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società italiana per le malattie respiratorie infantili

XXVIII CONGRESSO NAZIONALE SIMRI

Il respiro: scienza e terapia per la salute del bambino

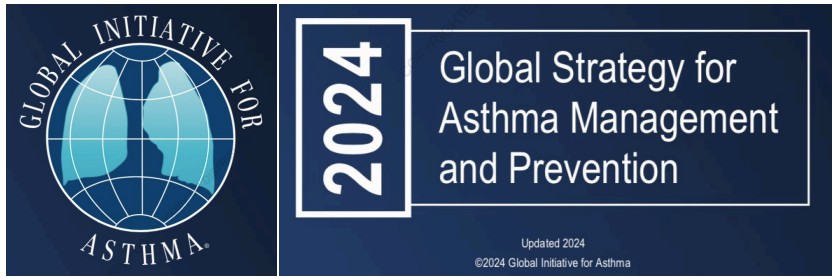
Torino, 10-12 ottobre 2024

UNIVERSITA' DEGLI STUDI DI MESSINA
DIPARTIMENTO DI PATOLOGIA UMANA DELL'ADULTO E DELL'ETÀ EVOLUTIVA "G. BARRESI"

APPLICAZIONE *DEL CORE OUTCOME MEASURES FOR SEVERE ASTHMA (COMSA)* NELLA VALUTAZIONE DELL'EFFICACIA E DELLA SICUREZZA DELLE TERAPIE BIOLOGICHE IN BAMBINI E ADOLESCENTI: UNO STUDIO *REAL-LIFE*

Francesca Galletta
UOC Pediatria
Amb. Allergologia-Pneumologia pediatrica
AOU G. Martino, Messina

Background

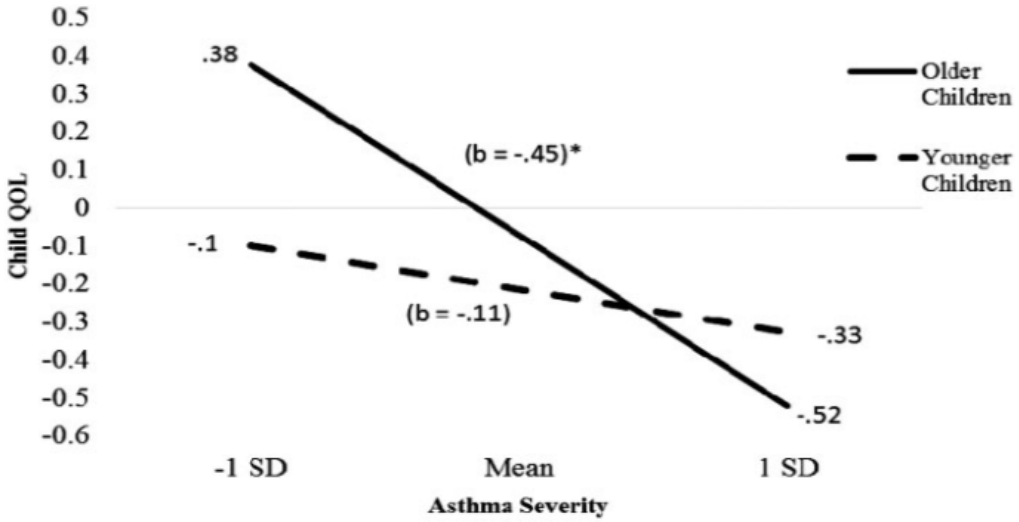


Severe asthma is defined as asthma that remains uncontrolled despite optimized treatment with high-dose ICS-LABA, or that requires high-dose ICS-LABA to prevent it from becoming uncontrolled.

Severe asthma is a significant global health issue that affects approximately **5% of children and 7% of adolescents with asthma.**

Asher MI, García-Marcos L, Pearce NE, Strachan DP. Trends in worldwide asthma prevalence. Eur Respir J. 2020;56(6):2002094.

Impact on Quality of Life



- 192 patients, aged 5-12 y
- An increase in asthma severity is significantly correlated with a worsening quality of life, especially in older children (8-12 years)

Miadich SA, et al.. J Pediatr Psychol. 2015

Pediatric Pulmonology. 2021

Relationship between anxiety symptoms, clinical control and quality of life of children with asthma: A cross-sectional study

Renata Ramos Tomaz Barbosa PT, PhD[1] | Karolinne Souza Monteiro PT, PhD[2] | Álvaro Campos Cavalcanti Maciel PT, PhD[1] | Fernanda Elizabeth Pereira da Silva PT[1] | Lucas Menescal Jales PT[1] | Thayla Amorim Santino PT, MSc[1] | Cleia Teixeira do Amaral MD, MSc[3] | Karla Morganna Pereira Pinto de Mendonça PT, PhD[1]

Scientific Reports ,2020

Relationship between quality of life and behavioural disorders in children with persistent asthma: a Multiple Indicators Multiple Causes (MIMIC) model

Laura Montalbano[1,36], Giuliana Ferrante[2,36], Silvia Montella[3], Giovanna Cilluffo[1✉], Antonio Di Marco[4], Sara Bozzetto[5], Emanuela Di Palmo[6], Amelia Licari[7], Lucia Leonardi[8], Valeria Caldarelli[9], Michele Ghezzi[10], Stefania La Grutta[1,37], Franca Rusconi[11,37] & the Italian Pediatric Severe Asthma Network (IPSAN) Program of Italian Paediatric Respiratory Society (IPRS)[†]

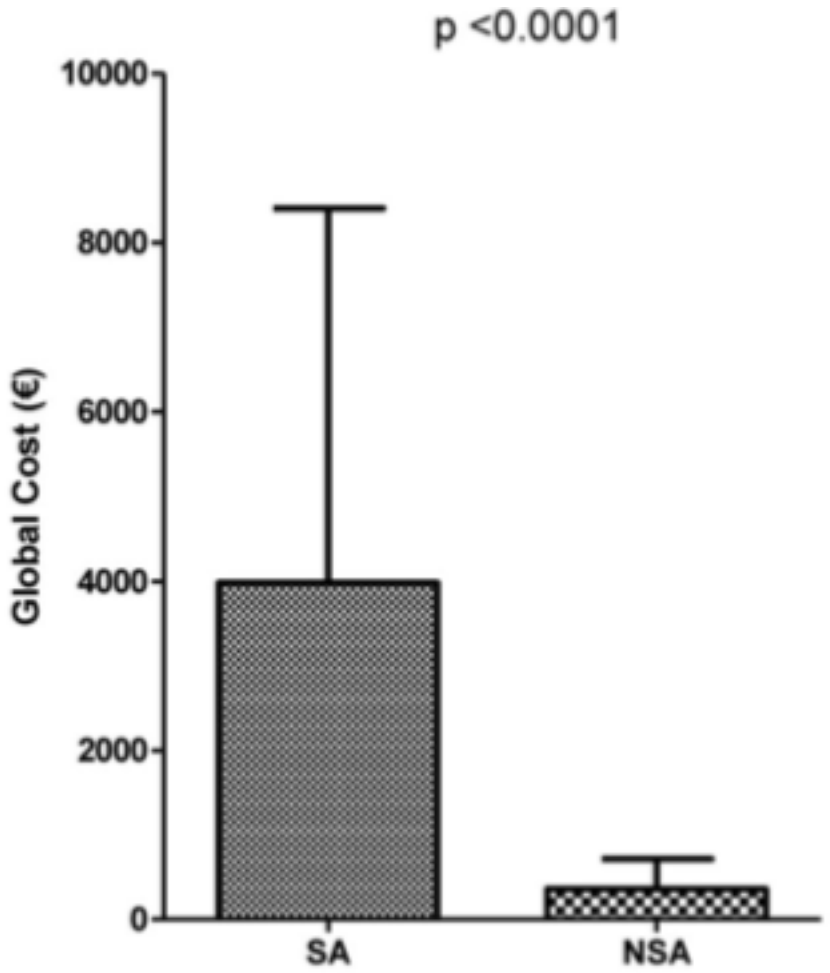
Respiratory Medicine, 2019

Targeting quality of life in asthmatic children: The MyTEP pilot randomized trial

Laura Montalbano[a,1], Giuliana Ferrante[b,1], Giovanna Cilluffo[a,*], Manuel Gentile[c], Marco Arrigo[c], Dario La Guardia[c], Mario Allegra[c], Velia Malizia[a], Rosalia Paola Gagliardo[a], Matteo Bonini[d], Stefania La Grutta[a]

Economic burden

Global costs (mean ± SD;) of asthma over six month according to asthma severity



SA= Severe Asthma
NSA= Non severe asthma

Pamuk G, et al. J Asthma. 2021 .

