JACI IN PRACTICE – FEVEREIRO 2026

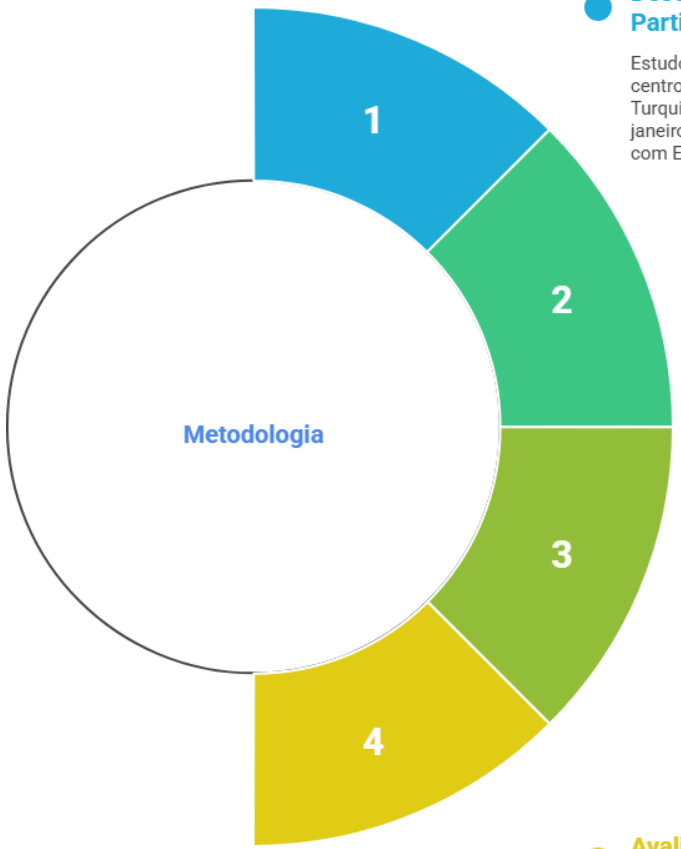
PEDRO CAMPOLINA NAHASS
RESIDENTE DE PNEUMOLOGIA DO HIJPII

Original Article

The Skin Tells the Story: Early Signs of Inborn Errors of Immunity

Zeynep Meric, MD[a], Betul Kosa, MD[b], Betul Gemici Karaaslan, MD[a], Sezin Aydemir, MD[a], Muhammed Aydin, MD[a], Dilan Demir Gumus, MD[a], Nergis Akay, MD[c], Emre Ozer, MD[d], Ahmet Kan, MD[e], Sevgi Sipahi Çimen, MD[f], Muhlis Cem Ar, MD[g], Ayse Deniz Yucelten, MD[h], Ozgur Kasapcopur, MD[c], Tugba Kevser Uzuncakmak, MD[i], Esra Yucel, MD[a], and Ayca Kiykim, MD[a] *Istanbul, Ankara, and Diyarbakır, Turkey*

Metodologia



Desenho do Estudo e Participantes

Estudo retrospectivo e de centro único realizado na Turquia entre abril/18 a janeiro/25 com 389 pacientes com EII.

Coleta de Dados e Critérios de Diagnóstico

Dados coletados por entrevistas e prontuários médicos.

Parâmetros Clínicos e Laboratoriais Analisados

Análise de dados demográficos, imunológicos e genéticos.

Avaliação das Manifestações Cutâneas

Documentação e classificação de lesões cutâneas.

RESULTADOS

- Perfil demográfico
  - 59,3% do sexo masculino
  - 63,8% era filho de pais consanguíneos
  - 40% apresentando história familiar de IDP ou morte precoce na família
- Manifestações cutâneas
  - 39.8% (155) pacientes apresentavam manifestação cutânea
  - 48,3% a lesão foi o primeiro sintoma da doença
  - Idade mediana de início das manifestações foi de 8,5 meses
  - Idade mediana de diagnóstico final foi de 49,5 meses
  - 56,7% dos pacientes apresentava múltiplas lesões

