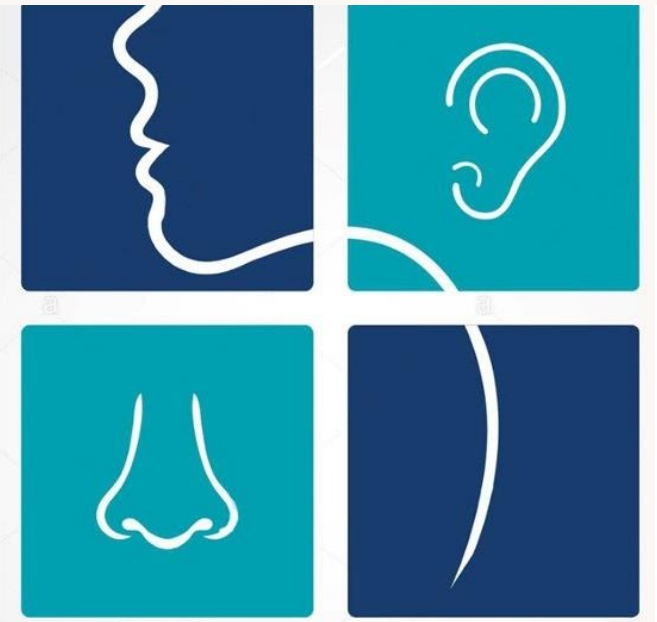
Πανελλήνια Εταιρεία Ωτορινολαρυγγολογίας, Χειρουργικής Κεφαλής & Τραχήλου

ΕΚΠΑΙΔΕΥΤΙΚΑ ΔΙΑΔΙΚΤΥΑΚΑ ΣΕΜΙΝΑΡΙΑ 2020-2021

Σύγχρονες Θεραπευτικές προσεγγίσεις στην αλλεργική ρινίτιδα

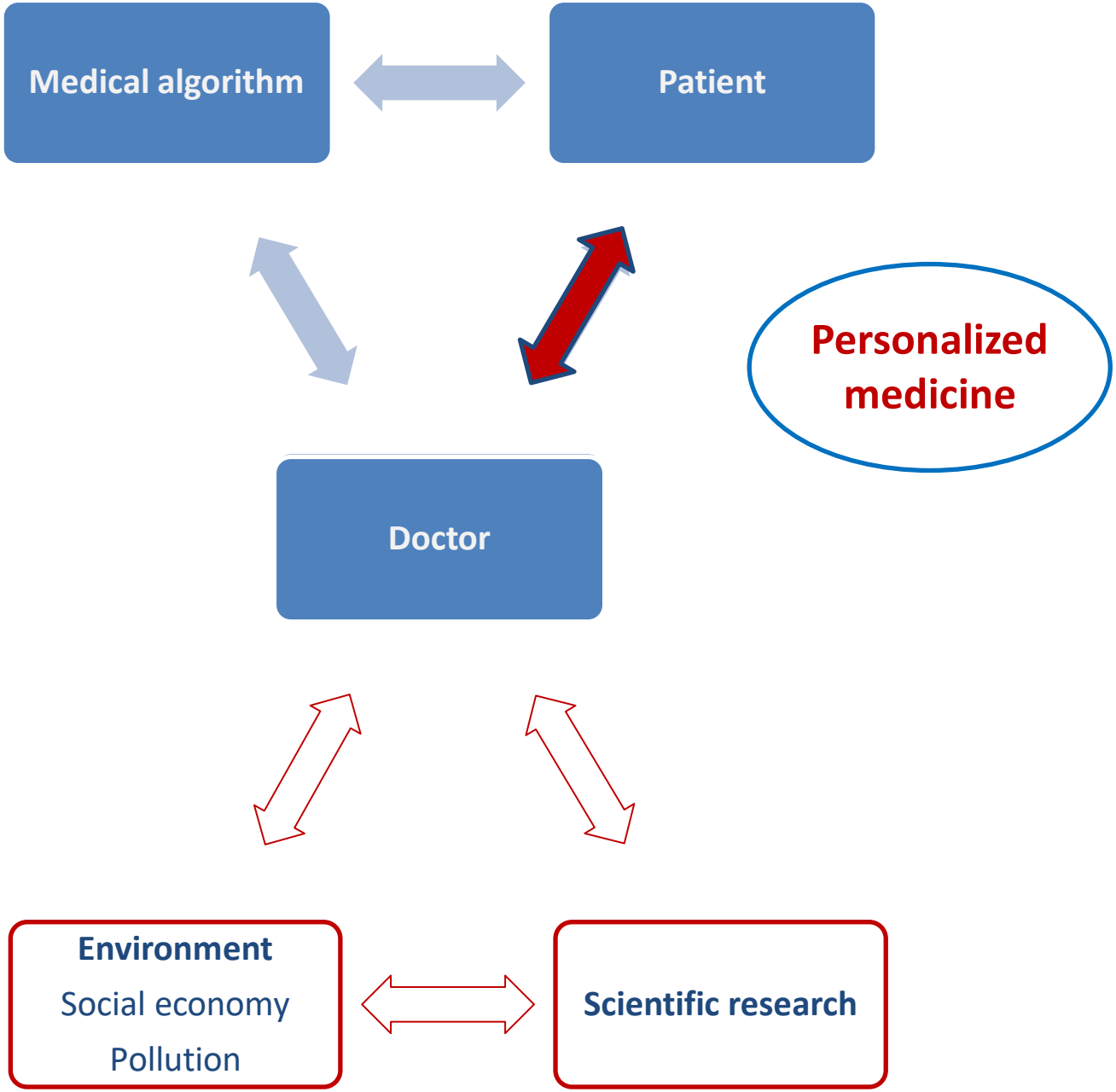
2020

21 Οκτωβρίου 2020
Θέμα: ¨Αλλεργική ρινίτιδα¨
Ώρα 13.30 – 14.45 μμ



Άρης Πάγκαλος

ARIA guideline: treatment of allergic rhinitis


Medical algorithm
Patient
Personalized medicine
Doctor
Environment
Social economy
Pollution
Scientific research

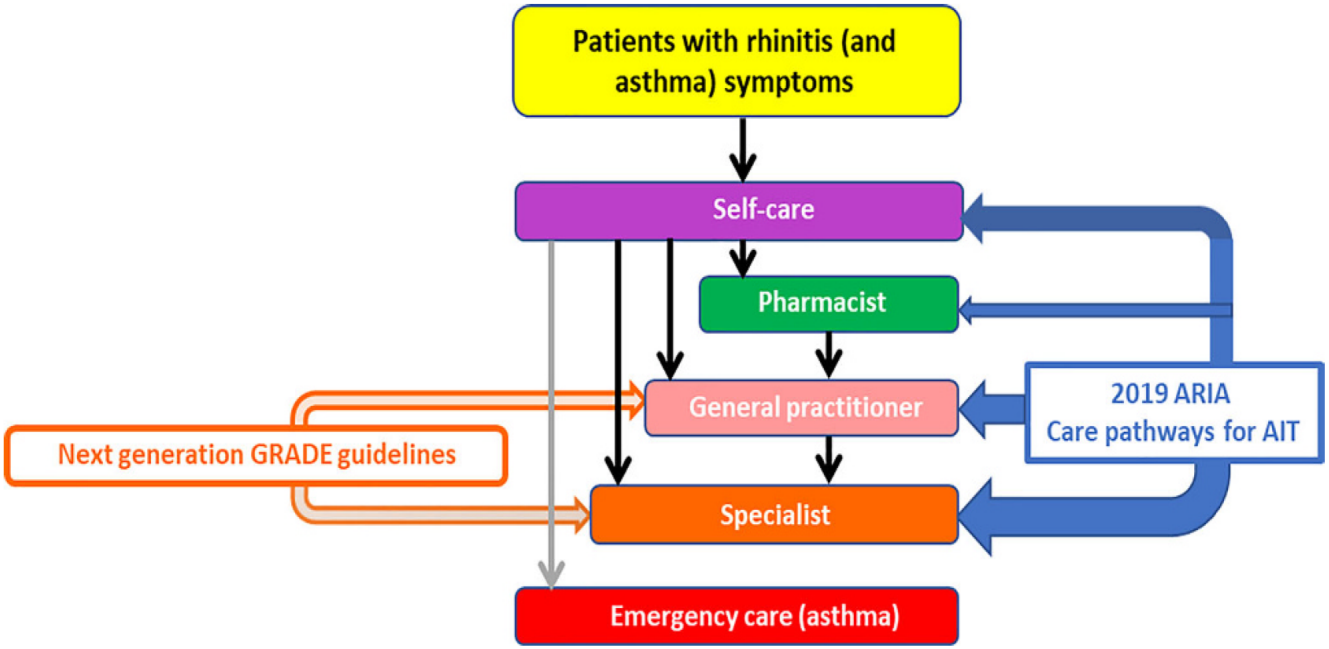


Fig. 4 The next-generation ARIA care pathways considered in this publication

- The number of patients affected by allergies is increasing worldwide
- Significant **costs** for health care and social systems
- **I**ntegrated **C**are P**a**thways are needed
- Internationally applicable guidelines for allergic respiratory diseases (ARIA)

Pharmacotherapy for AR patients is considered to control the disease

It depends on

(i) **patient empowerment** and **preferences**,

(ii) prominent symptoms, **symptom severity** and **multimorbidity**,

(iii) efficacy and safety of the treatment,

(iv) speed of onset of action of treatment,

(v) **current treatment**,

(vi) **historic response** to treatment,

(vii) **impact on sleep** and **work productivity**,

(viii) **self-management strategies**,

(ix) **resource use**

- *Bousquet J, et al. Allergic Rhinitis and its Impact on Asthma (ARIA) Phase 4 (2018): **change management** in allergic rhinitis and asthma multimorbidity using mobile technology. JAllergyClin Immunol. 2018;143(3):864–79.*

- *Bousquet J, et al. **MASK** (Mobile Airways Sentinel Network) 2017: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma multimorbidity using real-world-evidence. Clin Transl Allergy. 2018;8:45.*

- *Bousquet J, et al. **POLLAR**: impact of air POLLution on Asthma and Rhinitis; a European Institute of Innovation and Technology Health (EIT health) project. Clin TranslAllergy. 2018;8:36.*

Fig. 1 Organizations supporting the ARIA meeting in Paris

Treatment of allergic rhinitis (AR) with comorbid asthma

a digitally assisted

Integrative

Individualized

Environmental exposure

*A comprehensive **I**ntegrated **C**are **P**athways guideline can reflect*

real-life care better than traditional guideline models

ARIA 2019 - Σχέδια φροντίδας για την αλλεργική ρινίτιδα: Ελλάδα

Ν.Γ. Παπαδόπουλος,[1] Κ. Πίτσιος,[2]
Μ.Β. Δήμου,[1] Ξ. Αγγελίδης,[3] Μ. Βαλλιανάτου,[1]
Θ. Βοντετσιάνος,[4] Δ. Βούρδας,[5]
Π. Γιάλλουρος,[2] Μ. Γκάγκα,[6] Χρ. Γρηγορέας,[7]
Β. Δανιηλίδης,[8] Ν. Δουλαδίρης,[1]
Μ. Δουλαπτσή,[9] Μ. Κατωτομιχελάκης,[10]
Τ. Καψάλη,[7] Ε. Κομπότη,[11] Μ. Κυριακάκου,[1]
Σ. Λουκίδης,[12] Μ. Μακρής,[3] Ε. Μανουσάκης,[1]
Π. Μαραγκουδάκης,[13] Ν. Μήκος,[11]
Δ. Μήτσιας,[1] Π. Μπακάκος,[14]
Σ. Μποτσκαρίοβα,[1] Π. Ξεπαπαδάκη,[1]
Α. Πάγκαλος,[15] Β. Παπανικολάου,[16]
Ι. Παρασκευόπουλος,[17] Κ. Πίσκου,[18]
Ε. Προκοπάκης,[19] Ν. Ροβίνα,[20] Κ. Σάμιτας,[21]
Ν. Σιαφάκας,[22] Σ. Σταματάκη,[23]
Ε. Στεφανάκη,[24] Α. Συρίγου,[25] Ι. Τσιλιγιάννη,[26]
Λ. Χατζή,[27] Φ. Ψαρρός,[28] C. Bachert,[29]
A. Bedbrook,[30] W. Czarlewski,[31]
P.W. Hellings,[32] O. Pfaar,[33] H.J. Schünemann,[34]
D. Wallace,[35] J. Bousquet[36–41]