Risk of Adverse Events Related to Prolonged Therapy with High Doses of Inhaled Corticosteroids

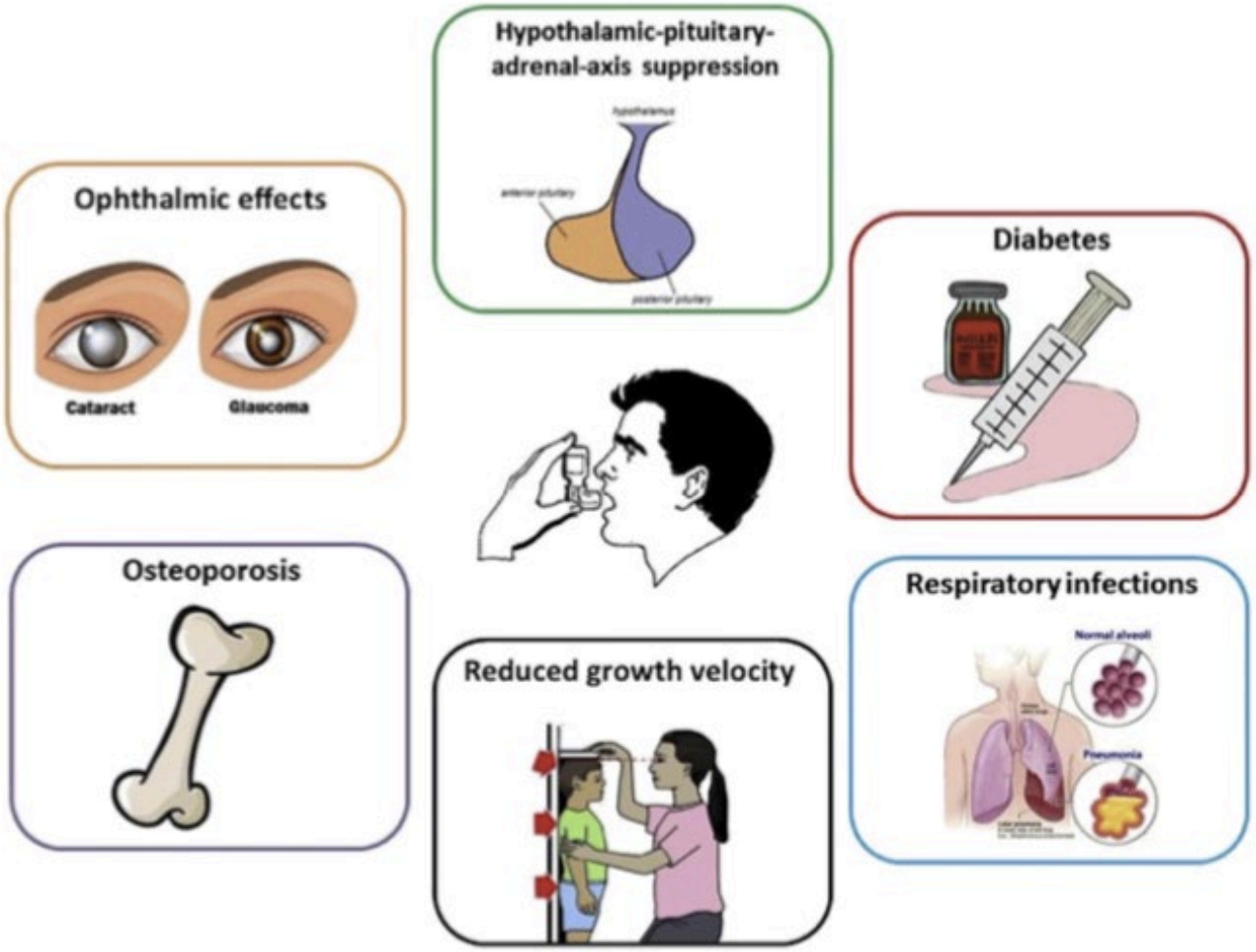


FIGURE 1. Common adverse effects related to the chronic use of inhaled corticosteroids.

Heffler E, et al. J Allergy Clin Immunol Pract. 2018

Risks of Adverse Events Associated with Systemic Steroid Therapy

Table 3. Potential side effects of short courses of oral steroids, and the longer-term potential effects of recurrent use[1,30,49]

Potential side effects of short courses of oral steroids	Effects of long-term dosing with steroids
• Sleep disturbance	• Weight gain
• Behavioural disturbance	• Cushingoid facies
• Vomiting	• Mood changes (irritability, hyperactivity)
• Gastritis	• Reduction in final height or growth velocity
• Gastrointestinal disturbance	• Osteoporosis
• Facial flushing	• Cataracts
• Nocturia	• Hypertrichosis
• Dry skin	• Cutaneous atrophy
	• Hypertension
	• Hypothalamic–pituitary–adrenal axis suppression

Harding T, et al. Aust J Gen Pract. 2021

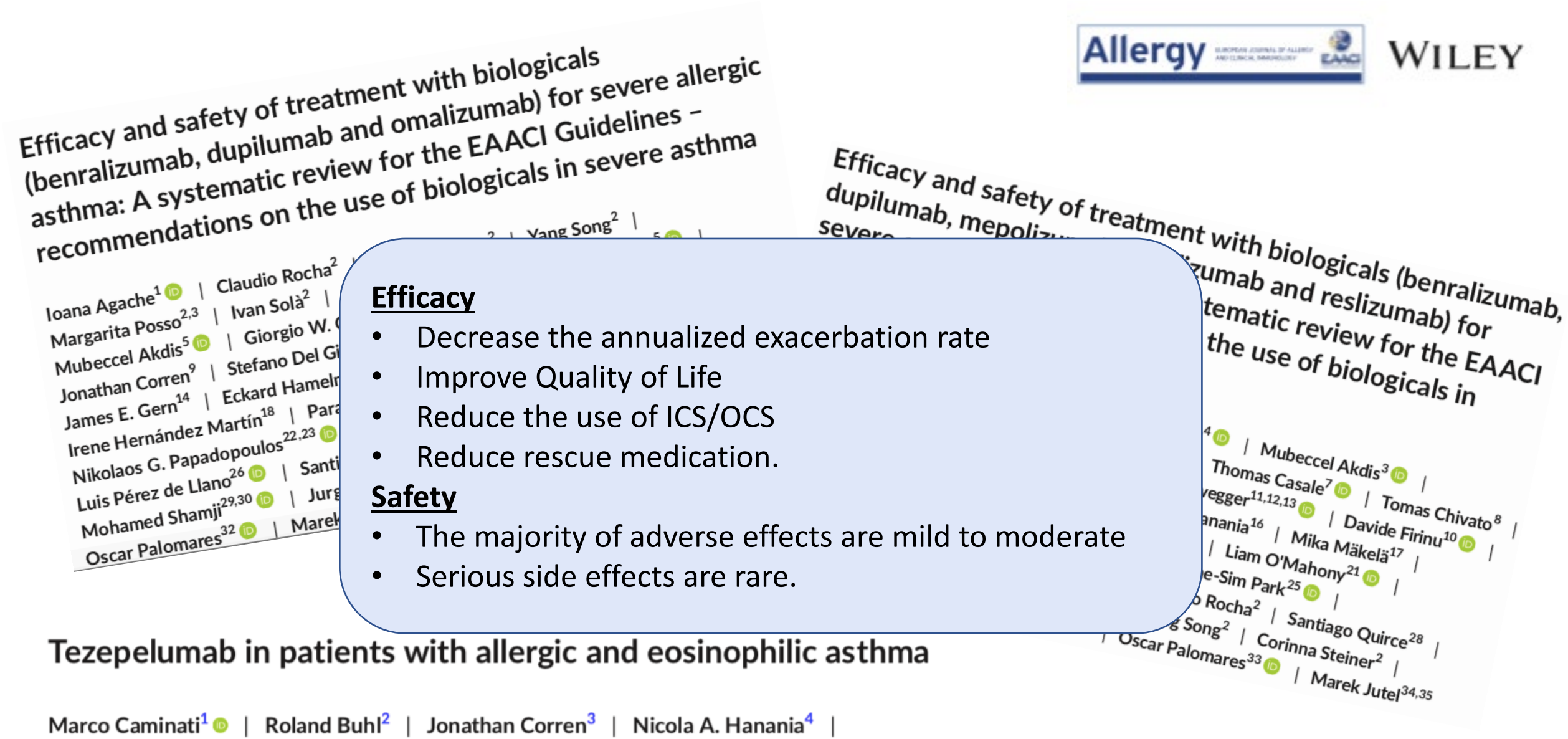
BIOLOGIC DRUGS

The NEW ENGLAND JOURNAL of MEDICINE

Table 1. Biologic Agents Approved by the Food and Drug Administration for the Treatment of Severe Asthma.*