RESULTADOS

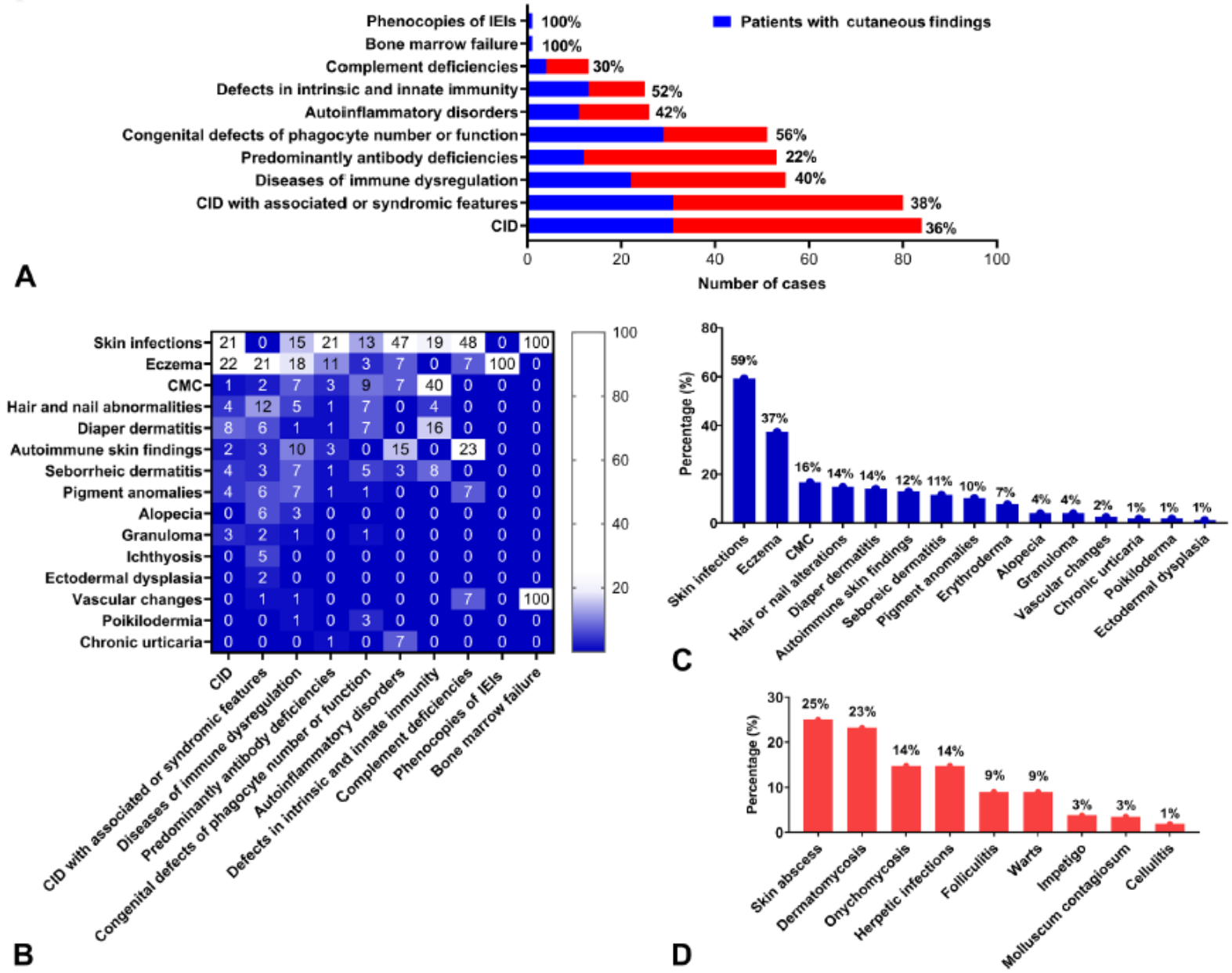


FIGURE 1. (A) Distribution of patients with cutaneous findings in various IEI groups. (B) A heatmap displaying the distribution of cutaneous findings among various IEI groups, with the numbers in each cell indicating the percentage of each feature in a given column. (C) Distribution of cutaneous findings. (D) Distribution of infectious cutaneous findings.

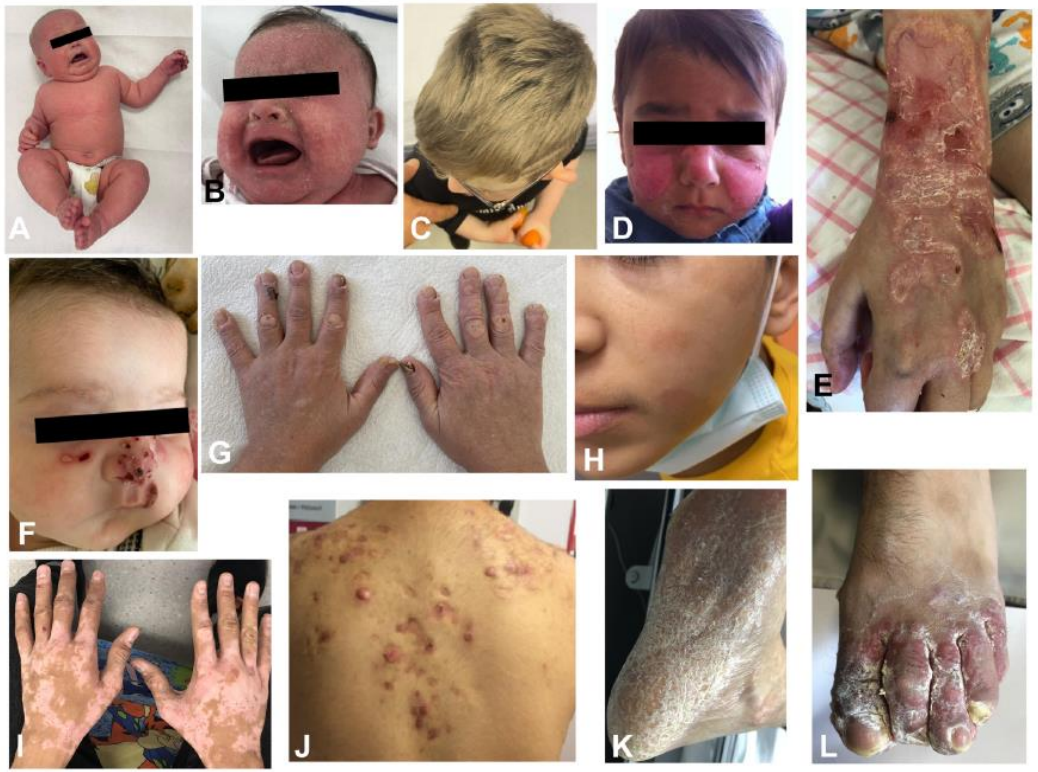


FIGURE E3. Cutaneous findings of patients. (A) Severe erythroderma in RAG1 deficiency. (B) Seborrheic dermatitis in MALT1 deficiency. (C) Hair hypopigmentation in Chediak-Higashi syndrome. (D) Severe malar rash in C1s deficiency. (E) Cutaneous granuloma in ataxia-telangiectasia. (F) Facial abscess and impetigo in CGD. (G) Recalcitrant warts in SPENCD. (H) Facial hyperpigmentation in APECED. (I) Vitiligo in DNA ligase 4 deficiency. (J) Papuloulcerative back lesions with scarring in prolidase deficiency. (K) Plantar keratoderma in poikiloderma with neutropenia. (L) Severe tinea pedis in DOCK8 deficiency. *APECED*, Autoimmune polyendocrinopathy—candidiasis—ectodermal dystrophy; *MALT1*, mucosa-associated lymphoid tissue lymphoma translocation protein 1; *SPENCD*, spondyloenchondrodysplasia with immune dysregulation.