1η συνάντηση της Ελληνικής Ομάδας ARIA Ιουνιος 2017

Τα **ICPs**

- είναι δομημένα, διεπιστημονικά σχέδια φροντίδας που εστιάζουν στα βασικά βήματα φροντίδας του ασθενή
- σκοπός η δημιουργία τοπικών πρωτοκόλλων καθώς και την εφαρμογή τους στην κλινική πράξη

- Τα AIRWAYS ICPs (Integrated care pathways for airway diseases) ήταν το πρώτο βήμα προς τη δημιουργία ICPs για τη συννοσηρότητα ρινίτιδας και άσθματος

Κατευθυντήριες οδηγίες ARIA-GRADE επόμενης γενιάς

- Μεθοδολογία GRADE (Grading of Recommendations Assessment, Development and Evaluation)
- (real-world evidence - RWE)
- Συνδυασμός των δύο

Βασίστηκαν

- σε ήδη υπάρχουσες οδηγίες για την AR κατά την GRADE
- Σε πραγματικά κλινικά δεδομένα που συλλέχθηκαν μέσω κινητών συσκευών
- σε αποτελέσματα μελετών με χρήση θαλάμων ελεγχόμενης έκθεσης

Δεδομένα που ελήφθησαν υπόψη για τη δημιουργία των ARIA ICPs

Αλγόριθμος MASK για τη φαρμακευτική αντιμετώπιση της AP

- (visual analogue scale, **VAS**)
- **Προτείνει κλιμάκωση ή αποκλιμάκωση** της θεραπείας AP

AR is often associated with atopic dermatitis, food allergy, and asthma; this allergic disease progression known as

the atopic march

Zheng T. The atopic march: progression from atopic dermatitis to allergic rhinitis and asthma. J Clin Cell Immunol. 2014. https://doi.org/10.4172/2155-9899.1000202.

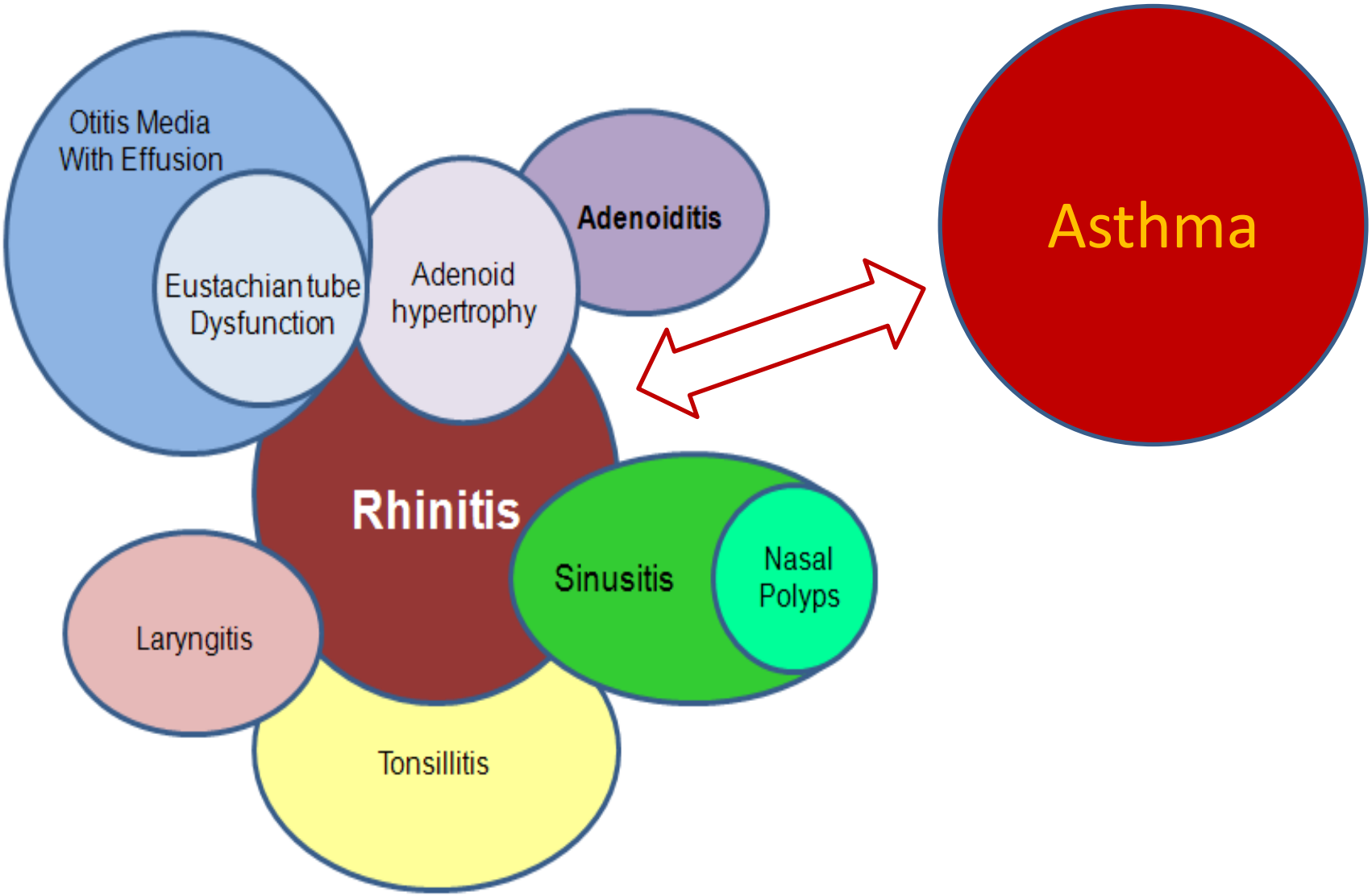
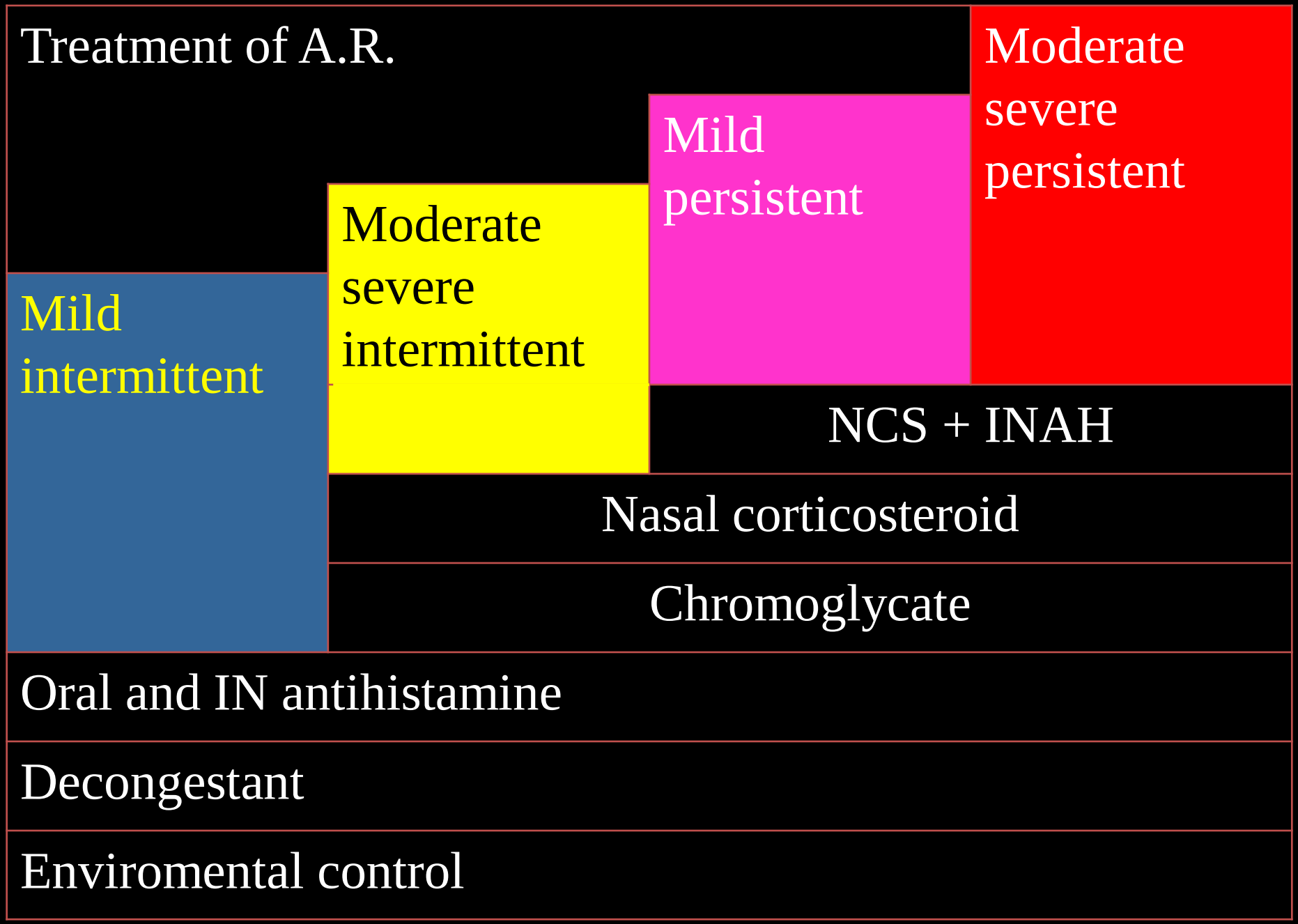
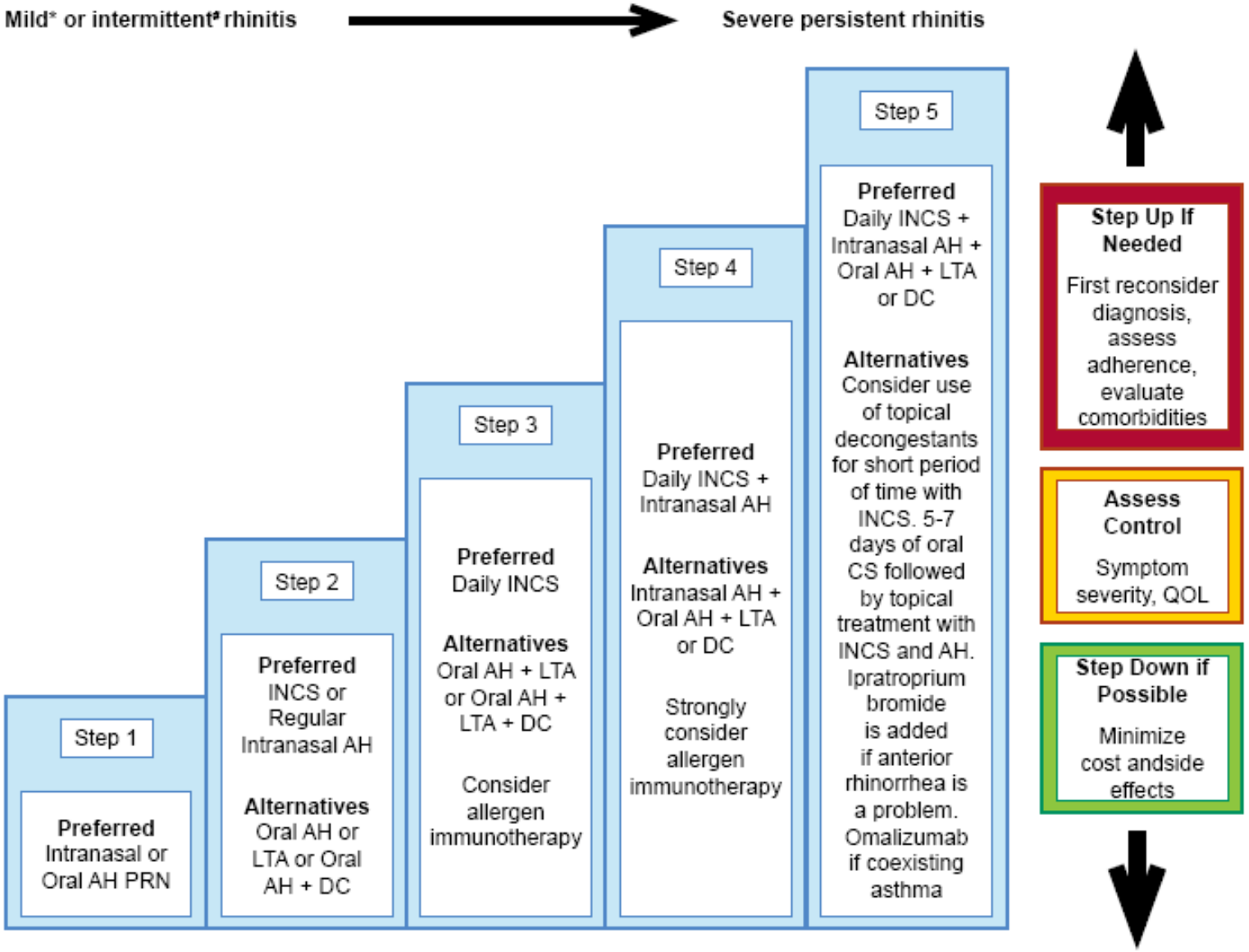