Biologic Agent (Therapeutic Target and Mechanism of Action)	Route of Administration and Dose†	Forms	Indication	Patient Yr of Age†	Efficacy	Safety Concerns
Benralizumab (interleukin-5Rα; antibody binds to interleukin-5Rα on eosinophils and basophils, depleting them through antibody-dependent, cell-mediated cytotoxicity)	SC; 30 mg every 4 wk (first 3 doses), followed by 30 mg every 8 wk	Prefilled syringe, autoinjector pen	Severe eosinophilic asthma	≥12	Reduced exacerbations, reduced symptoms, small or moderate effect on FEV_1; decrease or withdrawal of OGs if blood eosinophils >150/μl; improved quality of life	Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs
Dupilumab (interleukin-4Rα; antibody binds to interleukin-4Rα, inhibiting interleukin-4 and interleukin-13 signaling in hematopoietic cells [e.g., B cells, CD4+ helper T cells, and eosinophils], epithelial cells, and airway smooth-muscle cells)	Adults and adolescents: SC; initial dose of 400 mg, followed by 200 mg every 2 wk; for glucocorticoid-dependent patients or patients with concomitant moderate-to-severe atopic dermatitis, initial dose of 600 mg, followed by 300 mg every 2 wk Children, ages 6–11 yr: SC; dose depends on body weight‡	Prefilled syringe, autoinjector pen	Severe eosinophilic asthma (FDA), severe type 2 asthma (EMA), OG-dependent asthma; other indications: CRS with nasal polyposis, moderate-to-severe atopic dermatitis	≥6	Reduced exacerbations, reduced symptoms, improved lung function; decrease or withdrawal of OGs, irrespective of blood eosinophil count at baseline; improved quality of life	Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs, hypereosinophilic conditions (e.g., EGPA), conjunctivitis
Mepolizumab (interleukin-5; antibody binds to circulating interleukin-5)	Adults and adolescents: SC; 100 mg every 4 wk Children, ages 6–11 yr: SC; 40 mg every 4 wk	Prefilled syringe, autoinjector pen	Severe eosinophilic asthma; other indications: EGPA, hypereosinophilic syndrome	≥6	Reduced exacerbations, reduced symptoms, small or moderate effect on FEV_1; reduction or withdrawal of OGs if blood eosinophils >150/μl; improved quality of life	Helminthic infections, hypersensitivity reactions, abrupt discontinuation of OGs, herpes zoster infections (rare)
Omalizumab (IgE; antibody binds to Fc part of free IgE, inhibiting binding of IgE to FcεRI on mast cells and basophils and FcεRII on dendritic cells and eosinophils)	SC; 75 to 375 mg every 2 to 4 wk according to body weight and pretreatment level of serum total IgE	Prefilled syringe	Severe allergic asthma; other indication: chronic idiopathic urticaria	≥6	Reduced exacerbations, reduced symptoms, small effect on FEV_1; improved quality of life	Serum sickness, hypereosinophilic conditions (e.g., EGPA), abrupt discontinuation of OGs; black-box warning for anaphylaxis (occurring in ±0.2% of patients)
Reslizumab (interleukin-5; antibody binds to circulating interleukin-5)	IV; 3 mg/kg every 4 wk	IV infusion	Severe eosinophilic asthma	≥18	Reduced exacerbations, reduced symptoms, small or moderate effect on FEV_1; improved quality of life	Helminthic infections, abrupt discontinuation of OGs; black-box warning for anaphylaxis (occurring in ±0.3% of patients)
Tezepelumab (TSLP)	SC; 210 mg every 4 wk	Prefilled syringe	Severe asthma	≥12	Reduced exacerbations, reduced symptoms, improved lung function; improved quality of life	Pharyngitis, arthralgia, back pain

Brusselle GG, et al . N Engl J Med. 2022


Allergy
WILEY
Efficacy and safety of treatment with biologicals (benralizumab, dupilumab and omalizumab) for severe allergic asthma: A systematic review for the EAACI Guidelines – recommendations on the use of biologicals in severe asthma
Ioana Agache[1] | Claudio Rocha[2]
Margarita Posso[2,3] | Ivan Solà[2]
Mubeccel Akdis[5] | Giorgio W.
Jonathan Corren[9] | Stefano Del Gi
James E. Gern[14] | Eckard Hamelr
Irene Hernández Martín[18] | Para
Nikolaos G. Papadopoulos[22,23]
Luis Pérez de Llano[26] | Santi
Mohamed Shamji[29,30] | Jurg
Oscar Palomares[32] | Marek
Yang Song[2] |
Efficacy and safety of treatment with biologicals (benralizumab, dupilumab, mepoliz
severe
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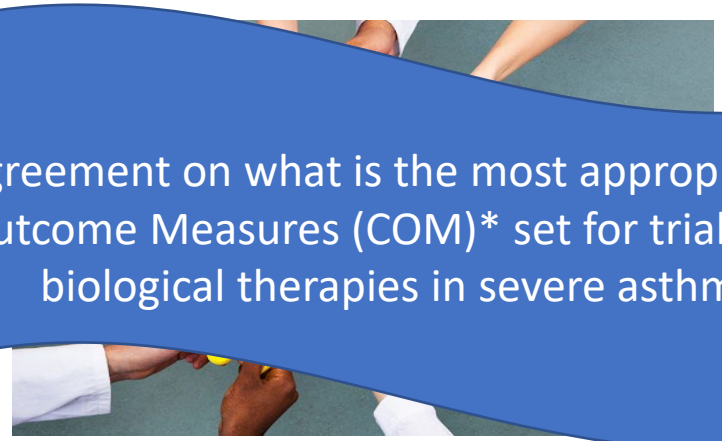
tematic review for the EAACI
the use of biologicals in
[4] | Mubeccel Akdis[3] |
Thomas Casale[7] | Tomas Chivato[8] |
egger[11,12,13] | Davide Firinu[10] |
anania[16] | Mika Mäkelä[17] |
| Liam O'Mahony[21] |
e-Sim Park[25] |
o Rocha[2] | Santiago Quirce[28] |
g Song[2] | Corinna Steiner[2] |
Oscar Palomares[33] | Marek Jutel[34,35]
Efficacy
• Decrease the annualized exacerbation rate
• Improve Quality of Life
• Reduce the use of ICS/OCS
• Reduce rescue medication.
Safety
• The majority of adverse effects are mild to moderate
• Serious side effects are rare.
Tezepelumab in patients with allergic and eosinophilic asthma
Marco Caminati[1] | Roland Buhl[2] | Jonathan Corren[3] | Nicola A. Hanania[4] |
Harold Kim[5,6] | Stephanie Korn[7,8] | Marek Lommatzsch[9] | Neil Martin[10,11] |
Andrea Matucci[12] | Shuaib M. Nasser[13] | Ian D. Pavord[14] | Christian Domingo[15]

Significant heterogeneity of outcome measures

Akinbami LJ, et al. **Asthma outcomes: healthcare utilization and costs.** J Allergy Clin Immunol 2012

Gliklich RE, Castro M, Leavy MB, et al. **Harmonized outcome measures for use in asthma patient registries and clinical practice.** J Allergy Clin Immunol 2019

Cloutier MM, et al. **Asthma outcomes: composite scores of asthma control.** J Allergy Clin Immunol 2012



No agreement on what is the most appropriate Core Outcome Measures (COM)* set for trials with biological therapies in severe asthma

Tejwani V, et al. **A multistakeholder Delphi consensus core outcome set for clinical trials in moderate-to-severe asthma (COMTHMA).** Ann Allergy Asthma Immunol 2021

Krishnan JA,et al. **Asthma outcomes: symptoms.** J Allergy Clin Immunol 201

[illegible] SR, Rand CS, Cabana MD, et al. **Asthma outcomes: quality of life.** J Allergy Clin Immunol 2012

Szefler SJ, et al. **Asthma outcomes: biomarkers.** J Allergy Clin Immunol 2012

Tepper RS, et al. **Asthma outcomes: pulmonary physiology.** J Allergy Clin Immunol 2012

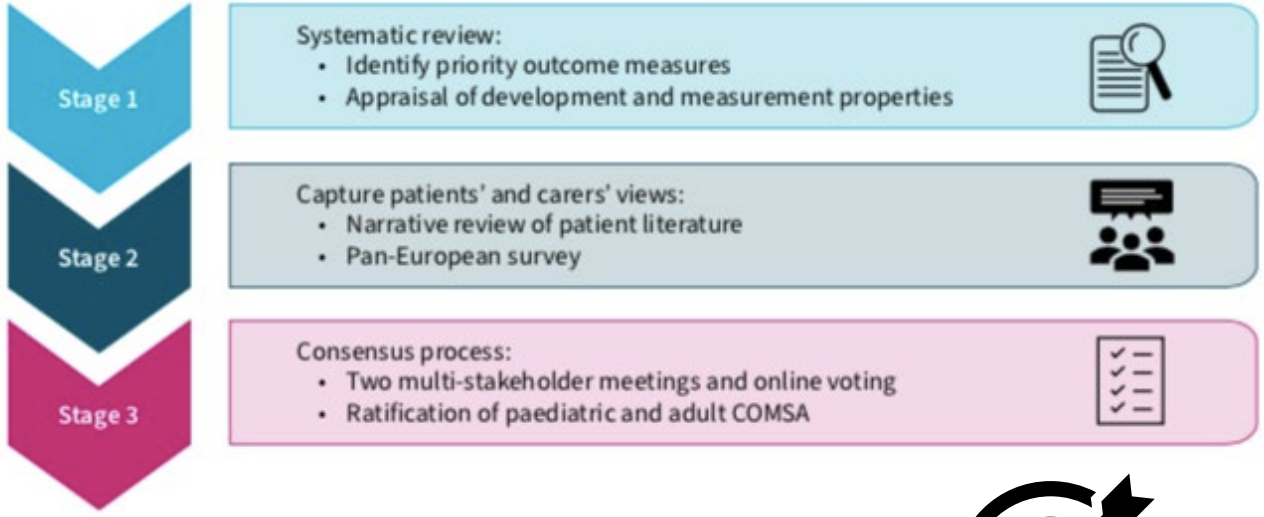
*Prinsen CA, et al. How to select outcome measurement instruments for outcomes included in a "Core Outcome Set" - a practical guideline. Trials. 2016