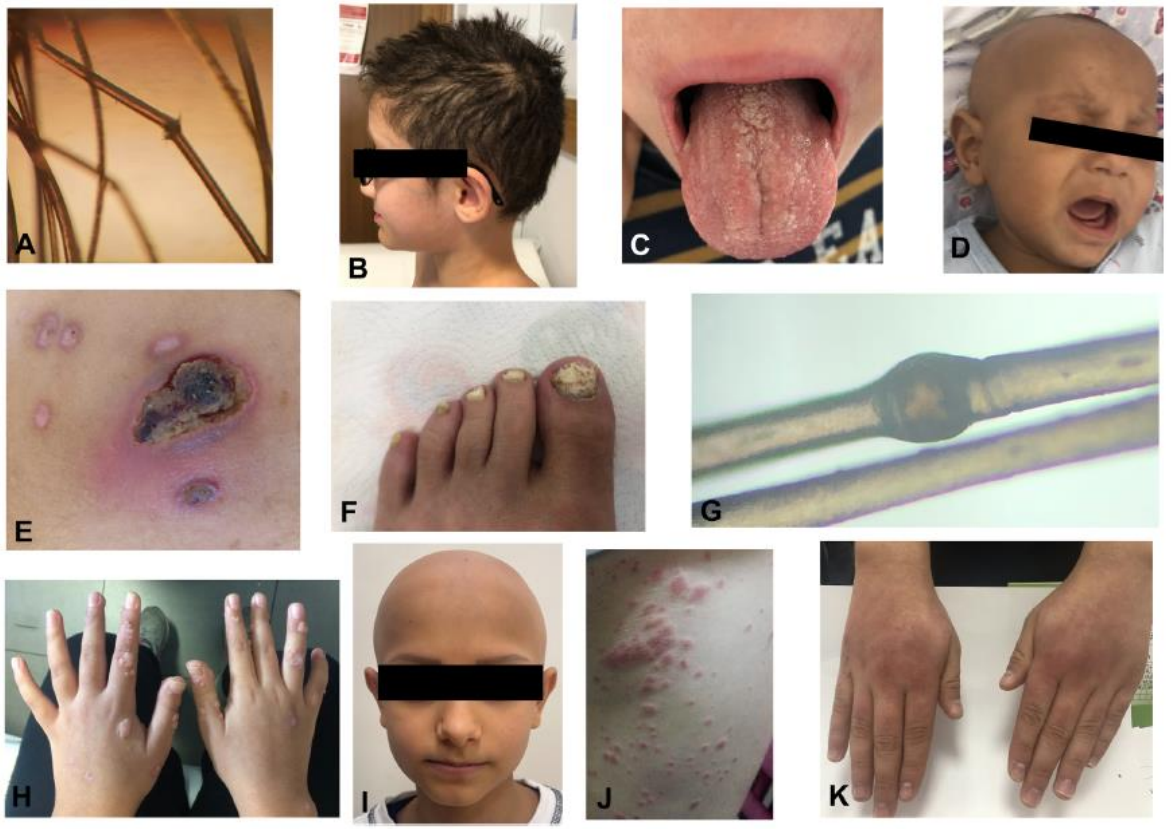
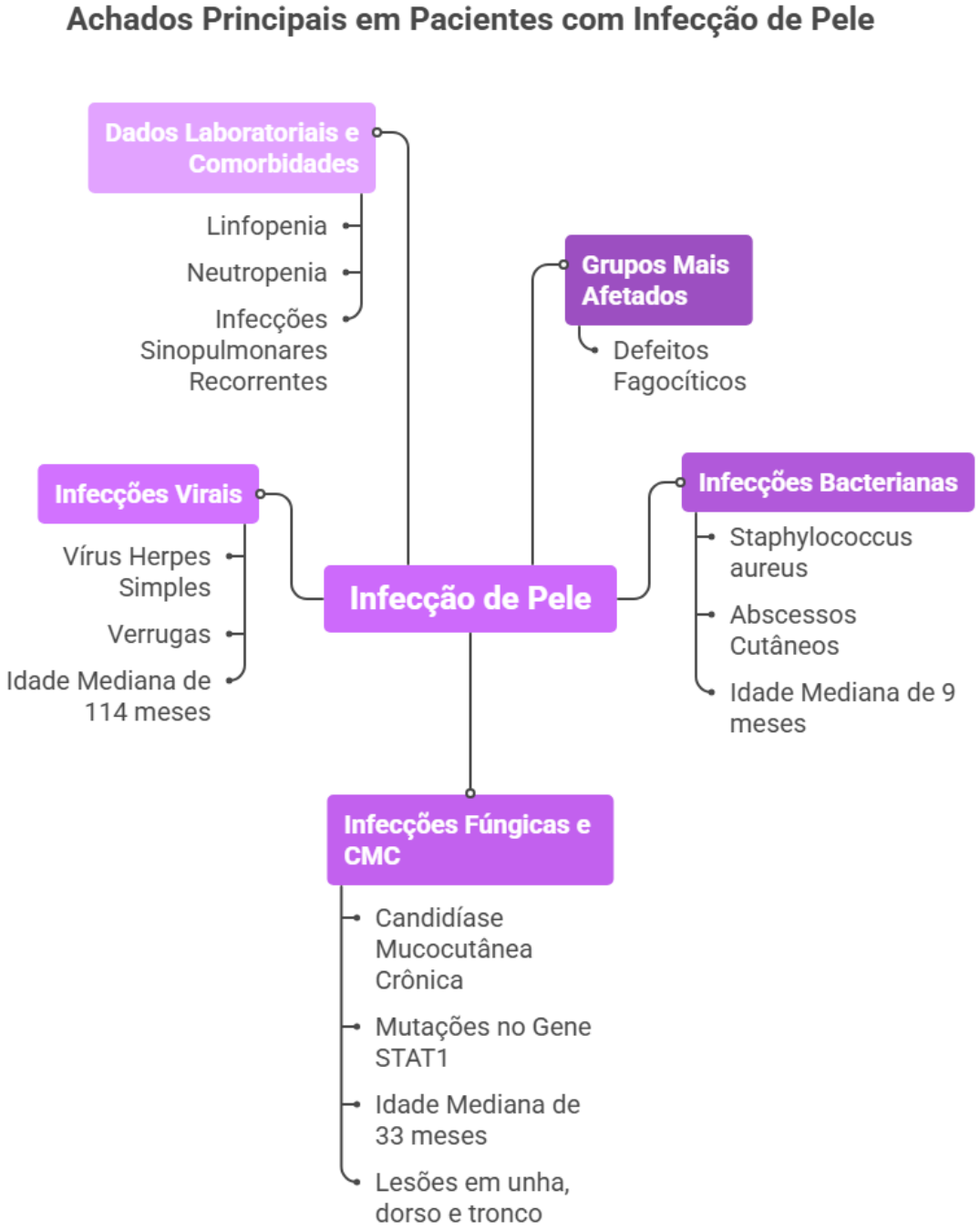
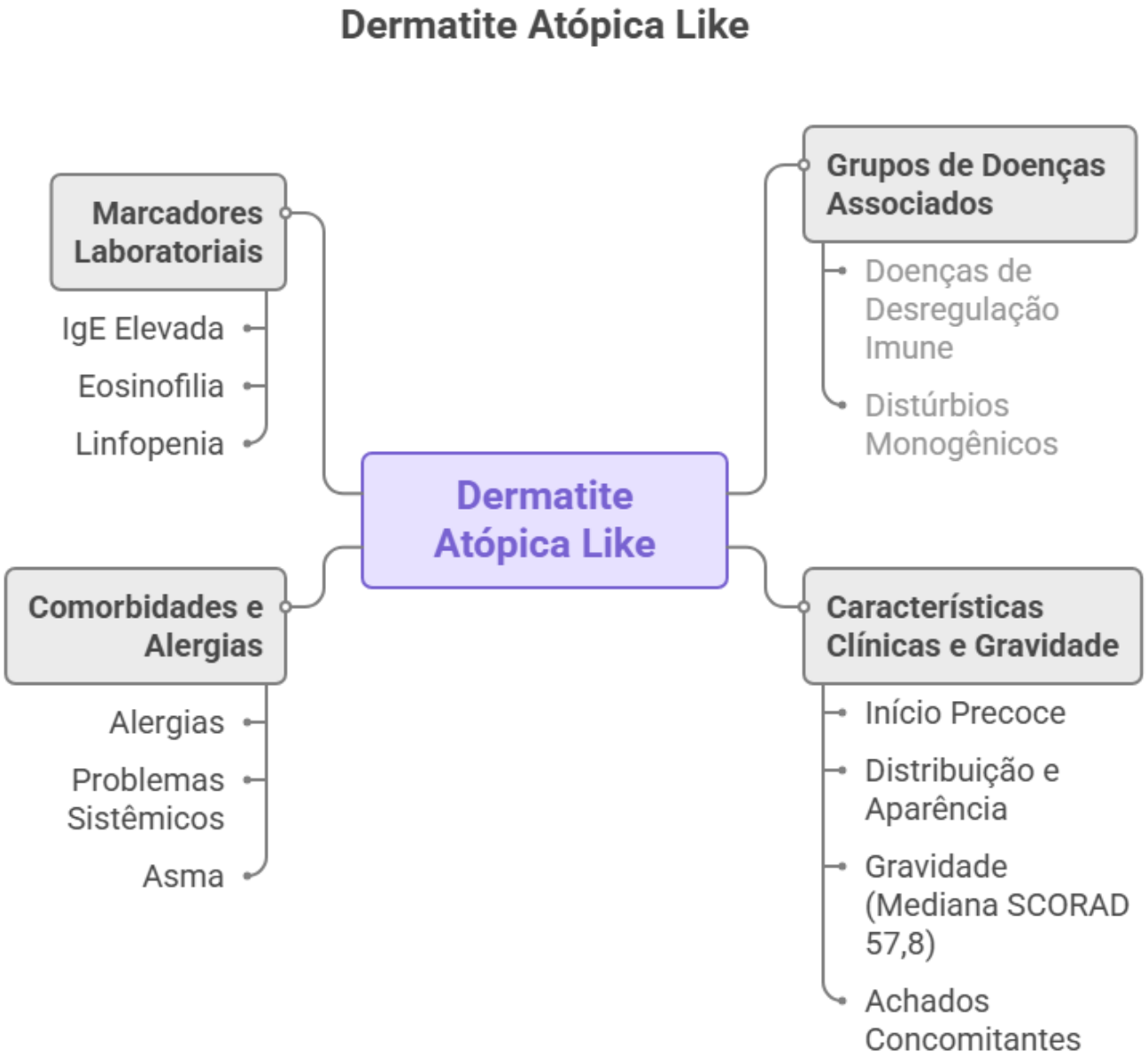