Otitis Media
With Effusion
Eustachian tube
Dysfunction
Adenoid
hypertrophy
Adenoiditis
Asthma
Rhinitis
Sinusitis
Nasal
Polyps
Laryngitis
Tonsillitis

TABLE 1

Comorbidities of Allergic Rhinitis

Primary	Secondary
Allergic asthma	Sleep deprivation
Atopic dermatitis	Social dysfunction
Allergic conjunctivitis	Decreased productivity
Acute and chronic sinusitis	Absenteeism
Nasal polyps (rare)	Increased fatigability
Increased upper respiratory tract viral infections	Learning impairment
Otitis media	Attention deficit
Food allergy	Snoring
Sleep apnea	Depression
Dental malocclusion	Irritability
Occupational rhinitis	


Treatment of A.R.
Moderate severe persistent
Mild persistent
Moderate severe intermittent
Mild intermittent
NCS + INAH
Nasal corticosteroid
Chromoglycate
Oral and IN antihistamine
Decongestant
Enviromental control



Meltzer Allergy Asthma Proceedings 2013)

Κλινικά δεδομένα μέσω της χρήσης κινητής τεχνολογίας. - MASK

Πίνακας 3. Αποτελέσματα από πραγματικά κλινικά δεδομένα για την αντιμετώπιση της ΑΡ.

- Οι ασθενείς δεν ακολουθούν τις κατευθυντήριες οδηγίες και συχνά λαμβάνουν φάρμακα χωρίς συνταγή
- Υπήρξε χαμηλή συμμόρφωση με τη θεραπεία
- Οι ασθενείς λαμβάνουν τη θεραπευτική αγωγή κατά βούληση, ανάλογα με το πόσο υπό έλεγχο είναι η ασθένεια τους, και αυξάνουν την αγωγή όταν δεν νιώθουν καλά. Ωστόσο, η ταυτόχρονη αγωγή δεν προσφέρει καλύτερο έλεγχο
- Το MP-AzeFlu είναι αποτελεσματικότερο των ενδορρινικών κορτικοστεροειδών, τα οποία είναι αποτελεσματικότερα των από του στόματος Η1-αντιισταμινικών

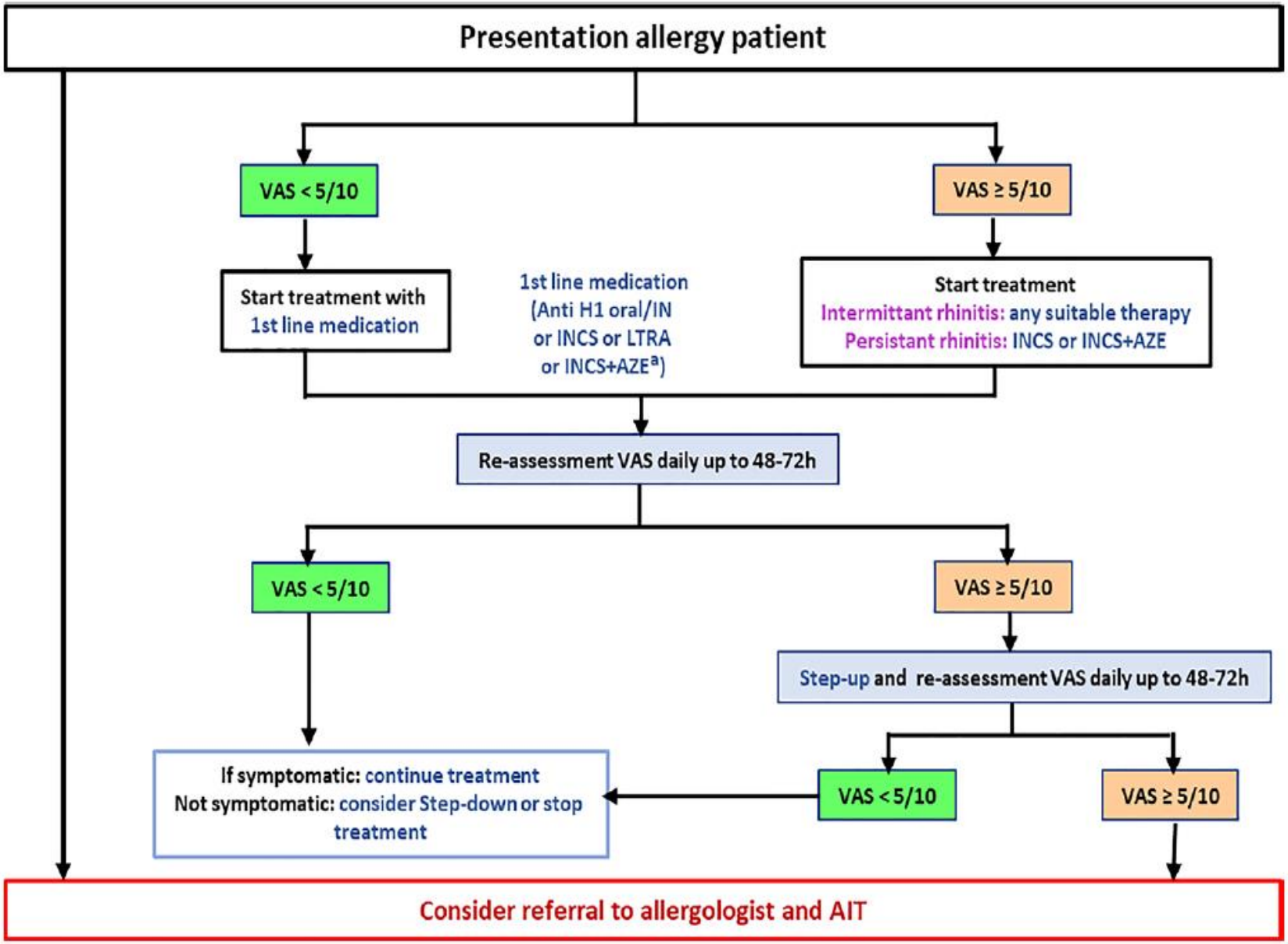
Διαχωρισμός ανάμεσα στην προοπτική του ασθενούς και του ιατρού

Bousquet J, Arnavielhe S, Bedbrook A et al. MASK 2017: ARIA digitally-enabled, integrated, person-centred care for rhinitis and asthma multimorbidity using real-world-evidence. Clin Transl Allergy 2018, 8:45

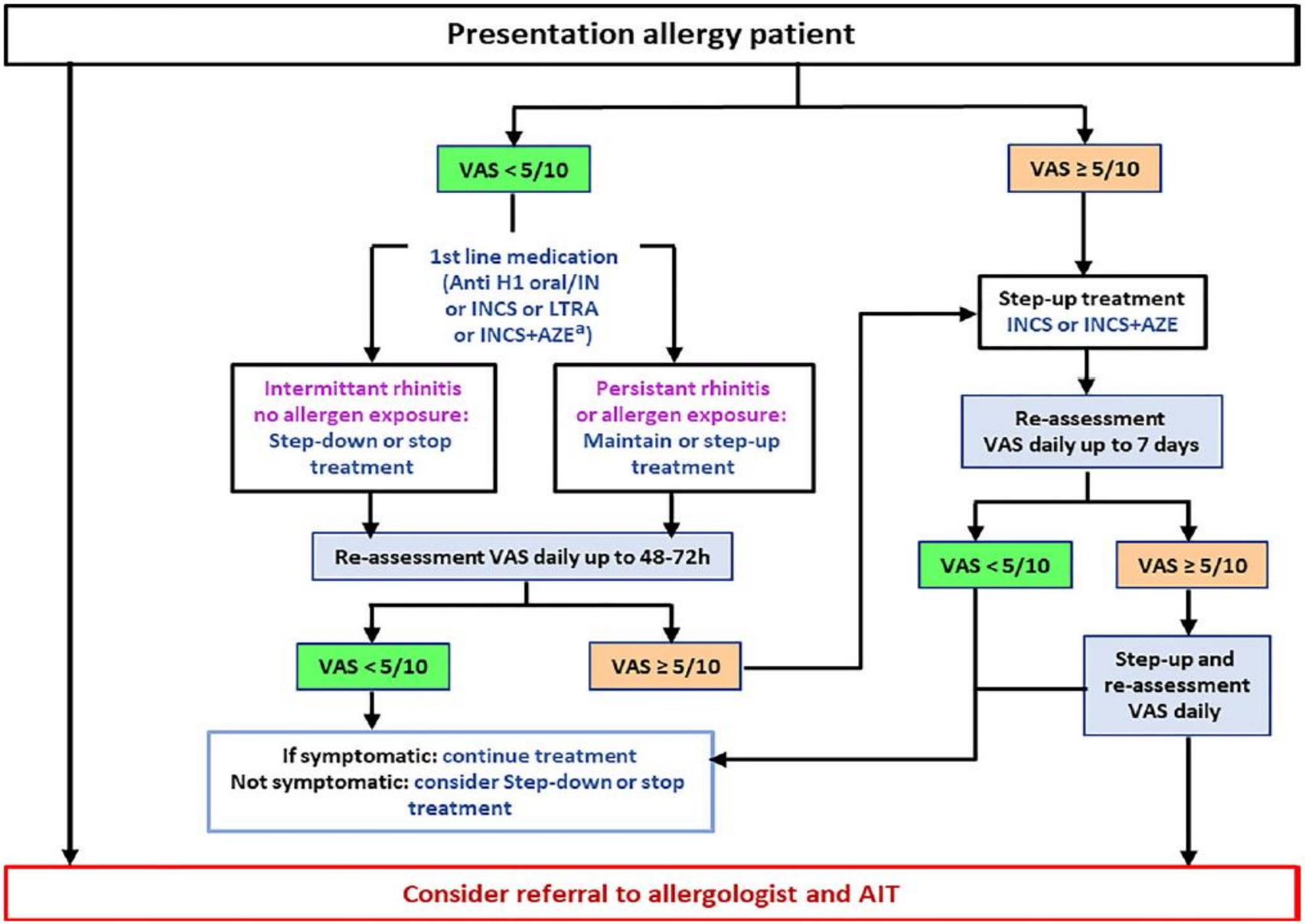
Price D, Scadding G, Ryan D et al. The hidden burden of adult allergic rhinitis: UK healthcare resource utilisation survey. Clin Transl Allergy 2015, 5:39

όταν οι ίδιοι οι ιατροί είναι ασθενείς, και εκείνοι συμπεριφέρονται όπως οι ασθενείς

Bousquet J, Murray R, Price D et al. The allergic allergist behaves like a patient. Ann Allergy Asthma Immunol 2018



Step-up algorithm in **untreated patients** (adolescents over 12 years and adults) based on visual analogue scales. The proposed algorithm considers the patient's preferences: If ocular symptoms persist after initiation of treatment, local conjunctival therapy should be added.



Step-up algorithm in treated patients (adolescents over 12 years and adults) based on visual analogue scales. The proposed algorithm considers the patient's preferences: If ocular symptoms persist after initiation of treatment, local conjunctival therapy should be added.