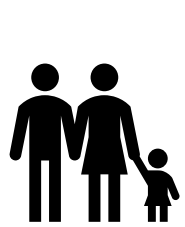
2023

EUROPEAN RESPIRATORY JOURNAL

Development of Core Outcome Measures sets for paediatric and adult Severe Asthma (COMSA)

Ekaterina Khaleva[1], Anna Rattu[1], Chris Brightling[2], Andrew Bush[3], Apostolos Bossios[4], Arnaud Bourdin[5], Kian Fan Chung[6], Rekha Chaudhuri[7], Courtney Coleman[8], Sven-Erik Dahlén[4], Ratko Djukanovic[1,9], Antoine Deschildre[10,11], Louise Fleming[6], Stephen J. Fowler[12], Atul Gupta[13], Eckard Hamelmann[14], Simone Hashimoto[15,16], Gunilla Hedlin[17], Gerard H. Koppelman[18,19], Erik Melén[20], Clare S. Murray[12], Charles Pilette[21], Celeste Porsbjerg[22], Katharine C. Pike[23], Franca Rusconi[24], Clare Williams[8], Birgit Ahrens[25], Peter Alter[26], Freja Anckers[27], Maarten van den Berge[19,28], Katharina Blumchen[29], Guy Brusselle[30], Graham W. Clarke[31], Danen Cunoosamy[32], Barbro Dahlén[4], Piers Dixey[6,33], Andrew Exley[34], Urs Frey[35], Erol A. Gaillard[36], Lisa Giovannini-Chami[37,38], Jonathan Grigg[39], Diana Hartenstein[25], Liam G. Heaney[40], Bülent Karadag[41], Susanne Kaul[25], Inger Kull[20], Amelia Licari[42], Anke H. Maitland-van der Zee[15,16], Vera Mahler[25], Ann-Marie M. Schoos[43,44], Prasad Nagakumar[45,46], Jenny Negus[27], Hanna Nielsen[27,47], James Paton[48], Mariëlle Pijnenburg[49], Valeria Ramiconi[50], Sofia Romagosa Vilarnau[50], Stefania Principe[16,51], Niels Rutjes[15], Sejal Saglani[6], Paul Seddon[52], Florian Singer[53,54], Heribert Staudinger[55], Steve Turner[56,57], Susanne Vijverberg[15,16], Tonya Winders[58,59], Valentyna Yasinska[4] and Graham Roberts[1,9,60] on behalf of the COMSA Working Group in the 3TR Consortium





Patients

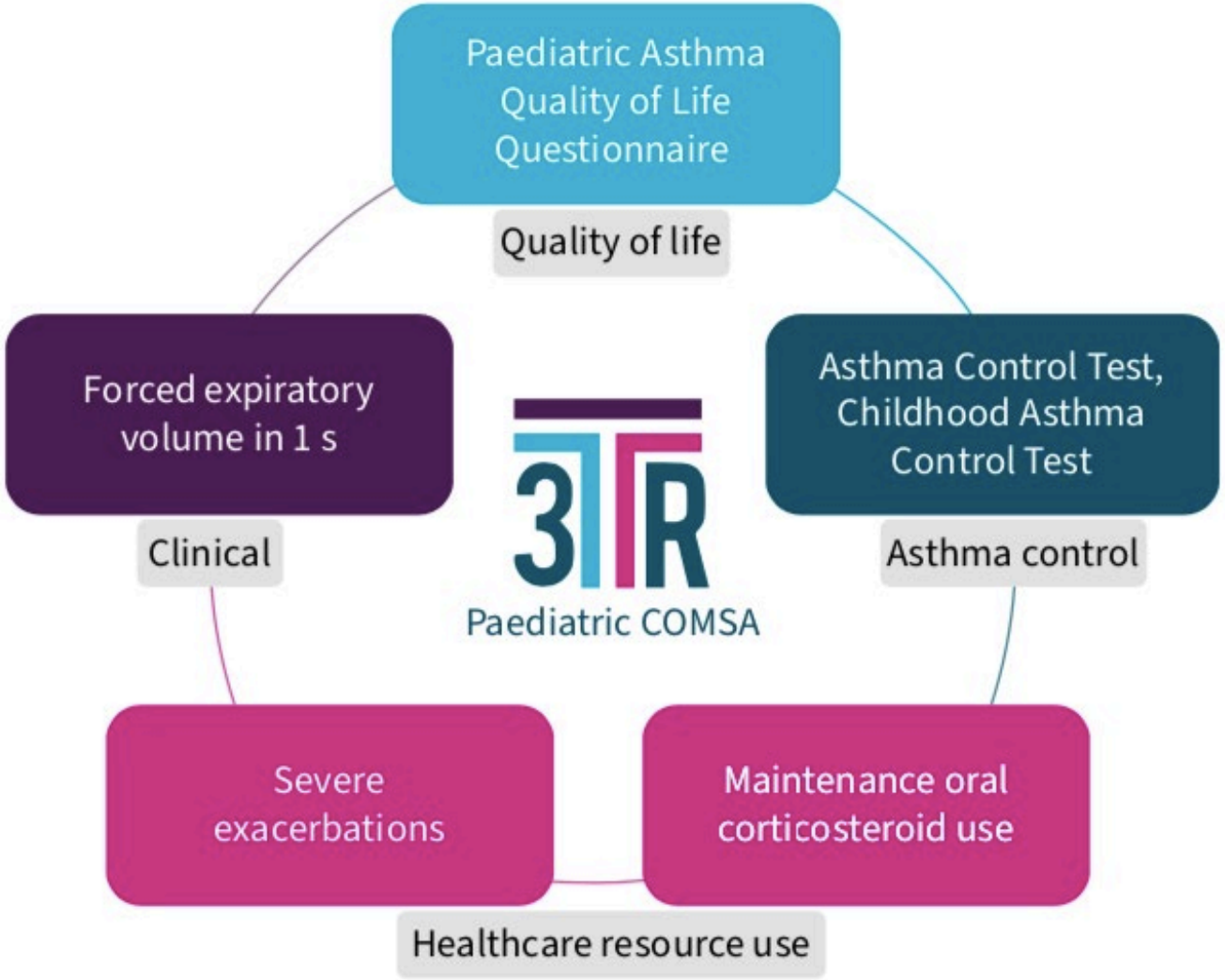
Adult and pediatric clinicians

Health regulators

Pharmaceutical representatives

- To enhance the consistency and comparability of clinical trial results, thus improving the synthesis of data and supporting better policy decisions and clinical practices for treating severe asthma.
- To enhance patient care.

COMSA parameters



The paediatric Core Outcome Measures set for severe asthma clinical trials. Forced expiratory volume in 1 s should be reported as z-scores using the Global Lung Function Initiative predictive equations, annual severe exacerbations as per the European Respiratory Society/American Thoracic Society definition and maintenance oral corticosteroid (mOCS) use defined as daily or alternate day use (median (25th, 75th centiles) dose and proportion on mOCS should be reported). The Childhood Asthma Control Test should be used for children 4–11 years old and the Asthma Control Test should be used for children 12–18 years old.

Khaleva E et al., Eur Respir J. 2023

Our study

Prospective, real-life study

To evaluate efficacy and safety of biologic drugs in the treatment of severe asthma, evaluating the applicability of COMSA.

INCLUSION CRITERIA

- Children and adolescents, aged 6-18 years
- Diagnosis of severe uncontrolled or partially controlled asthma, according to GINA consensus
- Candidates for treatment with omalizumab or dupilumab

EXCLUSION CRITERIA

- History of known allergy or previous reaction to biologic drugs
- Patients who had used other biological drug, β-blockers, angiotensin-converting enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARB), calcium channel blockers or systemic steroids for indications other than asthma for more than 3 weeks in the past 6 months
- Patients with cystic fibrosis, ciliary dyskinesia, immunodeficiencies

Timeline

Baseline (T0)

- PAQLQ
- ACT/cACT
- Maintenance OCS use
- Severe exacerbations
- preBD-FEV1

Omalizumab/ Dupilumab

6 months (T1)

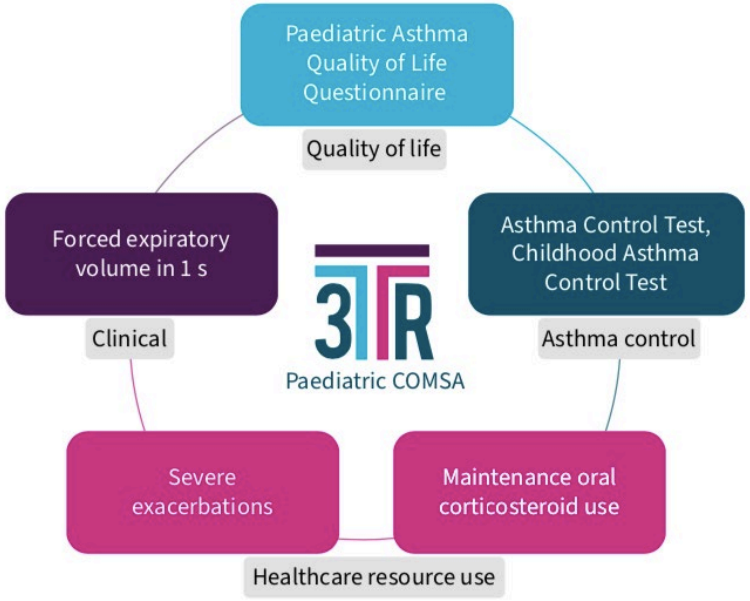
- PAQLQ
- ACT/cACT
- Maintenance OCS use
- Severe exacerbations
- preBD-FEV1