FIGURE E4. Cutaneous findings of patients. (A and B) Trichorrhexis nodosa in a patient with trichohepatoenteric syndrome. (C) CMC in IL-17RA deficiency. (D) Alopecia in FOXN1 deficiency. (E) Necrotic ulcerative lesion in ITK deficiency. (F) Onychomycosis in STAT3 GOF mutation. (G) Trichorrhexis invaginata in NS. (H) Recalcitrant warts in GATA2 deficiency. (I) Alopecia in APECED. (J and K) Vasculitic skin lesions in ADA2 deficiency, including palpable purpura and reticular livedoid changes. *FOXN1*, Forkhead box N1.

RESULTADOS


Achados Principais em Pacientes com Infecção de Pele
Dados Laboratoriais e Comorbidades
Linfopenia
Neutropenia
Infecções Sinopulmonares Recorrentes
Grupos Mais Afetados
Defeitos Fagocíticos
Infecções Virais
Vírus Herpes Simples
Verrugas
Idade Mediana de 114 meses
Infecção de Pele
Infecções Bacterianas
Staphylococcus aureus
Abscessos Cutâneos
Idade Mediana de 9 meses
Infecções Fúngicas e CMC
Candidíase Mucocutânea Crônica
Mutações no Gene STAT1
Idade Mediana de 33 meses
Lesões em unha, dorso e tronco

RESULTADOS



RESULTADOS

- Manifestações autoimunes
  - Alopecia, psoríase e vitiligo
- Anomalias de cabelo e unhas
- Granulomas
  - Alta taxa de mortalidade

RESULTADOS

- Tratamento

- Terapias definitivas e avançadas
  - Transplante de células tronco hematopoiéticas
  - Agentes biológicos
- Resposta por tipo de manifestação
  - Dermatite atópica like – resistentes ao tratamento padrão
    - Omalizumabe e dupilimab – respostas variáveis
    - Upadacitinibe – melhora em alguns pacientes