Κατευθυντήριες οδηγίες ARIA επόμενης γενιάς	Ένδειξη	Αποτελεσματικότητα	Ταχύτητα δράσης	Ασφάλεια
INAH	Ήπια μέτρια AP	**	**άμεσα**	Ασφαλή
Oral AH	Ήπια μέτρια AP Προτίμηση του ασθενούς	**	>2h	Προσοχή στα 1ης γενιάς AH
INCS	Σοβαρή AP	***	>2h (εξαίρεση η κικλεσονίδη)	Ασφαλή
Oral AH + INCS		***	>2h	Προσοχή στα 1ης γενιάς AH
MP-AzeFlu	Σοβαρή ανθεκτική AP Όταν ο ασθενής επιθυμεί ταχεία ανακούφιση	****	**άμεσα**	Ασφαλή
LTA		*	>2h	Ασφαλή
Oral AH + LTA		***	>2h	

Ρινίτιδα και ρινοεπιπεφυκίτιδα σε εφήβους και ενήλικες

Δεν ενδείκνυται

- Η1-αντιισταμινικά πρώτης γενιάς
- Ενδομυϊκά κορτικοστεροειδή μακράς διαρκείας

Church MK, Maurer M, Simons FE, Bindslev-Jensen C, van Cauwenberge P, Bousquet J et al. Risk of first-generation H(1)-antihistamines: a GA(2)LEN position paper. Allergy 2010, 65:459–466

Σχέδια φροντίδας ARIA 2019 για ανοσοθεραπεία έναντι αλλεργιογόνων (AIT)

Bousquet J, Pfaar O, Togias A et al. 2019 ARIA Care pathways forallergenimmunotherapy. Allergy 2019, doi:10.1111/all.13805

Η άποψη του ασθενούς

- shared decision making – SDM
- Τα αποτελέσματα σχετικά με τα ποσοστά προσήλωσης στην AIT είναι αντιφατικά, αλλά μπορεί να είναι χαμηλά

Pitsios C, Dietis N. Ways to increase adherence to allergen immunotherapy. Curr Med Res Opin 2018:1–9

Bender BG, Lockey RF. Solving the Problem of Nonadherence to Immunotherapy. Immunol Allergy Clin North Am 2016, 36:205–213

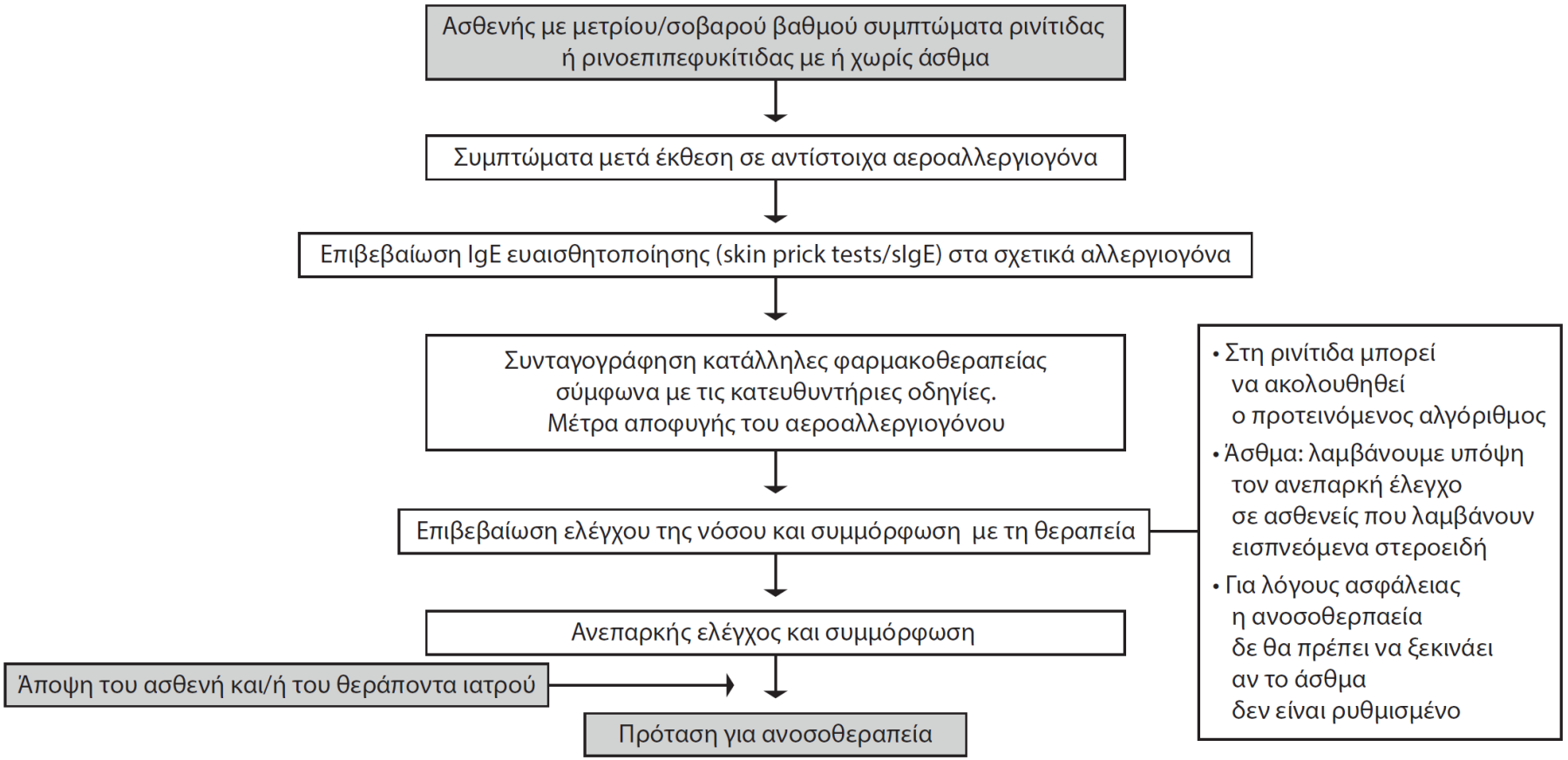
Η άποψη του φαρμακοποιού

- η ΑΡ είναι μία από τις πιο κοινές ασθένειες που διαχειρίζονται οι φαρμακοποιοί.

Bosnic-Anticevich S, Kritikos V, Carter V et al. Lack of asthma and rhinitis control in general practitioner-managed patients prescribed fixed-dose combination therapy in Australia. J Asthma 2018, 55:684–694

Bosnic-Anticevich S, Costa E, Menditto E et al. ARIA pharmacy 2018, Allergic rhinitis care pathways for community pharmacy. Allergy 2018

Διαστρωμάτωση αλλεργικών ασθενών για την AIT.



Σχήμα 4. Διάγραμμα ροής ιατρικής ακριβείας για την AIT (προσαρμοσμένη εκδοχή.[58,88]

Canonica GW, Bachert C, Hellings P et al.
Allergen Immunotherapy (AIT): a prototype of Precision Medicine. World Allergy Organ J 2015, 8:31

Fein *et al.*
Allergy Asthma Clin Immunol (2019) 15:61
https://doi.org/10.1186/s13223-019-0375-9

Allergy, Asthma & Clinical Immunology

REVIEW Open Access

CSACI position statement: Newer generation H_1-antihistamines are safer than first-generation H_1-antihistamines and should be the first-line antihistamines for the treatment of allergic rhinitis and urticaria

Michael N. Fein[1], David A. Fischer[2,3*], Andrew W. O'Keefe[4] and Gord L. Sussman[5]

Table 1 H1 Antihistamines: pharmacokinetics and pharmacodynamics in healthy adults. Reproduced with permission [5]

Orally administered H1-antihistamines	Time to maximum plasma concentration (h) after a single dose	Terminal elimination half-life (h)	Clinically relevant drug–drug interactions[a]	Onset of action (h)[b]	Duration of action (h)[b]
First (old) generation					
Chlorpheniramine[c]	2.8 ± 0.8	27.9 ± 8.7	Possible	3	24
Diphenhydramine[c]	1.7 ± 1.0	9.2 ± 2.5	Possible	2	12
Doxepin[c]	2	13	Possible	NA	NA
Hydroxyzine[c]	2.1 ± 0.4	20 ± 4.0	Possible	2	24
Second (new) generation					
Bilastine	1.2	14.5	Unlikely	2	24
Cetrizine	1.0 ± 0.5	6.5–10	Unlikely	0.7	≥ 24
Desloratidine	1.0–3.0	27	Unlikely	2–2.6	≥ 24
Fexofenadine[a]	1.0–3.0	11.0–15.0	Unlikely	1.0–3.0	24
Levocetirizine	0.8 ± 0.5	7 ± 1.5	Unlikely	0.7	> 24
Loratidine (metabolite: descarboethoxyloratidine)	1.2 ± 0.3 (1.5 ± 0.7)	7.8 ± 4.2 (24 ± 9.8)	Unlikely	2	24
Rupatadine	0.75–1.0	6 (4.3–14.3)	Unlikely	2	24

[a] Clinically relevant drug–drug interactions are unlikely with most of the 2nd generation H1-antihistamines. Clinically relevant drug-food interactions have been well studied for fexofenadine. Naringin, a flavonoid found in grapefruit juice, and hesperidin, a flavonoid in orange juice, reduce the oral bioavailability of fexofenadine through the inhibition of OATP 1A2. This interaction can be avoided by waiting for 4 h between juice ingestion and fexofenadine dosing

[b] Onset/duration of action is based on wheal and flare studies

[c] Six or seven decades ago, when many of the first-generation H_1-antihistamines were introduced, pharmacokinetic and pharmacodynamic studies were not required by regulatory agencies. They have subsequently been performed for some of these drugs; however, empiric dosage regimens persist. For example, the manufacturers' recommended diphenhydramine dose for allergic rhinitis is 25 to 50 mg every 4 to 6 h, and the diphenhydramine dose for insomnia is 25 to 50 mg at bedtime. Despite the long terminal elimination half-life values identified for some of the medications (e.g., > 24 h for chlorpheniramine), based on tradition, extended release formulations remain in use

Key points

- **First-generation AHs** are associated with significant and, at times, serious adverse effects including fatal outcomes, and they should not be used as first-line treatment in allergic disease.
- Despite package warnings, the level of CNS impairment caused by first generation AHs is not fully appreciated both by health care professionals and the public, which has resulted in preventable fatal injuries.
- **Newer generation AHs** are proven to be much safer than first-generation AHs, have a faster onset of action, and have superior potency, selectivity and efficacy.
- Despite the widespread availability of newer generation AHs, older AHs remain over-utilized.
- To encourage the cessation of the routine use of older AHs including diphenhydramine (Benadryl©), this class of medications should have eventual consideration for availability on a behind the counter basis only.
- Further efforts are needed to disseminate this information to healthcare providers and patients to help change practice and improve patient health and safety.
- The CSACI, therefore, recommends in agreement with other international bodies, that only less-sedating newer generation AHs should be first-line and preferred over older AHs and that **the use of firstgeneration AHs should be significantly curtailed**

Drugs
https://doi.org/10.1007/s40265-020-01406-9

SYSTEMATIC REVIEW

Efficacy of Montelukast in Allergic Rhinitis Treatment: A Systematic Review and Meta-Analysis

Madhusudhan Krishnamoorthy[1] · Norhayati Mohd Noor[2] · Norhafiza Mat Lazim[1] · Baharudin Abdullah[1]

© Springer Nature Switzerland AG 2020

15 studies of 10387 participants

primary outcomes

- daytime nasal symptom score (DNS)
- night-time nasal symptom score (NNS)

secondary outcomes

- composite nasal symptom score (CSS),
- daytime eyes symptom score (DES),
- rhinoconjunctivitis quality-of-life questionnaires (RQLQ)

The meta-analysis was conducted using Review Manager software based on the random-effects model

Results

- **Montelukast** was more effective than placebo in improving DNS, NNS, CSS, DES, RQLQ
- **Oral antihistamine** was superior to montelukast in improving DNS, CSS, DES, RQLQ
- **Montelukast** was superior to oral antihistamine in improving NNS
- **Intranasal fluticasone** spray was superior to montelukast in improving DNS, NNS
- **Combined montelukast and oral antihistamine** was superior to oral antihistamine in improving DNS, NNS, CSS, DES, RQLQ
- **Combined montelukast and OAH** was superior to montelukast in improving DNS, NNS, CSS, DES, RQLQ

International Archives of Allergy and Immunology

Experimental Allergy – Research Article

Int Arch Allergy Immunol
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Effect of the Use of Intranasal Spray of Essential Oils in Patients with Perennial Allergic Rhinitis: A Prospective Study

Davide Caimmi[a, b] Catherine Neukirch[c] Renaud Louis[d] Olivier Malard[e]
Gabriel Thabut[c] Pascal Demoly[a, b]