12 months (T2)

- PAQLQ
- ACT/cACT
- Maintenance OCS use
- Severe exacerbations
- preBD-FEV1

Results

Clinical features	Results
Patients enrolled, no. (%)	17 (100)
Female, no. (%)	9 (53)
White race, no. (%)	16 (94.2)
Body mass index (kg/m2), median (IQR)	21.4 (4.5)
History of bronchiolitis, no. (%)	8 (47)
Allergic comorbidities	
Atopic dermatitis,no. (%)	5 (29.5)
Allergic rhinitis, no. (%)	15 (88.2)
Food allergy, no. (%)	1 (5.8)
>2 comorbidites, no. (%)	6 (35.2)
Other comorbidities	
Obesity, n.o (%)	3 (17.6)
Adenoid hypertrophy, no. (%)	2 (11.7)
Hashimoto's Thyroiditis, no. (%)	1 (5.8)
Constipation, no. (%)	1 (5.8)
Type 1 Diabetes, no. (%)	1 (5.8)
Patients with uncontrolled asthma according to GINA, no. (%)	8 (47)
Patients with partially controlled asthma according to GINA, no. (%)	9 (53)
Age at severe asthma diagnosis (years),mean (SD)	8.5 (1.3)
Age at biological therapy beginning, mean (SD)	10.5 (3.5)
Type of biologic drug	
Omalizumab,no. (%)	14 (82.3)
Dupilumab,no. (%)	3 (17.7)



Results

Efficacy

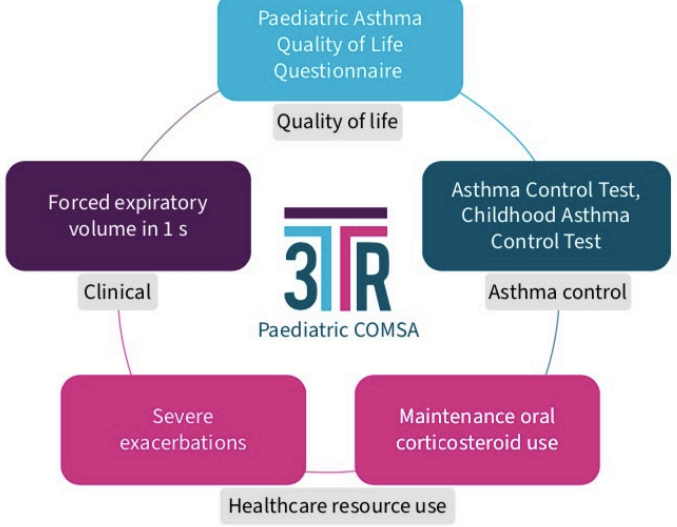
According to the **European Respiratory Society (ERS) /American Thoracic Society (ATS)**[1], a **severe exacerbation** is defined as **the need for systemic corticosteroids** for at least 3 days **and the need for hospitalization or emergency department visit**

COMSA parameters	T0	T1	T2	p-value (T0 vs T1; T0 vs T2)
PAQLQ, median (IQR)	69 (52;75)	103 (98;110)	130 (110;140)	<0.001*; <0.001*
ACT/cACT, median (IQR)	10 (8;12)	15 (13;19)	22 (19;23)	<0.001*; <0.001*
Severe exacerbations, median (IQR)	3.5 (2;4)	0.3 (0.1;0.7)	0.1(0;0.3)	<0.001*; <0.001*
FEV1 (z-score), median (IQR)	-0.3 (1.4;2.2)	-0.1 (0.66;1.73)	0.1 (-0.5;1.4)	0.575; 0.623

**p-value <0.05*

	T0	T1	T2	p-value (T0 vs T1; T0 vs T2)
Systemic steroids use, no (%)	15 (88.2)	6 (35.2)	2 (11.7)	0.004*; <0.001*
Hospitalizations, mean (range)	0.5 (0-3)	0	0	0.014*; 0.014*
Emergengy department admitted, mean (range)	0.6 (0-3)	0	0	0.011*; 0.011*

[1]Chung KF, *European Respiratory Journal*. 2014



Results

Efficacy

	T0	T1	T2
Patients with FEV1 >90%, no. (%)	11 (64.7)	15 (88.2)	15 (88.2)

COMSA parameters	T0	T1		
PAQLQ, median (IQR)	69 (52;75)	103 (98;110)		
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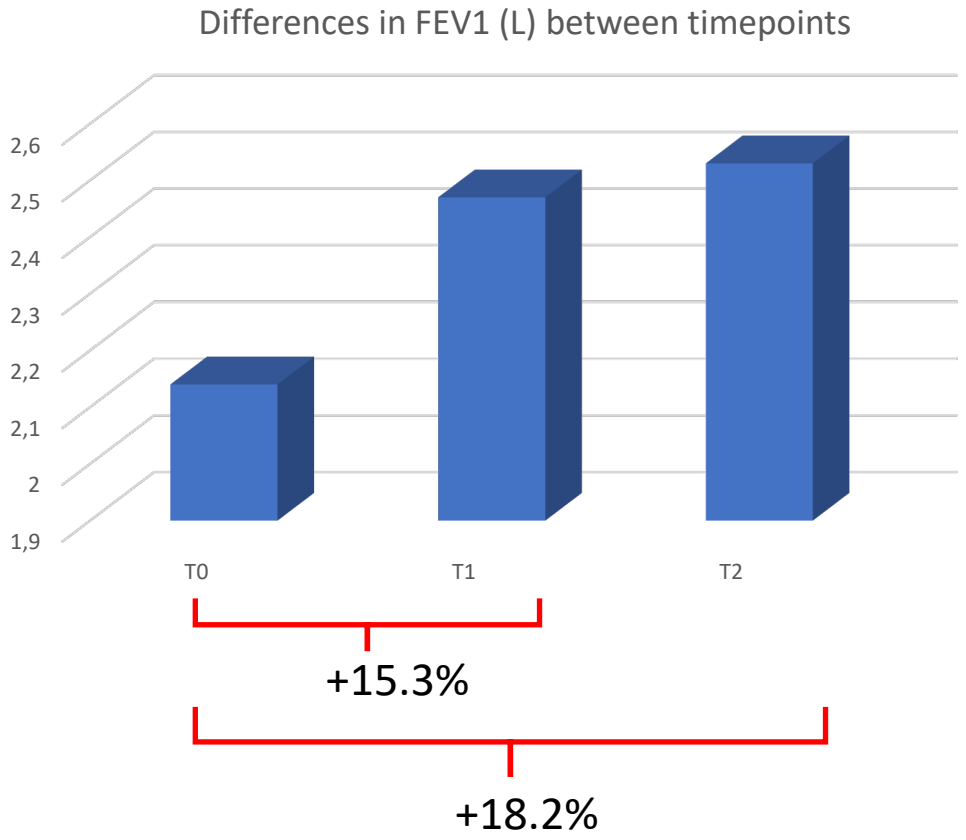
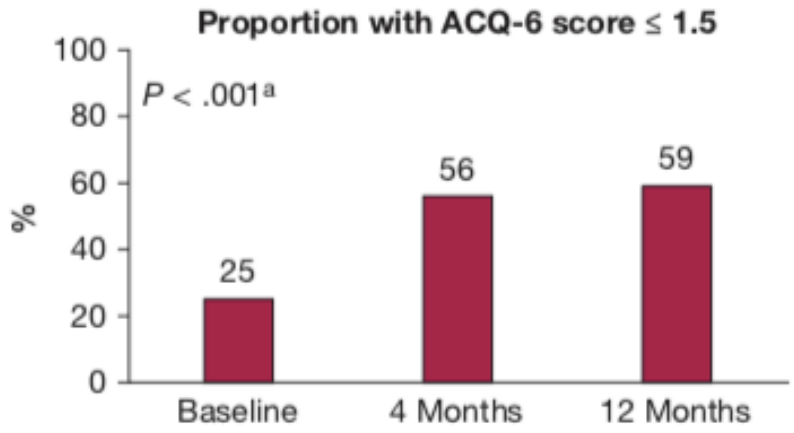


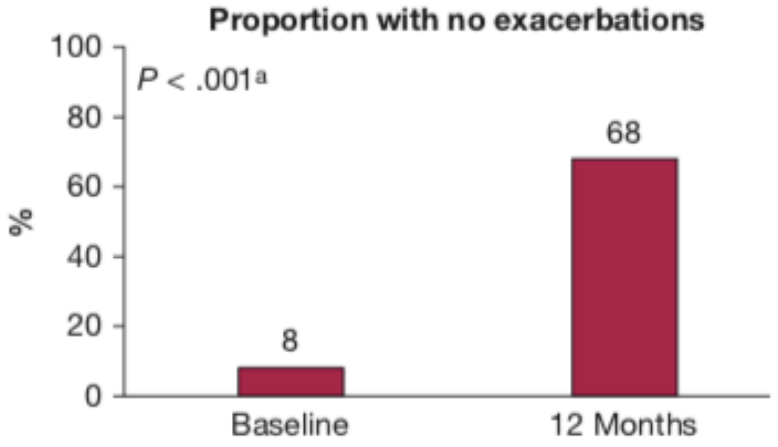
- **Limited sample size**.
- Allergic and non allergic comorbidities, heterogeneity in response to biologics
- Enrolled patients with severe asthma, with a mean age of 10.5 years, and a mean age at severe asthma diagnosis of 8.5 years, almost half of whom have uncontrolled asthma → chronic inflammation, airway remodeling.