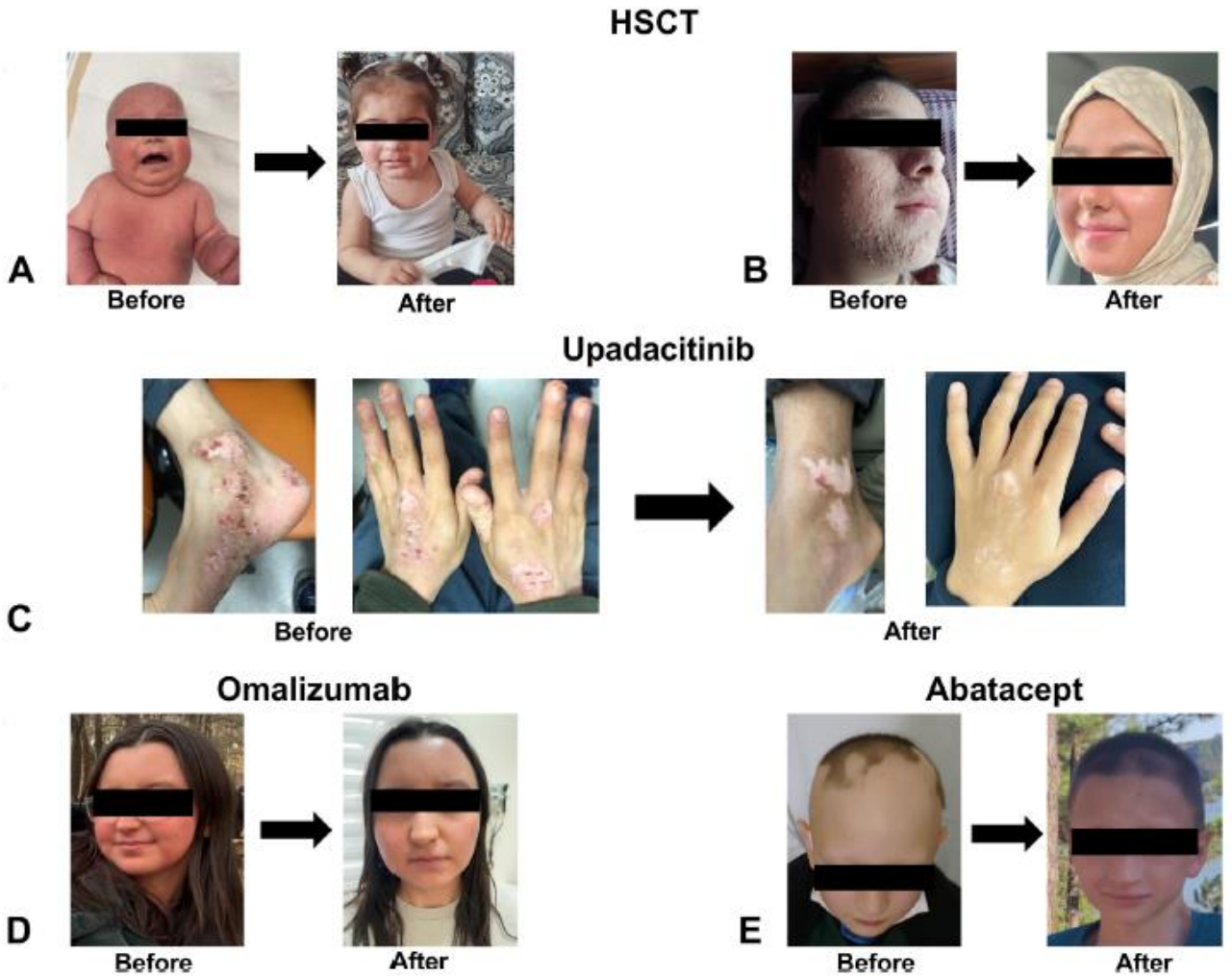


FIGURE 2. Clinical improvement following targeted therapies. (A) A patient with RAG1 deficiency showed marked resolution of erythroderma following HSCT. (B) A patient with STK4 deficiency showing clearance of extensive warts after HSCT. (C) Representative images of a patient with CARD11 LOF mutation demonstrating substantial improvement in eczema after treatment with the JAK inhibitor upadacitinib. (D) Clinical improvement following omalizumab therapy in a patient with NS. (E) Regrowth of hair and resolution of alopecia in a patient with CTLA4 deficiency after abatacept therapy.

CONCLUSÃO

- Pele como sinal de alerta precoce
- Redução do atraso diagnóstico
- Terapias direcionadas
  - Imunobiológicos
  - Transplante de células tronco hematopoiéticas
- Melhoria nos desfechos a longo prazo

Original Article

Long-Term Clinical Remission on Biologics: An Analysis of Real-World Data From the UK Severe Asthma Registry

Charlene Redmond, PhD[a], John Busby, PhD[b], Adel H. Mansur, PhD[c,d], Mitesh Patel, PhD[e], Pujan H. Patel, MD[f], Paul E. Pfeffer, PhD[g,h], Liam G. Heaney, PhD[a,i], and Hitasha Rupani, PhD[j,k], UKSAR *Belfast, Birmingham, Plymouth, London, and Southampton, United Kingdom*

METODOLOGIA

- Estudo retrospectivo e observacional
  - Dados do Registro de Asma Grave do Reino Unido
- Período
  - Janeiro/15 - Maio/22
- Critérios de inclusão
  - Idade igual ou superior a 18 anos
  - Diagnóstico de asma grave
  - Início do imunobiológico de acordo com as diretrizes nacionais
  - Pelo menos duas avaliações após início da medicação
- Critérios de exclusão
  - Paciente que receberam como parte de um ensaio clínico
  - Paciente que já fazia uso do medicamento antes do início do estudo
  - Dados insuficientes