[a]Department of Pulmonology, Division of Allergy, Hôpital Arnaud de Villeneuve, University Hospital of Montpellier, University of Montpellier, Montpellier, France; [b]UMR-S 1136 INSERM-Sorbonne Université, Equipe EPAR – IPLESP, Paris, France; [c]Departments of Pneumology A and B and INSERM U1152, Bichat-Claude Bernard University Hospital, Paris, France; [d]Department of Pulmonary Medicine, CHU Sart-Tilman, IGIGA Research Group, University of Liege, Liège, Belgium; [e]Service d'ORL et de Chirurgie Cervico-Faciale, University Hospital of Nantes, Hôtel Dieu, Nantes, France

a combination of hypertonic seawater

+

organic rosemary floral water

+

Essential Oils

ravintsara

geranium

eucalyptus radiata

niaouli

Table 1. Changes in Allergic Rhinitis Control Test and NIPF between baseline (D0) and after 30 days of treatment (D30)

Parameter	*N*	D0	D30	*p* value
Controlled rhinitis (score >19), *n* (%)	43	6 (14.0%)	31 (69.8%)	<0.001[a]
ARCT, mean (SD)	43	16.4 (3.2)	20.5 (3.7)	<0.001[b]
NIPF (L/min), mean (SD)	42	86.5 (37.3)	105.1 (32.7)	<0.001[b]

ARCT, Allergic Rhinitis Control Test; NIPF, nasal inspiratory peak flow. [a] McNemar test. [b] Student's *t* test for paired data.

patients with controlled rhinitis

after 30 days was **69.8%** versus

14%(n=6) before treatment

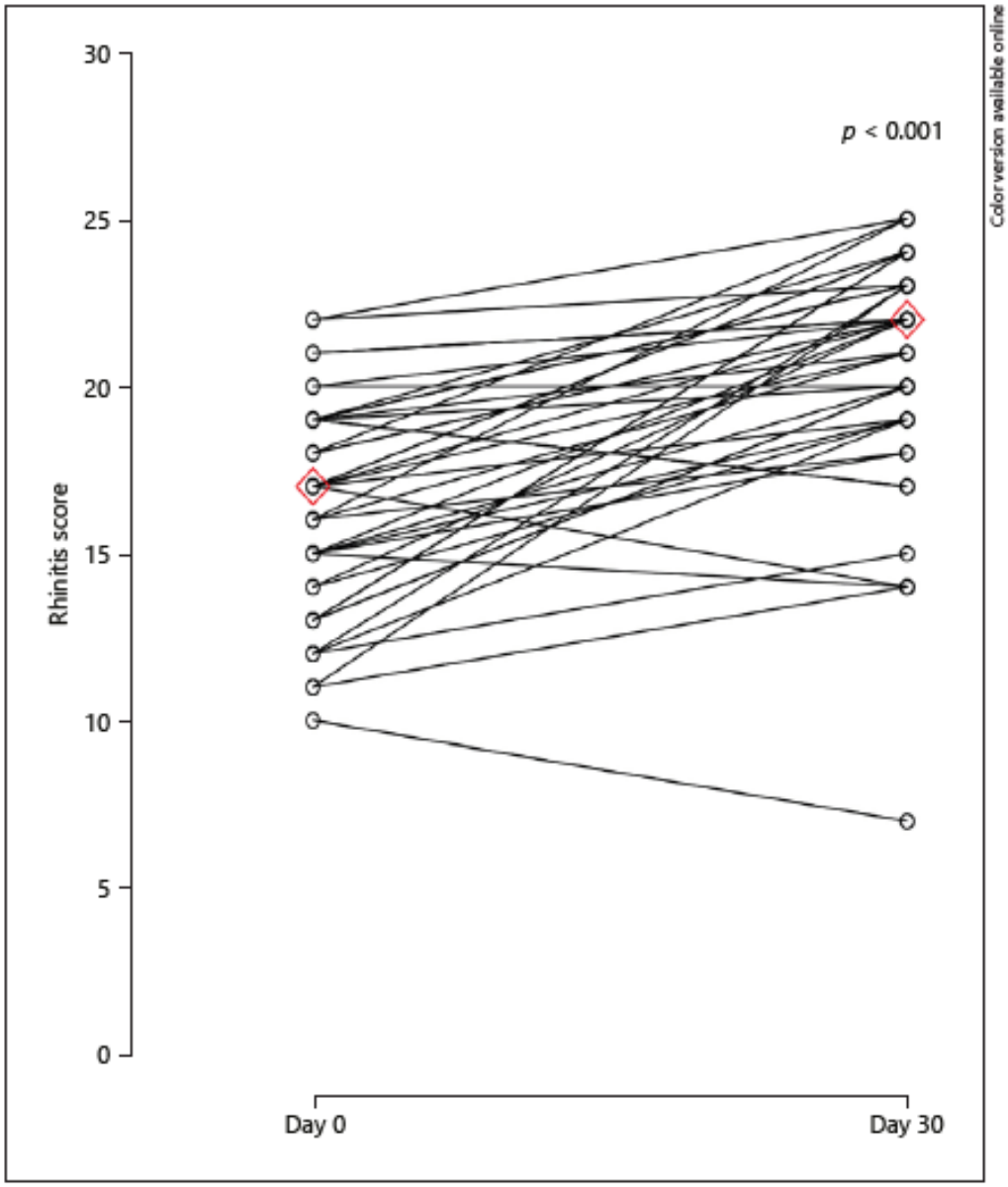


Fig. 1. Individual and median (red triangles) values of Allergic Rhinitis Control Test (ARCT) before (D0) and after 1 month of treatment (D30) with Puressentiel® Respiratory-Decongestant Nasal Spray (PRDNS).

Nasal Inspiratory

Peak Flow (NIPF)

D0: 86.5 L/min

D30: 105.1 L/min

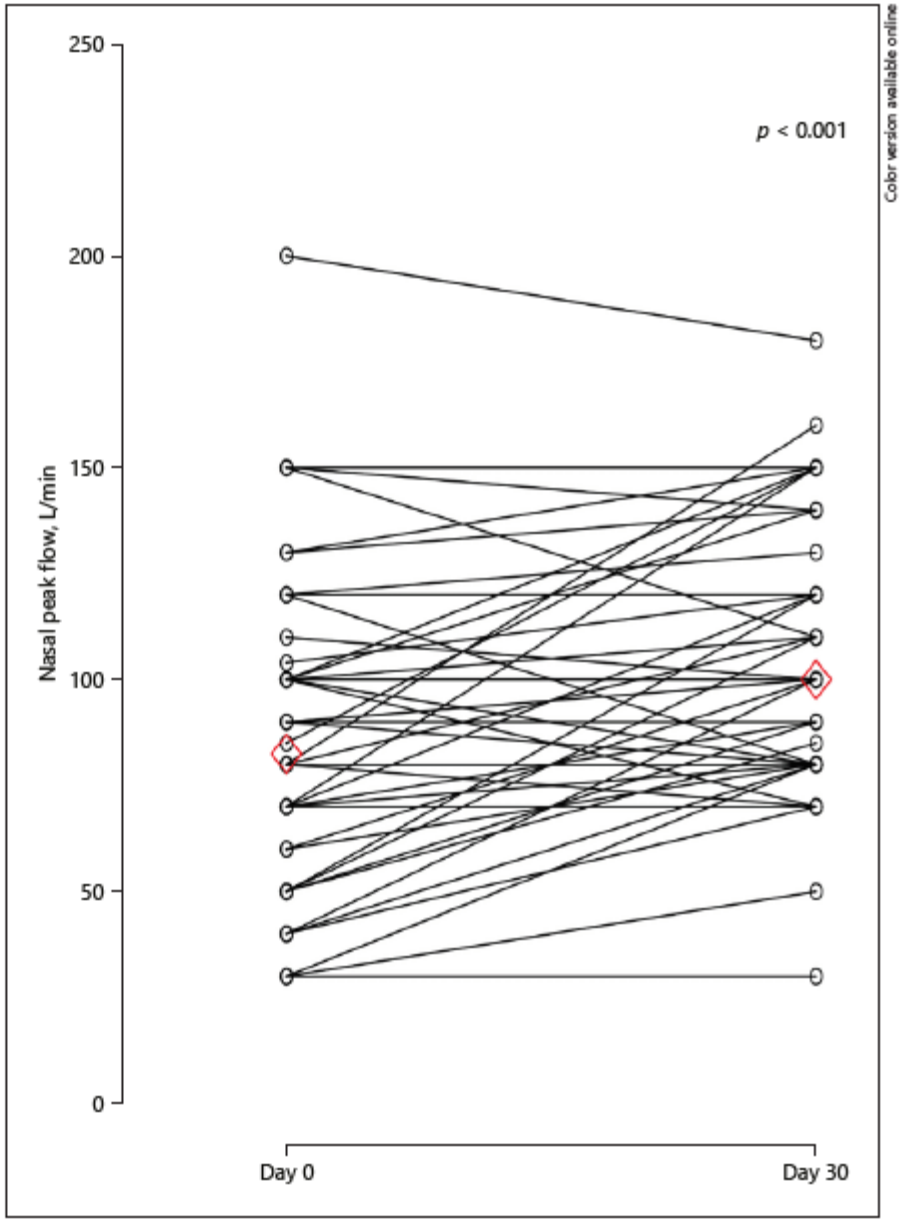


Fig. 2. Individual and median (red triangles) values of nasal inspiratory peak flow (NIPF) before (D0) and after 1 month of treatment (D30) with Puressentiel® Respiratory-Decongestant Nasal Spray (PRDNS).

Biologics that neutralize

- IgE (omalizumab)
- IL-5 (mepolizumab, reslizumab)
- IL-5 receptor (benralizumab)
- Both IL-4 and IL-13 (dupilumab)

TABLE 1 Type of available biologics and their indications

Name	Mechanism of action	Age (years)	Indications
Omalizumab	Anti-IgE	≥ 6	1. Moderate-to-severe persistent allergic asthma 2. Chronic idiopathic urticaria
Reslizumab	Anti-IL-5	≥ 18	Severe asthma with an eosinophilic phenotype
Mepolizumab	Anti-IL-5	≥ 12	1. Severe asthma and with an eosinophilic phenotype 2. Eosinophilic granulomatosis with polyangiitis (Churg-Strauss Syndrome)
Dupilumab	Anti-IL-4	≥ 12	1. Moderate-to-severe asthma with eosinophilic phenotype or corticosteroid dependent asthma 2. Moderate-to-severe atopic dermatitis 3. Chronic rhinosinusitis 4. Eosinophilic esophagitis
Benralizumab	Anti-IL-5	≥ 12	1. Severe asthma with an eosinophilic phenotype 2. Hypereosinophilic syndrome 3. Eosinophilic granulomatosis with polyangitis

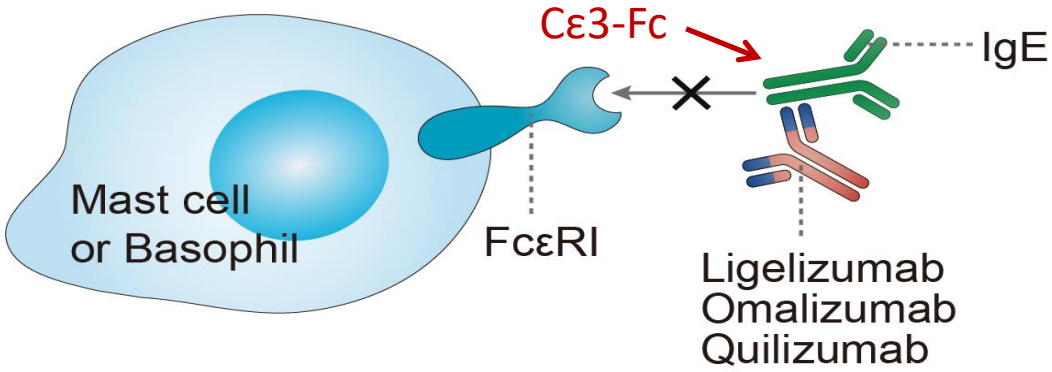
TABLE 1 Monoclonal antibodies assessed for their effect on airway mucosal biomarkers