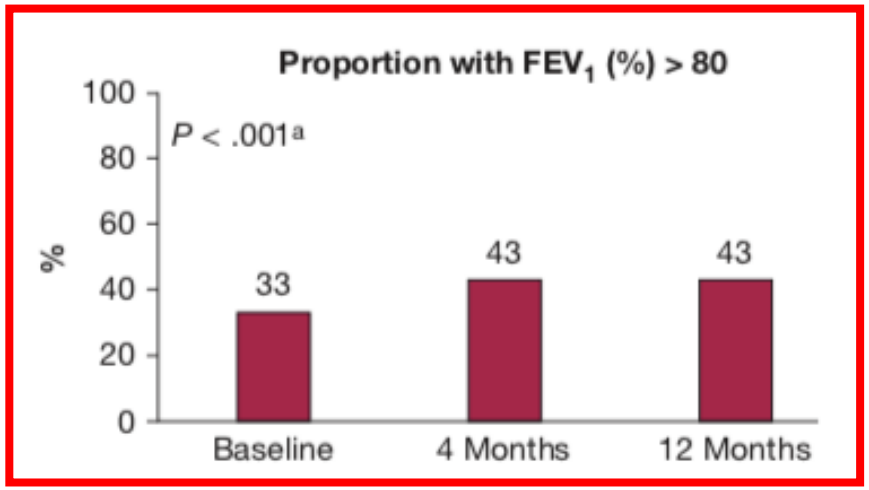
- FEV1 is the most difficult parameter to improve.

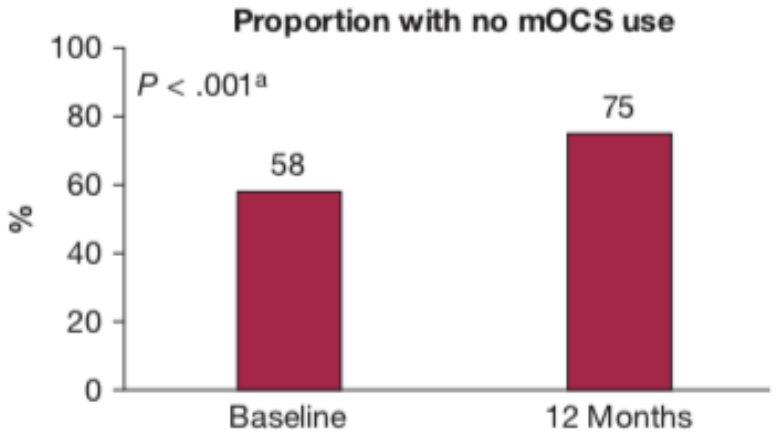
A total of 501 adults

- 75% →**Anti-IL-5/IL-5R**
- 16%→**Anti-IL-4Ra**
- 6% → **Anti-IgE**

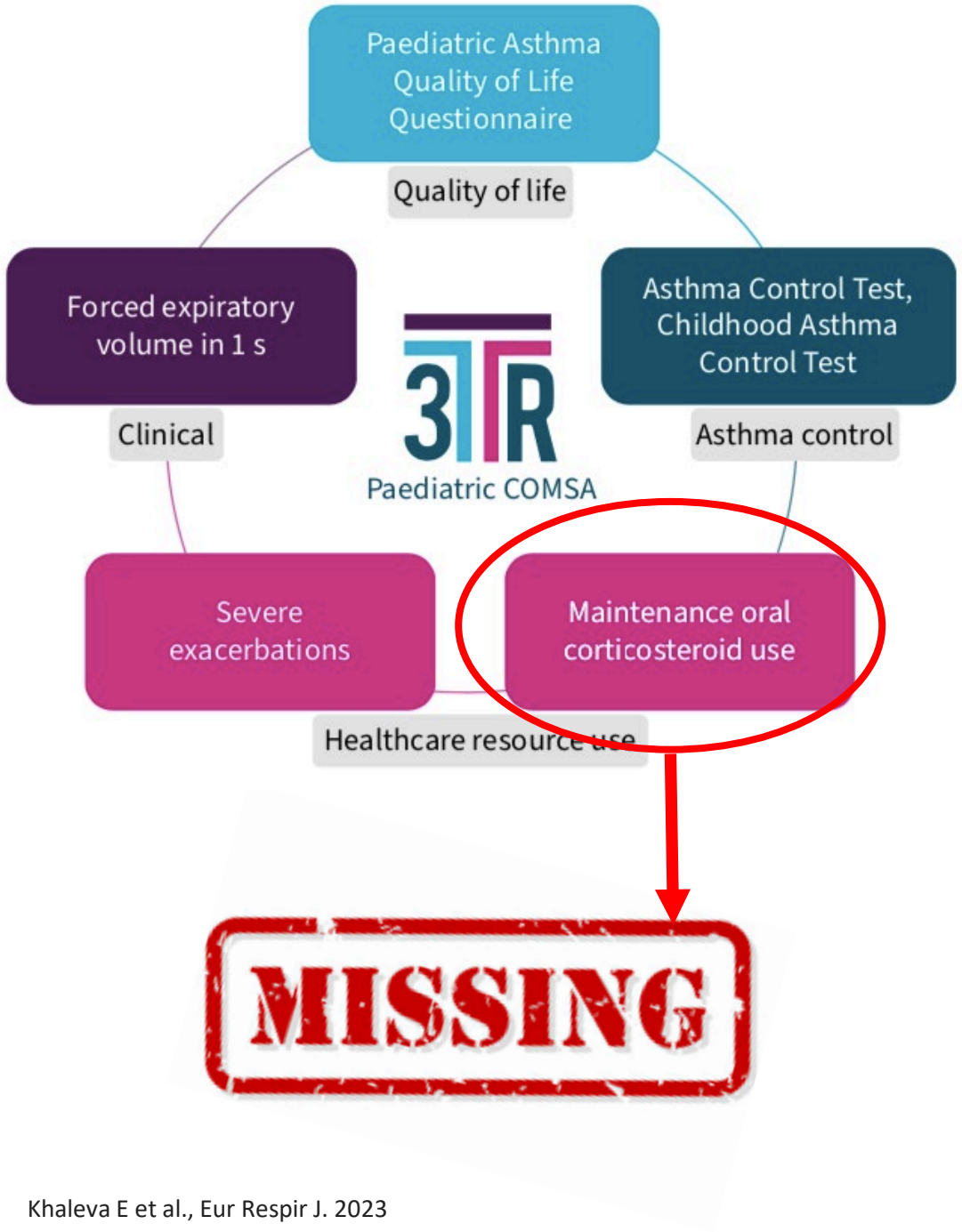








Hansen S et al., Chest, 2024



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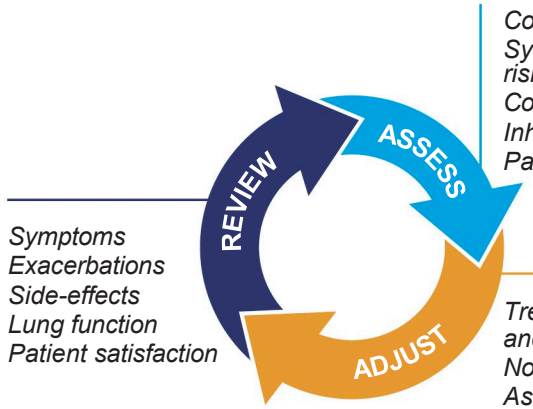
Khaleva E et al., Eur Respir J. 2023

2022

Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



CONTROLLER and **PREFERRED RELIEVER** (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP
RELIEVER: As-needed low-dose ICS-formoterol			

See GINA severe asthma guide

CONTROLLER and **ALTERNATIVE RELIEVER** (Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4R, anti-TSLP
RELIEVER: As-needed short-acting beta$_2$-agonist				

Other controller options for either track (limited indications, or less evidence for efficacy or safety)

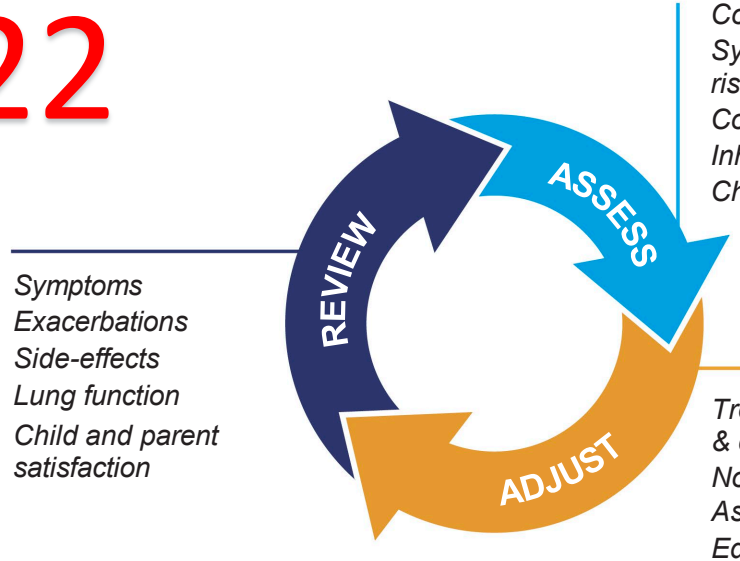
	Low dose ICS whenever SABA taken, or daily LTRA, or add HDM SLIT	*Medium dose ICS, or add LTRA, or add HDM SLIT*	*Add LAMA or LTRA or HDM SLIT, or switch to high dose ICS*	*Add azithromycin (adults) or LTRA. As last resort consider adding low dose OCS but consider side-effects*