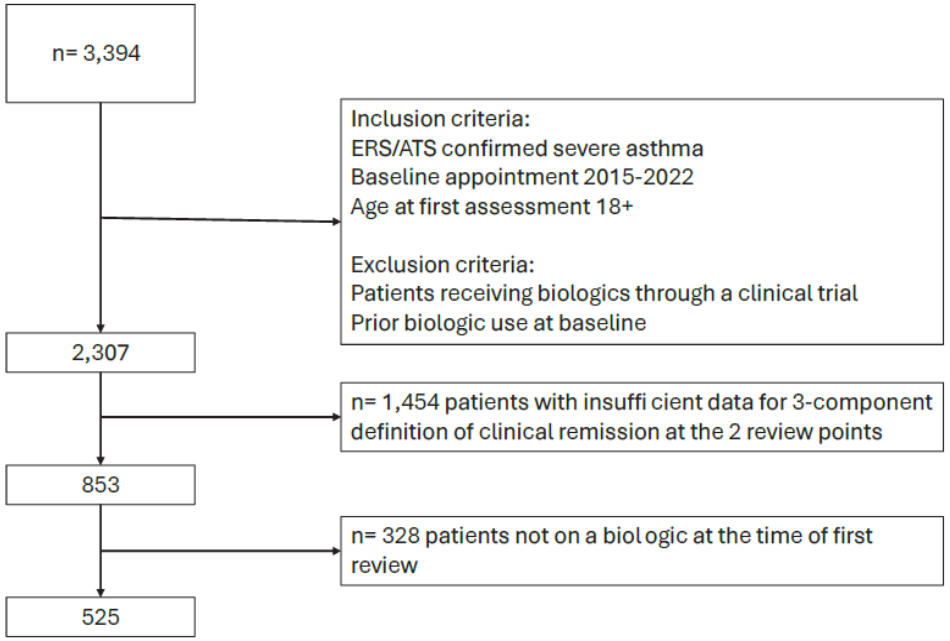


FIGURE E1. Study flowchart. *ERS/ATS,* European Respiratory Society/American Thoracic Society.

METODOLOGIA

- Definição de remissão clínica
  - Avaliada em dois momentos
    - Asma controlada - Pontuação no questionário de controle de asma <1,5 pontos
    - Ausência de exacerbações nos 12 meses anteriores à avaliação
    - Ausência de uso de corticoide oral para asma
- Avaliação temporal
  - Coleta de dados antes do início da terapia
  - Primeira avaliação entre 9 e 24 meses após início da terapia
  - Última avaliação entre 30 e 48 meses após início da terapia

RESULTADOS

TABLE I. Baseline characteristics of patients (n = 525)

Characteristic	Baseline
Sex	
Female	321 (61.4%)
Male	202 (38.6%)
Ethnicity	
Caucasian	424 (84.5%)
Non-Caucasian	78 (15.5%)
Age at first assessment (y)	51.6 (13.9%)
Age of onset (y)	
<12	143 (31.4%)
12–18	48 (10.5%)
>18	265 (58.1%)
Smoking status	
Never smoked	326 (63.2%)
Ex-smoker	170 (32.9%)
Current smoker	20 (3.9%)
BMI (kg/m^2)	30.7 (6.9)
FEV_1 (% predicted)	67.2 (21.5)
FVC (% predicted)	84.5 (19.6)
FEV_1/FVC (%)	63.6 (14.4)
ACQ-6 score	3.0 (2.2–3.8)
Blood eosinophil count ($\times 10^9$/L)	0.40 (0.20–0.63)
FeNO (ppb)	44 (23–81)
Maintenance OCS	259 (49.9%)
Median maintenance OCS dose (mg)	10 (8–15)
Exacerbations (last y)	5 (4–8)
Any ED attendance (last y)	205 (40.5%)
Any hospital admissions (last y)	199 (39.0%)
Atopic disease	283 (55.8%)
Depression or anxiety	64 (12.2%)
GERD	130 (24.9%)
Nasal polyps	134 (25.7%)

ED, Emergency department; *FeNO*, fractional exhaled nitric oxide; *FVC*, forced vital capacity.

RESULTADOS

- Taxa de remissão clínica foi de 25,1% (132) na primeira avaliação (média de 13,3 meses)
- Taxa de remissão clínica foi de 32,3% (169) na última avaliação (média de 36,1 meses)
- 45,6% (77) dos paciente que atingiram remissão na última avaliação, não apresentaram remissão na primeira avaliação
- 30% (40) dos pacientes que haviam atingido a remissão na primeira avaliação, perderam no acompanhamento a longo prazo

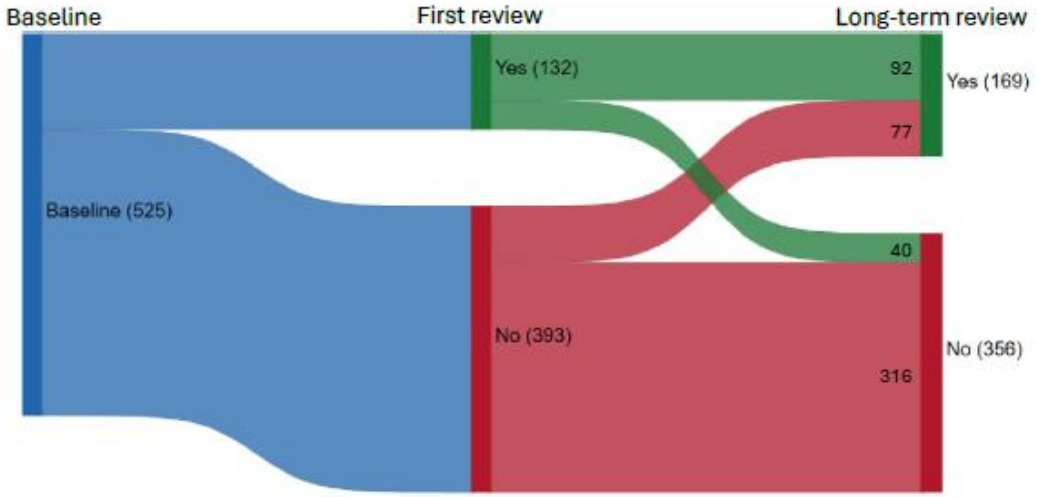


FIGURE 1. Movement between clinical remission status.