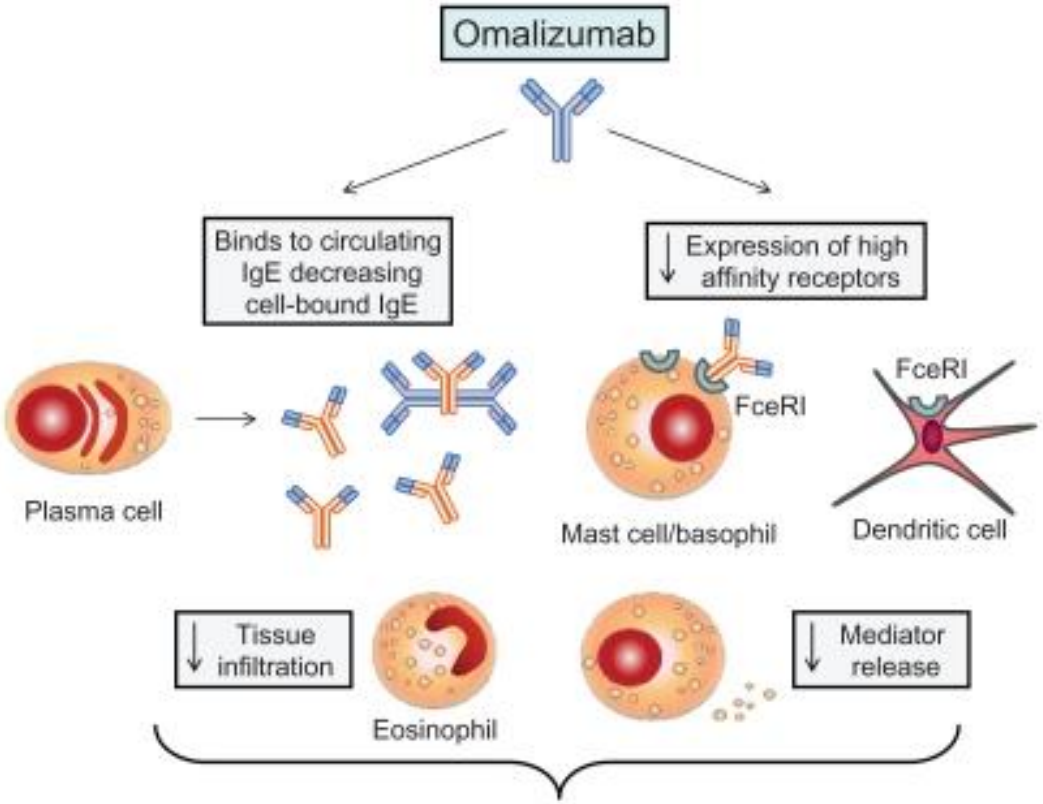
mAb name	mAb target	Disease	Studies
Omalizumab	Anti-IgE	Asthma AR CRS	21,23,28,29,31
Mepolizumab	Anti-IL-5	Asthma CRS	22,25,27
Benralizumab	Anti-IL-5Rα	Asthma	26
Tralokinumab	Anti-IL-13	Asthma	30
Dupilumab	Anti-IL-4Rα	Asthma CRS	24

Abbreviations: AR, allergic rhinitis; CRS, chronic rhinosinusitis; IgE, immunoglobulin E; IL, interleukin; Rα, receptor-α.

Omalizumab (United States in 2003)

95% humanized monoclonal antibody directed against the Fc portion of IgE





Allergic inflammation
AR and Asthma symptoms and exacerbation

Omalizumab

Food and Drug Administration (FDA)-approved for the treatment of moderate-to-severe persistent asthma and chronic idiopathic urticaria

According to the Global Initiative for Asthma 2020 update, anti-IgE therapy should be considered as add-on therapy for adolescents, adults, and children, aged 6 to 11 years, with asthma poorly controlled on moderate dose ICS and long-acting beta-agonist (ie, step 5 treatment)

Global initiative for asthma global strategy for maagement and prevention 2020 update. Available at: https://ginasthma.org/gina-reports. Accessed May 29, 2020.

Omalizumab has been extensively studied in the treatment of AR as a direct and as an add-on therapy

- Significant and rapid reductions in free serum IgE (96%)
- reduction in the expression Fc 3R1 receptor
  mast cells, basophils, dendritic cells, etc
  - 73% reduction in basophil Fc 3R1 expression / 7 days
  - 90% reduction in basophil responsiveness at 90 days
- resulted in reduced inhaled corticosteroid …..
- decrease the frequency of fall seasonal asthma exacerbations in adolescents and children
- reduced duration and frequency of rhinovirus infections

Omalizumab in patients with seasonal AR (SAR) and perennial AR (PAR)

- reduce IgE levels
- improve daily nasal symptoms
- reduce the use of rescue antihistamines
- Reduce steroid requirement in allergic asthmatics
- Reduce asthma exacerbations
- significant improvements in both asthma and rhinitis quality of life questionnaire scores.

Vignola AM, Humbert M, Bousquet J, Boulet LP, Hedgecock S, Blogg M, et al. Efficacy and tolerability of anti-immunoglobulin E therapy with omalizumab in patients with concomitant allergic asthma and persistent allergic rhinitis: SOLAR. Allergy. 2004;59:709-717.

Ghadersohi S, Tan BK. Contemporary pharmacotherapy for allergic rhinitis and chronic rhinosinusitis. Otolaryngol Clin North Am. 2017;50:1135-1151.

Adelroth E, Rak S, Haahtela T, Aasand G, Rosenhall L, Zetterstrom O, et al. Recombinant humanized mAb-E25, an anti-IgE mAb, in birch pollen-induced seasonal allergic rhinitis. J Allergy Clin Immunol. 2000;106:253-259.

Chervinsky P, Casale T, Townley R, Tripathy I, Hedgecock S, Fowler-Taylor A, et al. Omalizumab, an anti-IgE antibody, in the treatment of adults and adolescents with perennial allergic rhinitis. Ann Allergy Asthma Immunol

Walker S, Monteil M, Phelan K, Lasserson TJ, Walters EH. Anti-IgE for chronic asthma. Cochrane Database Syst Rev. 2003;3:CD003559

Omalizumabe - seasonal and perennial allergic rhinitis

- reducing nasal symptom scores
- improving quality of life

Polk P, Stokes J. Anti-IgE therapy. In: Cox LS, editor. Immunotherapies for allergic disease. 1. hiladelphia: Elsevier Health Sciences; 2019. p. 355–72.

- was not approved by the FDA for the treatment of AR
  The **cost** of treatment may have been a factor in the decision (**180 – 2100 Euro/m**, Gr)

Vashisht P, Casale T. Omalizumab for treatment of allergic rhinitis. Expert Opin Biol Ther 2013;13(6):933–45.

Omalizumab may be effective in

- allergic bronchopulmonary aspergillosis,
- systemic mastocytosis,
- eosinophilic granulomatosis with polyangiitis

Polk P, Stokes J. Anti-IgE therapy. In: Cox LS, editor. Immunotherapies for allergic disease. 1. hiladelphia: Elsevier Health Sciences; 2019. p. 355–72.

Omalizumab may be effective in

- rush and cluster aeroallergen immunotherapy
- oral food immunotherapy

Casale TB, Busse WW, Kline JN, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. J Allergy Clin Immunol 2006;117(1):134–40.

Massanari M, Nelson H, Casale T, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in patients with persistent symptomatic asthma inadequately controlled with inhaled corticosteroids. Ann Allergy Asthma Immunol 2009;102(1 supplement):17.

Nadeau KC, Schneider LC, Hoyte L, et al. Rapid oral desensitization in combination with omalizumab therapy in patients with cow's milk allergy. J Allergy Clin Immunol 2011;127(6):1622–4.

Wood RA, Kim JS, Lindblad R, et al. A randomized, double-blind, placebocontrolled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. J Allergy Clin Immunol 2016;137(4):1103–10.e11.

Omalizumab added to AIT provided an additional 48% improvement compared with AIT alone

Kuehr J, Brauburger J, Zielen S, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. J Allergy Clin Immunol 2002;109(2):274–80.

* Long-term omalizumab efficacy in allergic rhinitis

Carlo Cavaliere a,, Elona Begvarfaj b, Cristoforo Incorvaia c, Bruno Sposato d, Marco Brunori e, Andrea Ciofalo f, Antonio Greco f, Marco de Vincentiis a, Simonetta Masieri f,**

Patients with poorly controlled **severe asthma**

and

persistent allergic rhinitis

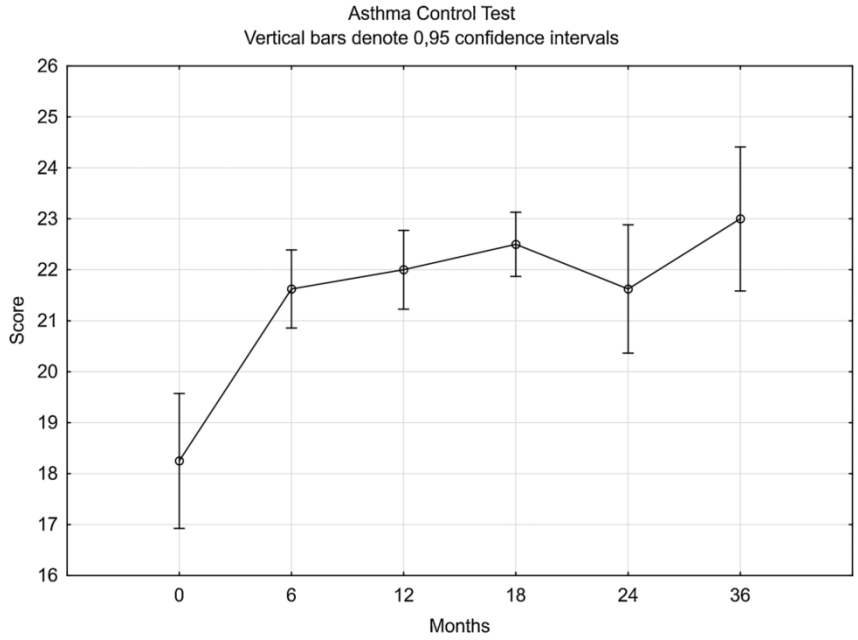


Fig. 1. Variation of Asthma Control Test (ACT) from baseline to 36 months. Statistical significance compared to baseline: $p < 0.001$ at 6, 12, 18, 24, and 36 months.

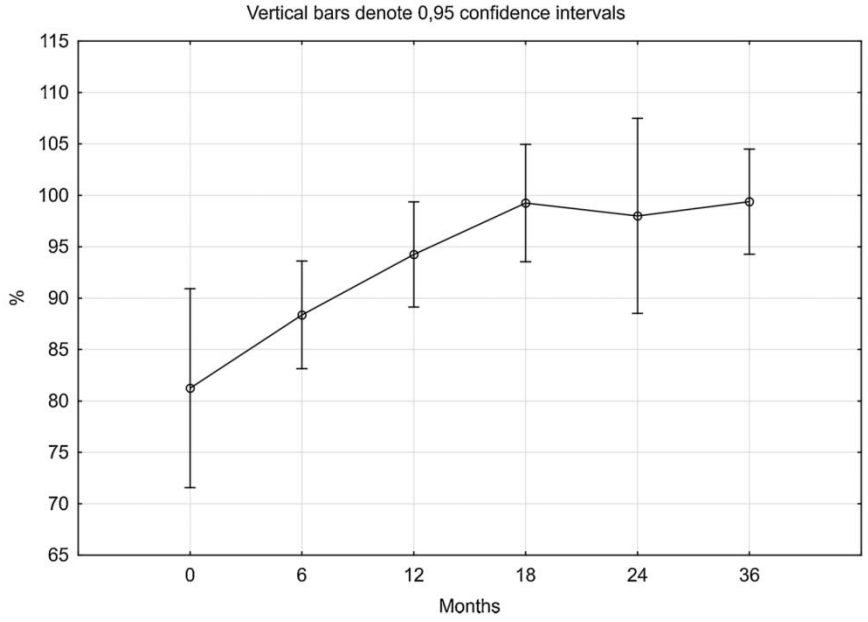


Fig. 4. Variation of FEV1 from baseline to 36 months. Statistical significance compared to baseline: $p = 0.10$ at 6 months; $p < 0.001$ at 12, 18, 24, and 36 months.