GINA 2022, Box 3-5A

2022

Children 6-11 years

Personalized asthma management:
Assess, Adjust, Review



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2B)
Comorbidities
Inhaler technique & adherence
Child and parent preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Child and parent satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Asthma medications (adjust down or up)
Education & skills training

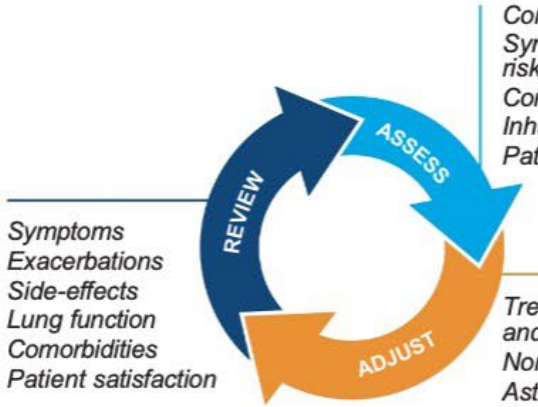
Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	Low dose ICS taken whenever SABA taken	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, OR medium dose ICS, OR very low dose* ICS-formoterol maintenance and reliever (MART)	Medium dose ICS-LABA, OR low dose† ICS-formoterol maintenance and reliever therapy (MART). Refer for expert advice	Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE, anti-IL4R
Other controller options (limited indications, or less evidence for efficacy or safety)	*Consider daily low dose ICS*	*Daily leukotriene receptor antagonist (LTRA), or low dose ICS taken whenever SABA taken*	*Low dose ICS + LTRA*	*Add tiotropium or add LTRA*	*Add-on anti-IL5 or, as last resort, consider add-on low dose OCS, but consider side-effects*
RELIEVER	As-needed short-acting beta$_2$-agonist (or ICS-formoterol reliever in MART in Steps 3 and 4)				

**Very low dose: BUD-FORM 100/6 mcg*
†Low dose: BUD-FORM 200/6 mcg (metered doses).

GINA 2024 – Adults & adolescents 12+ years

Personalized asthma management
Assess, Adjust, Review
for individual patient needs



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2)
Comorbidities
Inhaler technique & adherence
Patient preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Comorbidities
Patient satisfaction

Treatment of modifiable risk factors and comorbidities
Non-pharmacological strategies
Asthma medications including ICS (as below)
Education & skills training

TRACK 1: PREFERRED CONTROLLER and RELIEVER
Using ICS-formoterol as the reliever* reduces the risk of exacerbations compared with using a SABA reliever, and is a simpler regimen

STEPS 1 – 2	STEP 3	STEP 4	STEP 5
As-needed-only low dose ICS-formoterol	Low dose maintenance ICS-formoterol	Medium dose maintenance ICS-formoterol	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-formoterol, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP

RELIEVER: As-needed low-dose ICS-formoterol*

See GINA severe asthma guide

TRACK 2: Alternative CONTROLLER and RELIEVER
Before considering a regimen with SABA reliever, check if the patient is likely to adhere to daily controller treatment

STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
Take ICS whenever SABA taken*	Low dose maintenance ICS	Low dose maintenance ICS-LABA	Medium/high dose maintenance ICS-LABA	Add-on LAMA Refer for assessment of phenotype. Consider high dose maintenance ICS-LABA, ± anti-IgE, anti-IL5/5R, anti-IL4Rα, anti-TSLP

RELIEVER: As-needed ICS-SABA*, or as-needed SABA

Other controller options (limited indications, or less evidence for efficacy or safety – see text)

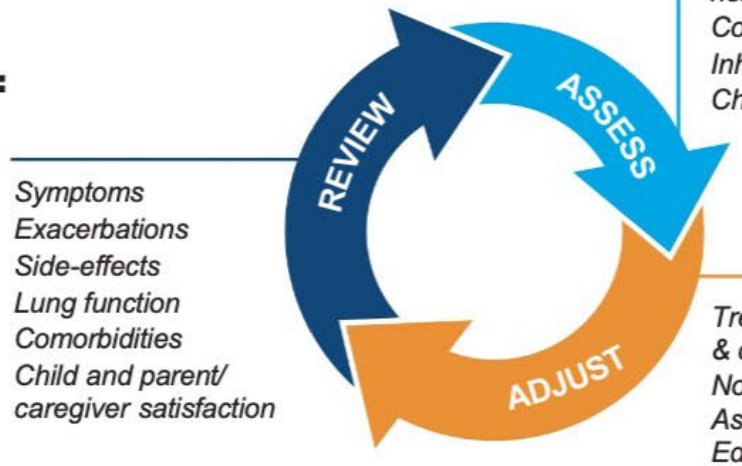
Low dose ICS whenever SABA taken, or daily LTRA†, or add HDM SLIT*	*Medium dose ICS, or add LTRA†, or add HDM SLIT*	*Add LAMA or add LTRA† or add HDM SLIT, or switch to high dose ICS-only*	*Add azithromycin (adults) or add LTRA†. As last resort consider adding low dose OCS but consider side-effects*

*Anti-inflammatory reliever; †advise about risk of neuropsychiatric adverse effects

GINA 2024 Box 4-6

GINA 2024 – Children 6–11 years

Personalized asthma management:
Assess, Adjust, Review



Confirmation of diagnosis if necessary
Symptom control & modifiable risk factors (see Box 2-2)
Comorbidities
Inhaler technique & adherence
Child and parent/caregiver preferences and goals

Symptoms
Exacerbations
Side-effects
Lung function
Comorbidities
Child and parent/ caregiver satisfaction

Treatment of modifiable risk factors & comorbidities
Non-pharmacological strategies
Asthma medications including ICS
Education & skills training

Asthma medication options:
Adjust treatment up and down for individual child's needs

	STEP 1	STEP 2	STEP 3	STEP 4	STEP 5
PREFERRED CONTROLLER to prevent exacerbations and control symptoms	Low dose ICS taken whenever SABA taken*	Daily low dose inhaled corticosteroid (ICS) (see table of ICS dose ranges for children)	Low dose ICS-LABA, OR medium dose ICS, OR very low dose ICS-formoterol maintenance and reliever therapy (MART)	Refer for expert advice, OR medium dose ICS-LABA, OR low dose ICS-formoterol maintenance and reliever therapy (MART)	Refer for phenotypic assessment ± higher dose ICS-LABA or add-on therapy, e.g. anti-IgE, anti-IL4Rα, anti-IL5
Other controller options (limited indications, or less evidence for efficacy or safety)		*Daily leukotriene receptor antagonist (LTRA†), or low dose ICS taken whenever SABA taken**	*Low dose ICS + LTRA†*	*Add tiotropium or add LTRA†*	*As last resort, consider add-on low dose OCS, but consider side-effects*
RELIEVER	As-needed SABA (or ICS-formoterol reliever* in MART in Steps 3 and 4)				

*Anti-inflammatory reliever; †advise about risk of neuropsychiatric adverse effects

COMSA parameters	T0	T1	T2	p-value (T0 vs T1; T0 vs T2)
PAQLQ, median (IQR)	69 (52;75)	103 (98;110)	130 (110;140)	<0.001*; <0.001*
ACT/cACT, median (IQR)	10 (8;12)	15 (13;19)	22 (19;23)	<0.001*; <0.001*
Severe exacerbations, median (IQR)	3.5 (2;4)	0.3 (0.1;0.7)	0.1(0;0.3)	<0.001*; <0.001*
FEV1 (z-score), median (IQR)	-0.3 (1.4;2.2)	-0.1 (0.66;1.73)	0.1 (-0.5;1.4)	0.575; 0.623