TABLE II. Baseline characteristics of patients, stratified according to remission status at first and long-term review

Characteristic	First review			Long-term review		
	No	Yes	*P* value	No	Yes	*P* value
n	393 (74.9%)	132 (25.1%)		356 (67.8%)	169 (32.2%)	
Sex						
Female	242 (61.9%)	79 (59.8%)	.677	223 (63.0%)	98 (58.0%)	.271
Male	149 (38.1%)	53 (40.2%)		131 (37.0%)	71 (42.0%)	
Ethnicity						
Caucasian	314 (84.2%)	110 (85.3%)	.769	286 (83.9%)	138 (85.7%)	.595
Non-Caucasian	59 (15.8%)	19 (14.7%)		55 (16.1%)	23 (14.3%)	
Age at first assessment (y)	50.3 (14.0)	55.1 (13.2)	**<.001**	50.2 (14.2)	54.2 (13.0)	**.002**
Age of onset (y)						
<12	117 (34.7%)	26 (21.8%)	**.017**	109 (36.5%)	34 (21.7%)	**.001**
12–18	37 (11.0%)	11 (9.2%)		34 (11.4%)	14 (8.9%)	
>18	183 (54.3%)	82 (68.9%)		156 (52.2%)	109 (69.4%)	
Smoking status						
Never smoked	235 (60.9%)	91 (70.0%)	**.014**	217 (62.0%)	109 (65.7%)	.228
Ex-smoker	131 (33.9%)	39 (30.0%)		116 (33.1%)	54 (32.5%)	
Current smoker	20 (5.2%)	0 (0.0%)		17 (4.9%)	3 (1.8%)	
BMI (kg/m^2)	31.2 (7.0)	29.1 (6.5)	**.003**	31.2 (7.0)	29.5 (6.7)	**.009**
FEV_1 (% predicted)	65.7 (21.7)	71.6 (20.3)	**.008**	65.3 (21.1)	71.2 (21.7)	**.004**
FVC (% predicted)	82.8 (19.2)	89.4 (19.9)	**.001**	82.1 (18.5)	89.3 (20.7)	**<.001**
FEV_1/FVC (%)	63.6 (14.9)	63.8 (12.7)	.877	63.8 (15.1)	63.1 (12.8)	.615
ACQ-6 score	3.3 (2.3–4.2)	2.3 (1.5–3.3)	**<.001**	3.3 (2.3–4.2)	2.5 (1.7–3.5)	**<.001**
Blood eosinophil count ($\times 10^9$/L)	0.40 (0.18–0.60)	0.46 (0.20–0.75)	0.057	0.37 (0.15–0.60)	0.49 (0.21–0.76)	**.002**
FeNO (ppb)	40 (22–79)	50 (28–86)	0.101	43 (22–76)	47 (23–91)	.096
Maintenance OCS	198 (51.0%)	61 (46.6%)	.377	192 (54.4%)	67 (40.4%)	**.003**
Maintenance OCS (mg)	10 (8, 20)	10 (5, 10)	**.001**	10 (8, 20)	10 (5, 10)	**<.001**
Exacerbations (last y)	5 (4, 9)	5 (3, 7)	**.006**	5 (4, 9)	5 (3, 8)	**.033**
Any ED attendance (last y)	162 (42.7%)	43 (33.9%)	.078	150 (44.0%)	55 (33.3%)	**.022**
Any hospital admissions (last y)	166 (43.5%)	33 (25.8%)	**<.001**	155 (44.9%)	44 (26.7%)	**<.001**
Atopic disease	214 (56.3%)	69 (54.3%)	.697	190 (55.1%)	93 (57.4%)	.622
Depression or anxiety	59 (15.1%)	5 (3.8%)	**<.001**	54 (15.3%)	10 (5.9%)	**.002**
GERD	105 (26.9%)	25 (18.9%)	.069	100 (28.2%)	30 (17.8%)	**.009**
Nasal polyps	81 (20.8%)	53 (40.2%)	**<.001**	75 (21.2%)	59 (34.9%)	**<.001**

Bold *P* values highlight analyses that are statistically signfiicant.

TABLE III. Univariate and multivariate analysis of remission at long-term review

	Univariate analysis			Multivariate analysis		
Exposure	n	Odds ratio	*P* value	n	Odds ratio	*P* value
Male	523	1.23 (0.85–1.79)	.272			
Age at assessment (y)	513	1.02 (1.01–1.04)	**.002**	436	1.02 (1.01–1.04)	**.005**
Non-Caucasian	502	0.87 (0.51–1.47)	.595			
Ex-/current smoker	516	0.85 (0.58–1.26)	.421			
Disease duration (y)	452	0.99 (0.98–1.00)	.051			
BMI (kg/m^2)	502	0.96 (0.93–0.99)	**.010**			
Obesity	502	0.64 (0.44–0.93)	**.020**			
FEV_1 (% predicted)	488	1.01 (1.00–1.02)	**.004**	436	1.01 (1.00–1.02)	**.009**
ACQ-6 score	458	0.64 (0.54–0.75)	**<.001**			
ACQ-6 uncontrolled	458	0.26 (0.14–0.48)	**<.001**	436	0.31 (0.16–0.62)	**.001**
FeNO (ppb)	443	1.00 (1.00–1.01)	**.015**			
Blood eosinophil count ($\times 10^9$/L)	509	1.94 (1.25–3.00)	**.003**			
Maintenance OCS	519	0.57 (0.39–0.83)	**.003**	436	0.53 (0.33–0.84)	**.007**
Nasal polyps	522	1.99 (1.32–2.98)	**.001**	436	1.79 (1.10–2.90)	**.018**
GERD	523	0.55 (0.35–0.87)	**.010**			
Depression/anxiety	523	0.35 (0.17–0.70)	**.003**	436	0.39 (0.16–0.91)	**.030**

Bold *P* values highlight analyses that are statistically signfiicant.