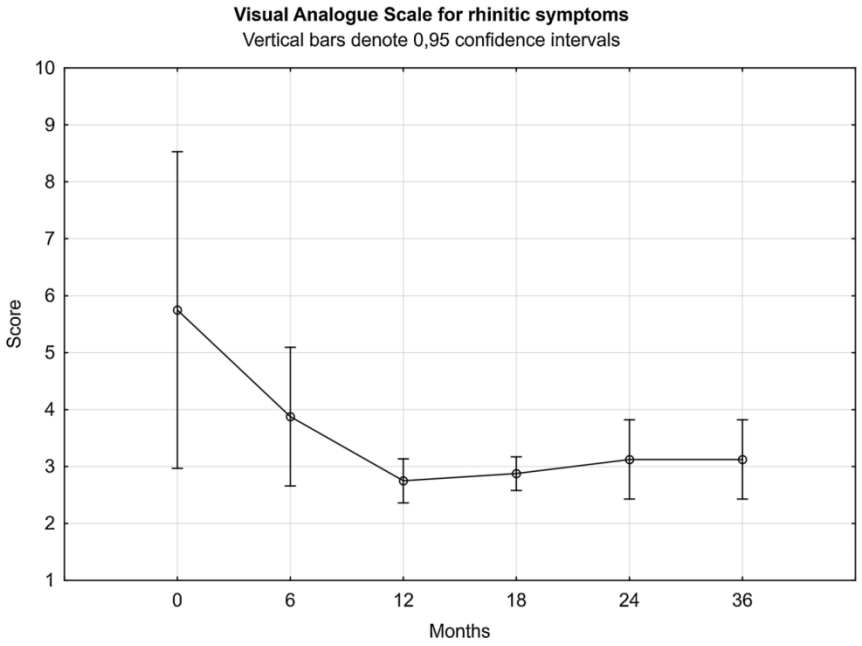


Fig. 2. Variation of Visual Analogue Scale (VAS) for rhinitis symptoms from bas
18, 24, and 36 months.

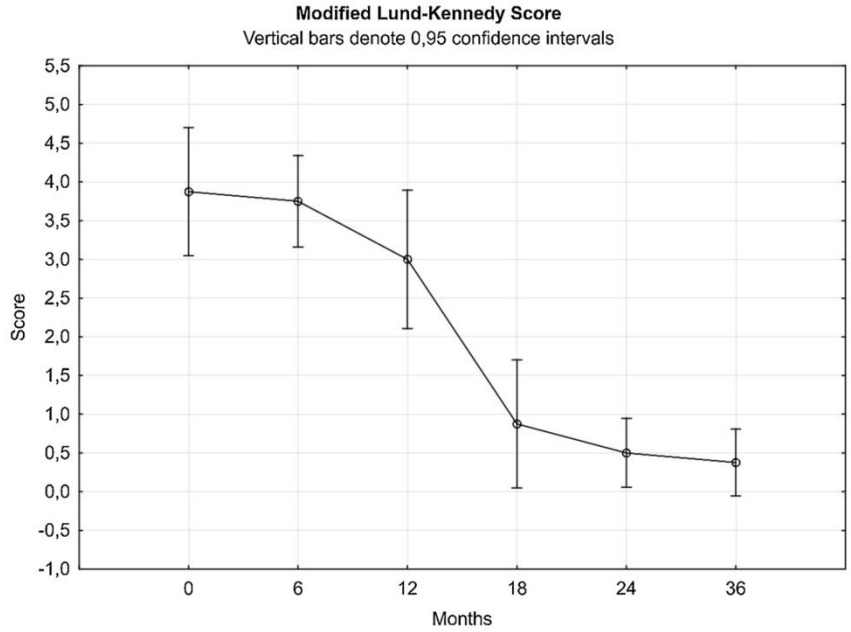


Fig. 3. Variation of the MLK score from baseline to 36 months. Statistical significance compared to baseline: $p = 0.71$ at 6 months; $p < 0.05$ at 12 months; $p < 0.001$ at 18, 24, and 36 months.

* Biologics for the Treatment of Allergic Rhinitis, Chronic Rhinosinusitis, and Nasal Polyposis

*William Eschenbacher, MDa, Matthew Straesser, MDa, Alice Knoeddler, MDa, Rung-chi Li, DOa, Larry Borish, MDa,b,**

CRSwNPs biomarkers

- elevations in blood absolute eosinophil counts
- airway eosinophils (sputum samples)
- eosinophilia on FESS-obtained tissue Samples

Steinke JW, Smith AR, Carpenter DJ, et al. Lack of efficacy of symptoms and medical history in distinguishing the degree of eosinophilia in nasal polyps. J Allergy Clin Immunol Pract 2017;5:1582–8.e3.

Nsouli and colleagues, 2016

6-month trial

9 subjects with NPs and asthma

51% improvement in nasal endoscopic polyp scores

25% improvement in nasal function

Bidder and colleagues, 2018

16-week study

severe asthma with coexistent CRSwNP

13 received omalizumab – 24 treated with FESS

similar improvements

Table 2
Omalizumab efficacy in nasal polyposis

Parameter	Mean Change (Polyp 1/Polyp 2 Study[a])	*P* Value (Polyp 1/Polyp 2 Study)
Nasal congestion score	−0.89/−0.70	.0004/0.0017
Nasal polyp score	−1.08/−0.90	<.0001/0.014
SNOT-22 (0–110)	−24.70/−21.59	<.0001/<0.0001
Sense of smell score (0–3)	−0.56/−0.58	.0161/0.0024
Total nasal symptom score (0–12)	−2.97/−2.53	.0001/<0.0001
UPSIT smell assessment (0–40)	4.44/4.31	.0024/0.0011

Abbreviations: SNOT, sinonasal outcome test; UPSIT, University of Pennsylvania Smell Identification Test.

[a] Polyp 1 study, n = 138; Polyp 2 study, n = 127.

Gevaert P, Bachert C, Corren J, et al. Omalizumab efficacy and safety in nasal polyposis: results from two parallel, double-blind, placebo-controlled trials. Ann Allergy Asthma Immunol 2019;123:S17.

The most common adverse reaction from omalizumab

- injection-site pain and bruising

the package insert contains additional warnings regarding

- malignancies,
- geohelminth infections,
- cardiovascular diseases, and
- a “black box” warning concerning anaphylaxis.

Casale TB, Busse WW, Kline JN, et al. Omalizumab pretreatment decreases acute reactions after rush immunotherapy for ragweed-induced seasonal allergic rhinitis. J Allergy Clin Immunol 2006;117(1):134–40.

Massanari M, Nelson H, Casale T, et al. Effect of pretreatment with omalizumab on the tolerability of specific immunotherapy in patients with persistent symptomatic asthma inadequately controlled with inhaled corticosteroids. Ann Allergy Asthma Immunol 2009;102(1 supplement):17.

Nadeau KC, Schneider LC, Hoyte L, et al. Rapid oral desensitization in combination with omalizumab therapy in patients with cow’s milk allergy. J Allergy Clin Immunol 2011;127(6):1622–4.

Wood RA, Kim JS, Lindblad R, et al. A randomized, double-blind, placebocontrolled study of omalizumab combined with oral immunotherapy for the treatment of cow’s milk allergy. J Allergy Clin Immunol 2016;137(4):1103–10.e11.

at least 0.2% of patients who received Xolair (omalizumab) experienced anaphylaxis

Limb SL, Starke PR, Lee CE, et al. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with asthma. J Allergy Clin Immunol 2007;120(6):1378–81.

a higher incidence of malignancies in omalizumab-treated group compared with the control group (0.5% vs 0.2%) **?**

Xolair (Omalizumab) for Subcutaneous Use—Genentech, Inc.. 2008. Availableat: http://www.xolair.com/prescribing_information.html.

Biologics Targeting Interleukin 5

- **Interleukin 5** (IL-5) is a TH2 cytokine that plays a key role in eosinophil activation.
- Since2017, the FDA has approved 3 anti-IL-5 therapies as add-on therapy for **severe asthmatics** with an **eosinophilic phenotype**:
- benralizumab (Fasenra; AstraZeneca), a humanized monoclonal antibody directed against IL-5Ra;
- mepolizumab (Nucala;GalxoSmithKline), a neutralizing anti-IL-5 antibody; and
- reslizumab (Cinqair), an IgG4k monoclonal antibody targeting circulating IL-5.

all 3 anti-IL-5 associated with significant reductions in asthma exacerbation with no superiority of one biological over the others

Wang FP, Liu T, Lan Z, et al. Efficacy and safety of anti-interleukin-5 therapy in patients with asthma: a systematic review and meta-analysis. PLoS One 2016; 11(11):e0166833.

eosinophilic phenotype and **asthma exacerbation**

- Mepolizumab and benralizumab trials required that patients have eosinophil counts greater that 150 cells/mL (subcutaneously/4W)
- reslizumab required that patients have an eosinophil count greater than or equal to 400 cells/mL.(intravenously/4W - “black box”)

Mepolizumab

- is a humanized anti-IL-5 antibody
- significantly reduced **asthma exacerbations**
- also **improved quality of life** assessments in patients with severe asthma and self-reported upper airway disease

Prazma CM, Albers F, Mallett S, et al. Mepolizumab improves patient outcomes and reduces exacerbations in severe asthma patients with comorbid upper airway disease. American Academy of Asthma, Allergy, and Immunology National Meeting, San Francisco, February 22 - February 26, 2019.

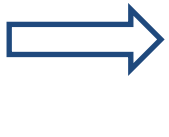
Interleukin-5 and Interleukin-5 Receptor

Targeting Therapies ?

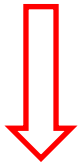
Stimulation

maturation

Survival

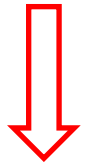


IL-5



eofeosinophils

CRSwNP



Elevated

tissue eosinophilia

IL-5 levels

Gevaert P, Van Bruaene N, Cattaert T, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. J Allergy Clin Immunol 2011;128:989–95.e1-8.

- double-blind placebo-controlled study
- **reduction in total polyp score**
- **improvement in symptom scores** for smell, congestion, and posterior pharyngeal drainage

- **reduced the need for surgery** in patients with severe recurrent bilateral NP

  (30% compared with only 10% of the placebo group)

- significant reductions in SNOT-22 scores

Bachert C, Sousa AR, Lund VJ, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: randomized trial. J Allergy Clin Immunol 2017;140:1024–31.e14.

Chupp GL, Bradford ES, Albers FC, et al. Efficacy of mepolizumab add-on therapy on health-related quality of life and markers of asthma control in severe eosinophilic asthma (MUSCA): a randomised, double-blind, placebo-controlled, parallel-group, multicentre, phase 3b trial. Lancet Respir Med 2017;5:390–400.