MISSING

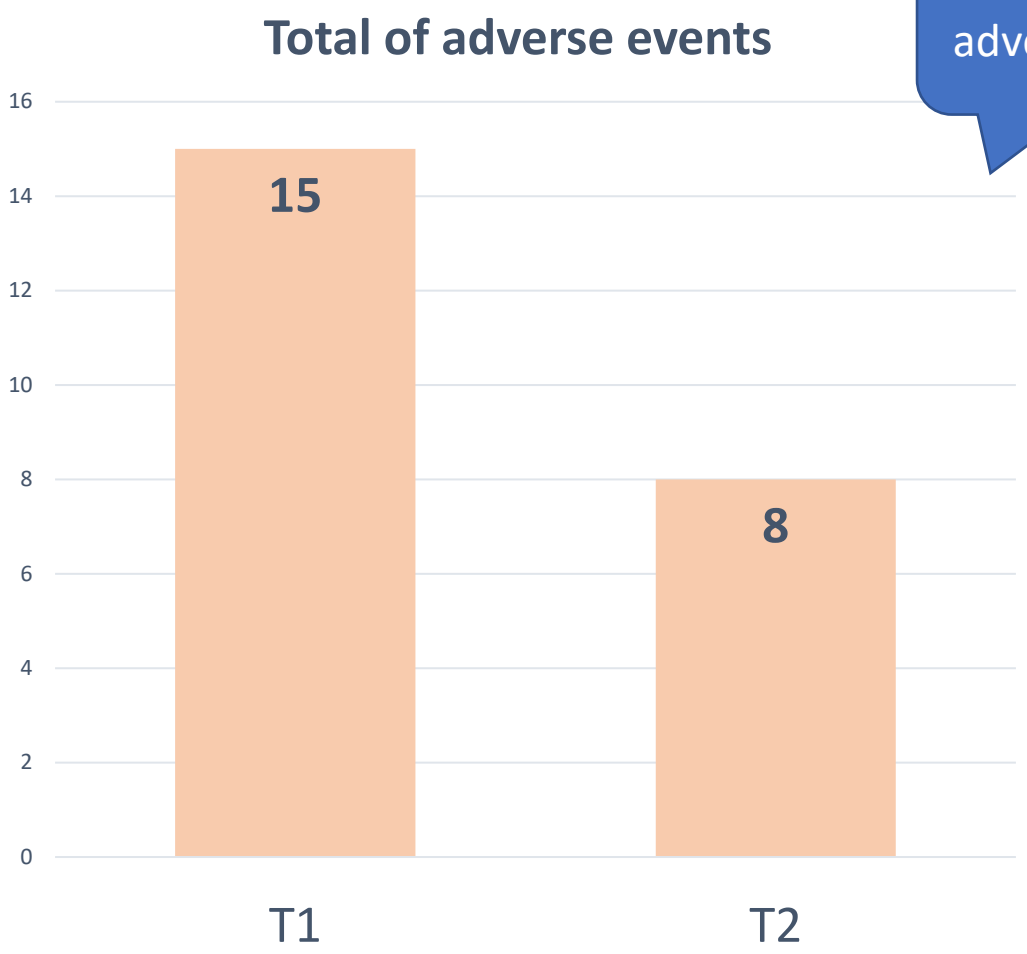
None of our patients were treated with low-dose maintenance OCS before starting biologic therapy.

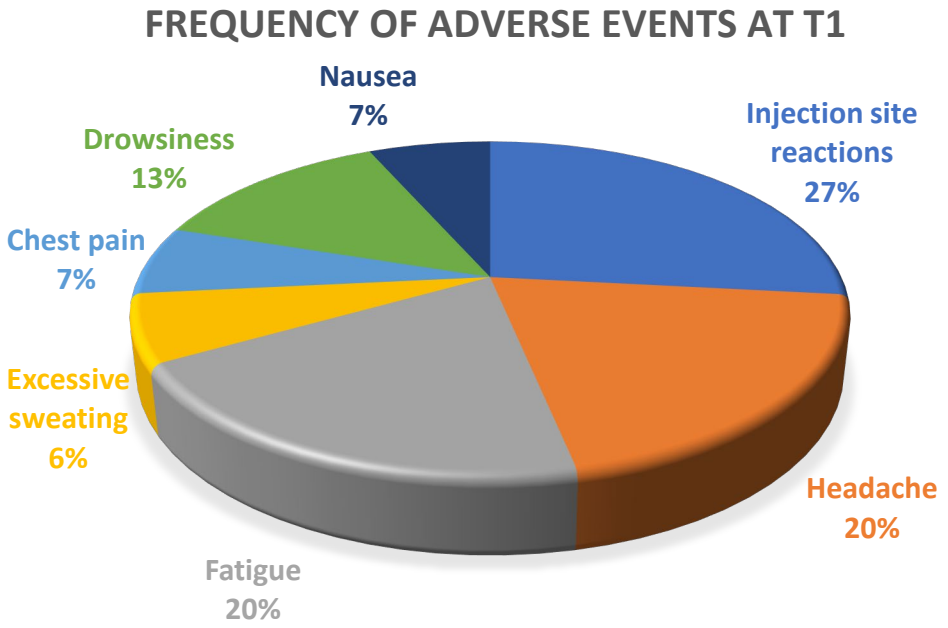
Khaleva E et al., Eur Respir J. 2023

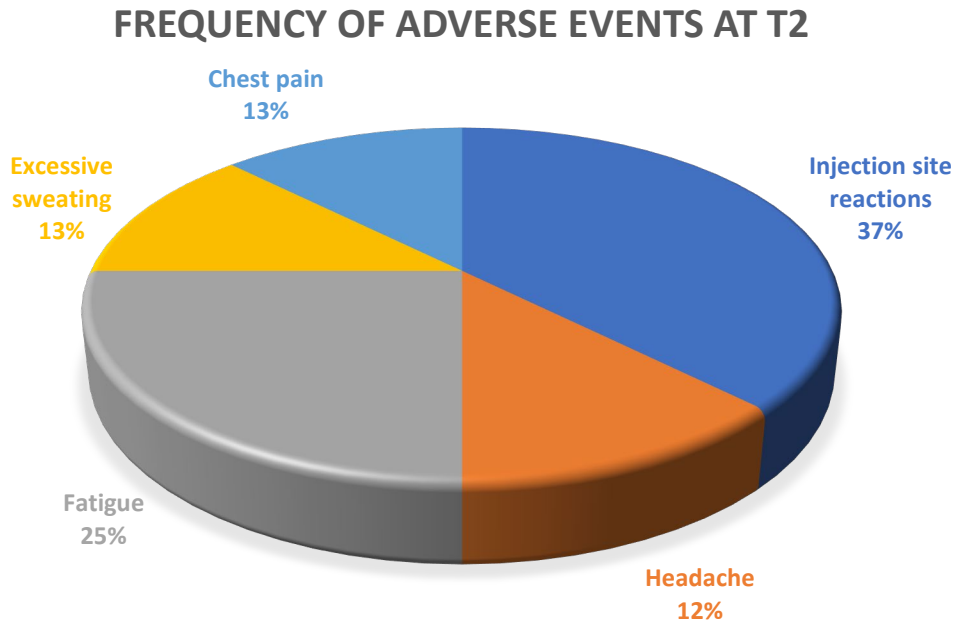
Safety

Results

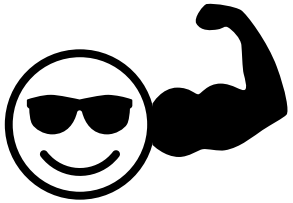
No severe adverse events







Strengths

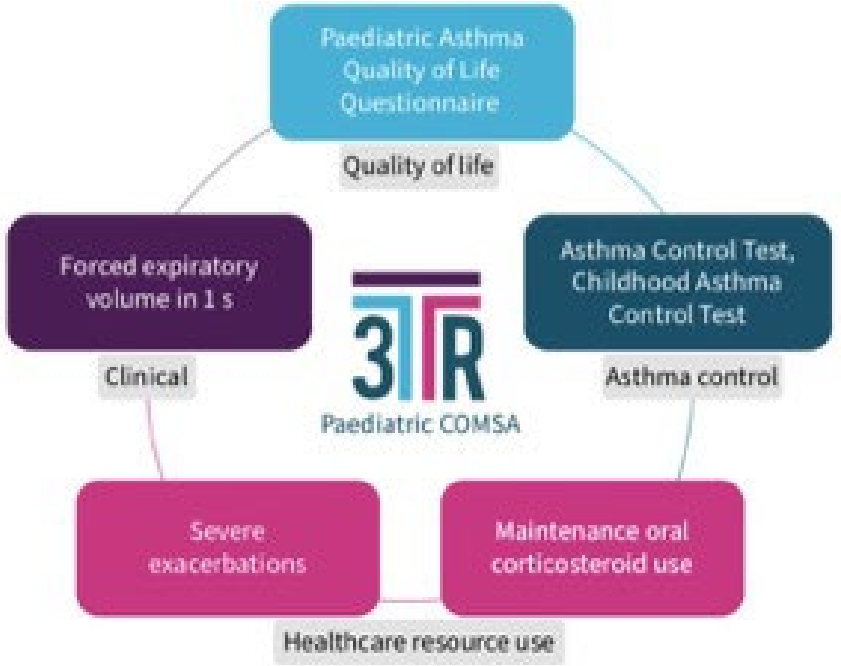


- ✓ One of the first studies to evaluate the applicability of COMSA
- ✓ Prospective, real-life
- ✓ The monocentric design ensures uniformity in patient management.

Limitations

- ✓ Limited sample size.
- ✓ Inclusion of only two biologics.
- ✓ Heterogeneity in response to biologic therapy.

Conclusions



- The pediatric COMSA parameters represent a potentially valid tool for the standardization of clinical studies.
- However, in our experience, some parameters should be updated to make them more applicable to real-world settings.
- Safety data on biologics should be considered as important outcome measures.
- Larger studies are required to validate the role of COMSA in evaluating the effectiveness of biological therapies for asthma.

Grazie per l’attenzione!