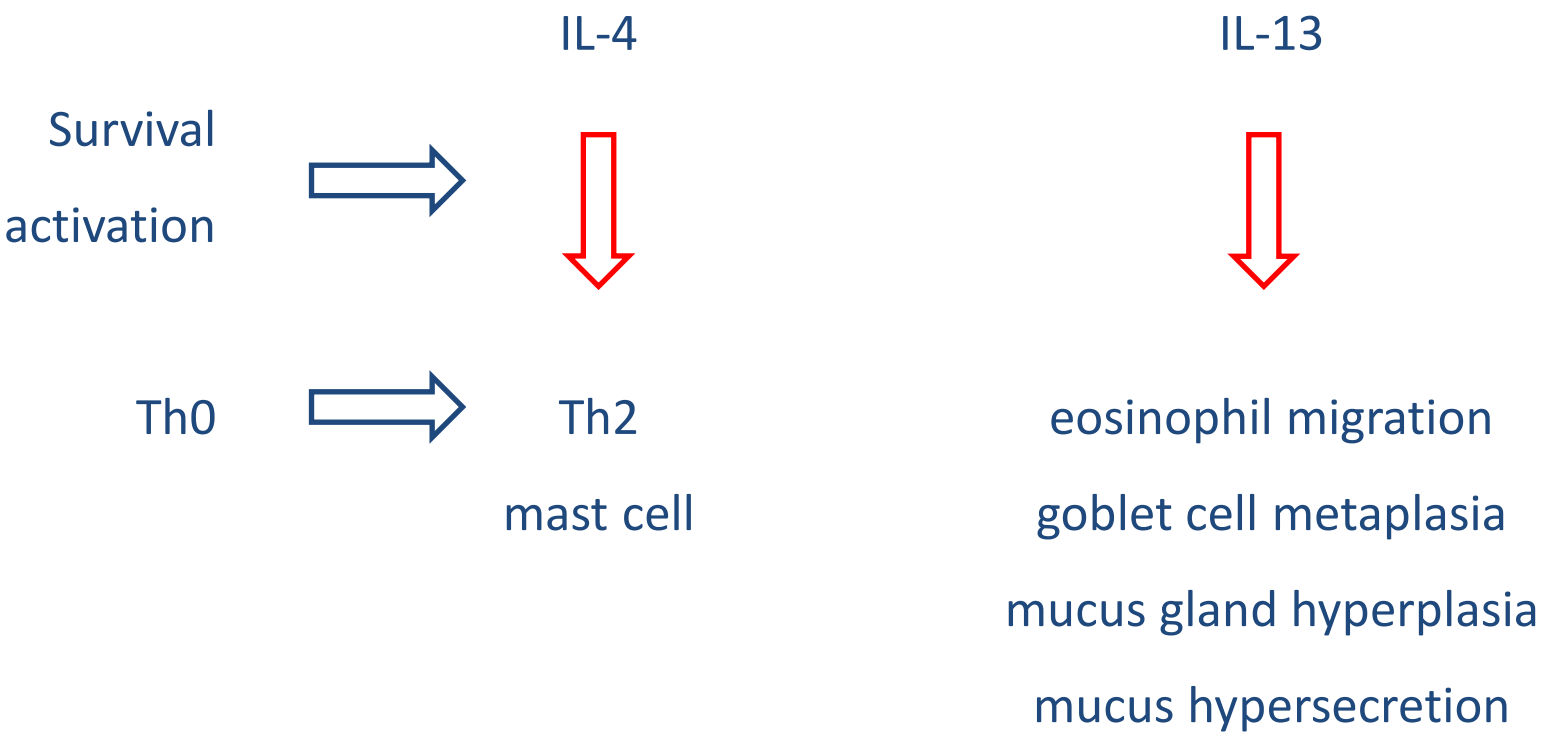
Dupilumab

- is an anti-IL-4 receptor a (IL-4Ra)
- 300 mg every 2 weeks - significantly reduce AR associated symptoms
- asthma + perennial AR

Weinstein SF, Katial R, Jayawardena S, et al. Efficacy and safety of dupilumab in perennial allergic rhinitis and comorbid asthma. J Allergy Clin Immunol 2018;142:171–177 e1.

Dupilumab

(2017, moderate to severe atopic dermatitis – 2018, moderate to severe asthma)



tissue remodeling and NP formation in CRS

- Dupilumab was the first biological approved for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP)

Franzese CB. The role of biologics in the treatment of nasal polyps. Immunol Allergy Clin North Am 2020;40(2):295–302.

- CRSwNP is a chronic inflammatory condition associated with significant morbidity and decreased quality of life with an estimated prevalence of 4,2% in the United States and 4,3% in Europe

Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, doubleblind, placebo-controlled, parallel-group phase 3 trials. Lancet 2019; 394(10209):1638–50.

- Approximately 25% to 30% of patients with chronic rhinosinusitis have CRSwNP

Stevens WW, Schleimer RP, Kern RC. Chronic Rhinosinusitis with Nasal Polyps. J Allergy Clin Immunol In Pract 2016;4(4):565–72.

Dupilumab (Dupixent; Regeneron)

is a humanized monoclonal antibody directed at IL-4a, which blocks the signaling of IL-4 and IL-13, which are key cytokines involved in the differentiation of TH2 lymphocytes

- 2017 for treatment of moderate to severe atopic dermatitis
- 2018 for the treatment of moderate to severe asthma

- 2019 for the treatment of chronic rhinosinusitis with nasal polyps every 2 weeks (subcutaneously)
  Administration can be performed at home or in the clinic setting

- *Rosenwasser L, Patel N. Effect of immunomodulators on allergen immunotherapy.In: Cox L, editor. Immunotherapies for allergic disease. Philadelphia: Elsevier;2019.*

- add-on therapy
- Two multinational, multicenter, randomized DBPC parallel-group studies
- 728 adults with severe CRSwNP.

Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, doubleblind, placebo-controlled, parallel-group phase 3 trials. Lancet 2019; 394(10209):1638–50.

Severe CRSwNP inclusion criteria

- **bilateral nasal polyps**
- **symptoms of chronic rhinosinusitis** despite intranasal corticosteroid use
- a bilateral **endoscopic nasal polyp score** of at least 5 (maximum 8)
- a **history of received systemic corticosteroids** in the preceding 2 years
- or **previous sinonasal surgery**.

Table 3
Dupilumab efficacy in nasal polyposis

Parameter	Least Squared Mean Change from Baseline (SINUS-24/SINUS-52 Trial[a])	*P* Value (SINUS-24/SINUS-52 Trial)
Nasal polyp score (0–8)	−2.06/−1.80	<.0001/<0.0001
Nasal congestion or obstruction score (0–3)	−0.89/−0.87	<.0001/<0.0001
Lund-Mackay CT score (0–24)	−7.44/−5.13	<.0001/<0.0001
Total symptom score (0–9)	−2.61/−2.44	<.0001/<0.0001
UPSIT smell assessment (0–40)	10.56/10.52	<.0001/<0.0001
Loss of smell score (0–3)	−1.12/−0.98	<.0001/<0.0001
SNOT-22 (0–110)	−21.12/−17.36	<.0001/<0.0001

[a] SINUS-24 study, n = 276; SINUS-52 study, n = 448.

Dupilumab became the first biologic treatment FDA approved for CRSwNP and can now be offered **to patients failing conventional therapy (2019)**

Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, doubleblind, placebo-controlled, parallel-group phase 3 trials. Lancet 2019;394:1638–50. Biologics for AR, CRS, and NPs 547

The safety profile of biologics is not fully understood

Ghadersohi S, Tan BK. Contemporary pharmacotherapy for allergic rhinitis and chronic rhinosinusitis. Otolaryngol Clin North Am. 2017;50:1135-1151.

Smith KA, Pulsipher A, Gabrielsen Smith KA, Pulsipher A, Gabrielsen DA, Alt JA. Biologics in chronic rhinosinusitis: an update and thoughts for future directions. Am J Rhinol Allergy. 2018;32:412-423.

Chipps BE, Figliomeni M, Spector S. Omalizumab: an update on efficacy and safety in moderate-to-severe allergic asthma. Allergy Asthma Proc. 2012;33:377-385.

Khan DA. Hypersensitivity and immunologic reactions to biologics: opportunities for the allergist. Ann Allergy Asthma Immunol. 2016;117:115-120.

Cox L, Platts-Mills TA, Finegold I, Schwartz LB, Simons FE, Wallance DV, et al. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma and Immunology Joint Task Force Report on omalizumab-associated anaphylaxis. J Allergy Clin Immunol. 2007;120:1373-1377.

Cox L, Lieberman P, Wallace D, Simons FE, Finegold I, Platts-Mills TA, et al. American Academy of Allergy, Asthma & Immunology/American College of Allergy, Asthma & Immunology Omalizumab-Associated Anaphylaxis Joint Task Force follow-up report. J Allergy Clin Immunol. 2011;128:210-212.

Limb SL, Starke PR, Lee CE, Chowdhury BA. Delayed onset and protracted progression of anaphylaxis after omalizumab administration in patients with

The safety profile of biologics is not fully understood

localized injection site reactions (8%–45%)	Anaphylaxis 1%
headaches (6%–19%)	hypersensitivity reactions 1%
oropharyngeal pain	cardiovascular complications
increased blood creatine phosphokinase	(pulmonary embolism, deep vein
myalgia	thrombosis, myocardial infarction, and
herpes simplex reactivation	unstable angina)
conjunctivitis	Malignancy
risk of serum sickness	

*It is **recommended** that patients undergo an observation period in the clinic after administration*

*Patients should be **informed** about the signs and symptoms of anaphylaxis and issued with an epinephrine auto-injector*

- **The ARIA guidelines recommend the use of a monoclonal anti-IgE** antibody such as omalizumab *for the treatment of asthma in patients with concomitant AR* if there is a clear IgE-dependent allergic component and failure of other maximal therapy.
  Other biologics, such as anti-IL-5, have yielded positive results in the treatment of asthma and other atopic diseases, and the ARIA guidelines include similar recommendations with reference to them.

Brozek JL, Bousquet J, Baena-Cagnani CE, Bonini S, Canonica GW, Casale TB, et al. Allergic rhinitis and its impact on asthma (ARIA) guidelines: 2010 revision. J Allergy Clin Immunol. 2010;126:466-476.

* Biologics and Allergy Immunotherapy in the Treatment of Allergic Diseases

Linda Cox, MD

Immunology and Allergy Clinics of North America

Volume 40, Issue 4, November 2020, Page 687-700

SCIT

the rate of premature discontinuation of treatment

SLIT

was 45% to 93% of SLIT and 41% to 77% of SCIT

EPIT

Cox LS, Hankin C, Lockey R.
Allergy immunotherapy adherence and delivery route: location does not matter. J Allergy Clin Immunol In Pract 2014;2(2):156–60. patients

ILIT

- **EPIT** (epicutaneous): a double-blind, placebo-controlled (DBPC) trial

(98 grass pollen allergic rhinoconjuctivitis patients - one preseasonal EPIT course on 2 subsequent pollen seasons – patches 8 hours/d 6-weekly)

Improvement of 48% and 40% (placebo 10 and 15%)

significant decrease in conjunctival allergen reactivity

increase in allergen-specific IgG4

Adverse reactions

eczema at the application site

One patient experienced a grade 2 systemic allergic reaction

Senti G, von Moos S, Tay F, et al.

Determinants of efficacy and safety in epicutaneous allergen immunotherapy: summary of three clinical trials. Allergy 2015; 70(6):707–10

EPIT also seems to be a promising treatment of **food allergies**

Biologics License Application for Viaskin Peanut Patch for the treatment of peanut-allergic children aged 4 to 11 years to the FDA in October 2019

Waldron J, Kim EH.
Sublingual and Patch Immunotherapy for Food Allergy.
Immunol Allergy Clin North Am 2020;40(1):135–48

- **ILIT** (intralymphatic) offers the advantage of a short treatment course

  an efficacy similar to SCIT and SLIT

  may be difficult to locate inguinal lymph nodes in obese individuals

An open trial

3 injections of grass pollen administered at 4-week

significant improvement in nasal allergen challenge after 4 months

symptomatic improvement **comparable to 3 years of SCIT**

Senti G, Prinz Vavricka BM, Erdmann I, et al. Intralymphatic allergen administration renders specific immunotherapy faster and safer: a randomized controlled trial. Proc Natl Acad Sci U S A 2008;105(46):17908–12

- At present, **ILIT** and **EPIT** are considered *investigational*

- **SCIT** and **SLIT** are the only routes *recommended* in practice guidelines for the treatment of allergic rhinitis, asthma, and some cases of atopic dermatitis

Allergy Immunotherapy

- the only causal treatment for **AR** - the only **immune modifying treatment**
- **Indications**

  allergic asthma, allergic rhinitis, atopic dermatitis, and peanut allergy.
- **Adherence** with SCIT and SLIT is equally poor
- **S**ubcutaneous **I**mmuno**T**herapy is widely used but it is time-consuming and is associated with a risk of severe adverse reactions.
- **SLIT** offers the advantage of a better safety profile and home administration
- **SCIT, SLIT** are relatively inexpensive and has shown to significantly reduce health care costs compared with standard drug treatment Single-allergen

Kuehr J, Brauburger J, Zielen S, Schauer U, Kamin W, Von Berg A, et al. Efficacy of combination treatment with anti-IgE plus specific immunotherapy in polysensitized children and adolescents with seasonal allergic rhinitis. J Allergy Clin Immunol. 2002;109:274-280.

CLINICS CARE POINTS

- AR is mediated in large part by IgE and responds to IgE-targeting biologics (**omalizumab**)
- Efficacy of **biologics** in CRSsNPs is theoretically plausible but no efficacy studies have been performed
- **Biologics** that target IgE, IL-5/IL-5 receptors, and the IL-4 receptor have all demonstrated efficacy in the treatment of NP
- Currently **dupilumab** is the only biologic having FDA approval for the treatment of NPs
- **Biologics** are not a causal treatment
- **Future studies** are essential to evaluate the **cost** effectiveness of biologics in the treatment of these disorders and their **proper placement in therapy** in comparison with medical and surgical therapies

Η εξέλιξη είναι πάντα χρήσιμη για την οικονομία και την ευημερία του ανθρώπου, όμως δεν πρέπει να ξεχνάμε ποτέ την αφετηρία από την οποία ξεκινήσαμε

Ευχαριστώ