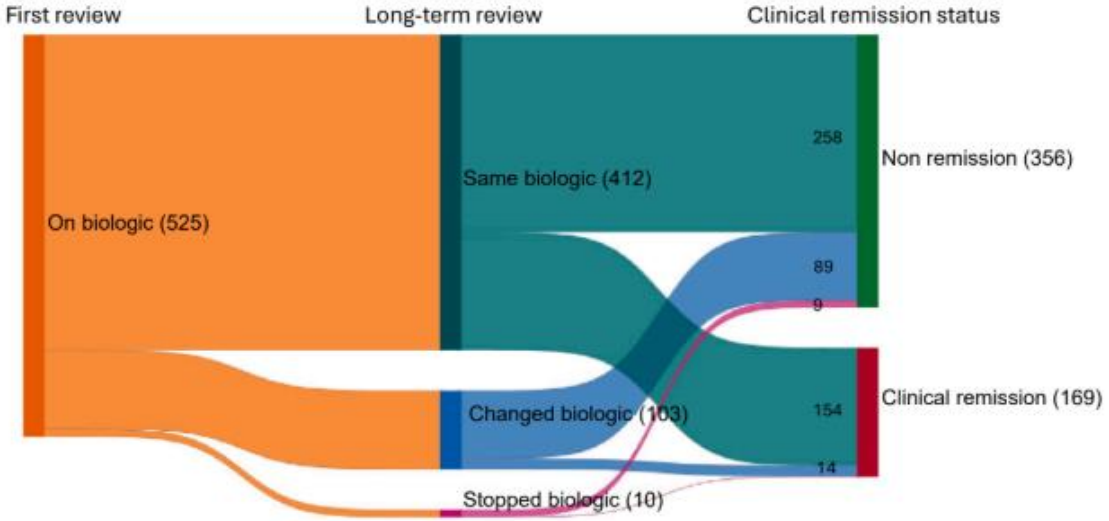


FIGURE 2. Biologic medication status and subsequent clinical remission status at the long-term review.

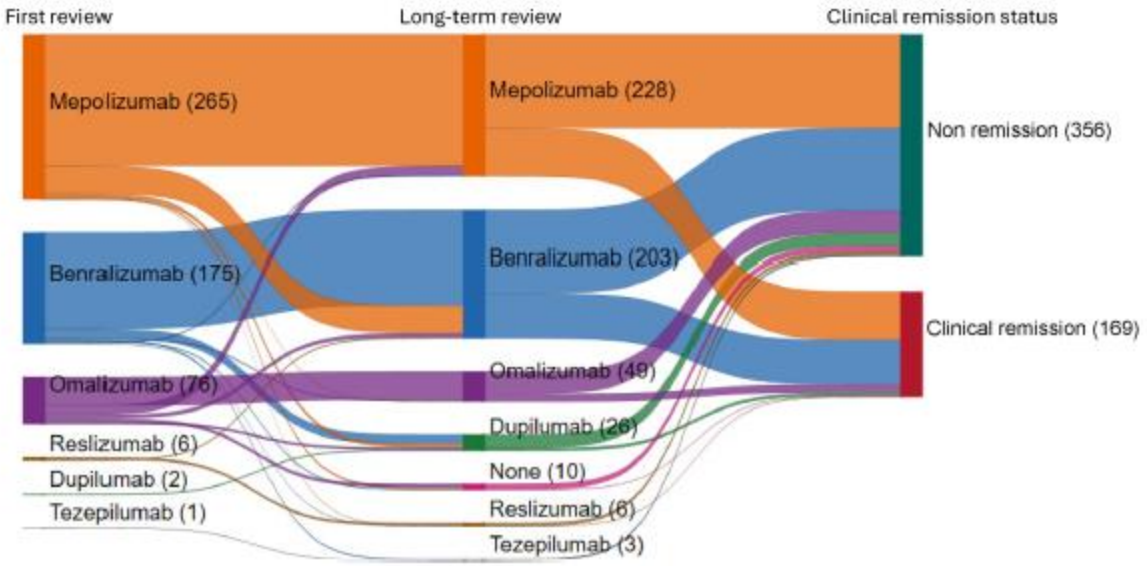


FIGURE E2. Biologic medication changes and subsequent clinical remission status at long-term remission.

TABLE IV. Patient characteristics at first review and long-term review; stratified by clinical remission status

	First review			Long-term review		
Patient characteristic	No	Yes	*P* value	No	Yes	*P* value
n	393 (74.9%)	132 (25.1%)		356 (67.8%)	169 (32.2%)	
BMI (kg/m^2)	31.6 (7.1)	29.3 (5.5)	**.006**	31.8 (7.2)	29.8 (6.4)	**.013**
Exacerbations (last y)	2 (1, 4)	0 (0, 0)	**<.001**	1 (1, 3)	0 (0, 0)	**<.001**
Rescue steroids in past year	297 (75.6%)	0 (0.0%)	**<.001**	272 (76.4%)	0 (0.0%)	**<.001**
Any ED attendance (last y)	80 (20.8%)	3 (2.3%)	**<.001**	59 (17.3%)	1 (0.6%)	**<.001**
Any hospital admissions (last y)	66 (17.2%)	3 (2.3%)	**<.001**	53 (15.6%)	0 (0.0%)	**<.001**
Blood eosinophil count ($\times 10^9$/L)	0.04 (0.00–0.12)	0.04 (0.00–0.08)	**.021**	0.03 (0.00–0.10)	0.02 (0.00–0.08)	.316
FEV_1 (% predicted)	70.6 (22.2)	82.3 (18.6)	**<.001**	72.3 (22.5)	86.4 (19.8)	**<.001**
FVC (% predicted)	84.8 (19.3)	95.9 (15.6)	**<.001**	87.2 (18.1)	96.3 (14.8)	**<.001**
FEV_1/FVC (%)	66.9 (14.4)	68.0 (12.0)	.496	66.0 (13.5)	70.8 (13.6)	**.003**
FeNO (ppb)	37 (19, 70)	37 (21–68)	.964	33 (20–60)	40 (24–68)	.100
ACQ-6 score	2.2 (1.3, 3.2)	0.3 (0.0–0.8)	**<.001**	2.2 (1.3–3.2)	0.3 (0.0–0.8)	**<.001**
Uncontrolled asthma (ACQ-6 $\geq$ 1.5)	290 (73.8%)	0 (0.0%)	**<.001**	259 (72.8%)	0 (0.0%)	**<.001**
Maintenance OCS	167 (42.5%)	34 (25.8%)	**<.001**	111 (31.2%)	23 (13.6%)	**<.001**
Maintenance OCS (mg)	8 (5–15)	5 (3–5)	**<.001**	6 (5–13)	5 (3–5)	**<.001**
Maintenance OCS > 5 mg/d	92 (55.1%)	0 (0.0%)	**<.001**	57 (51.4%)	0 (0.0%)	**<.001**

Bold *P* values highlight analyses that are statistically signfiicant.

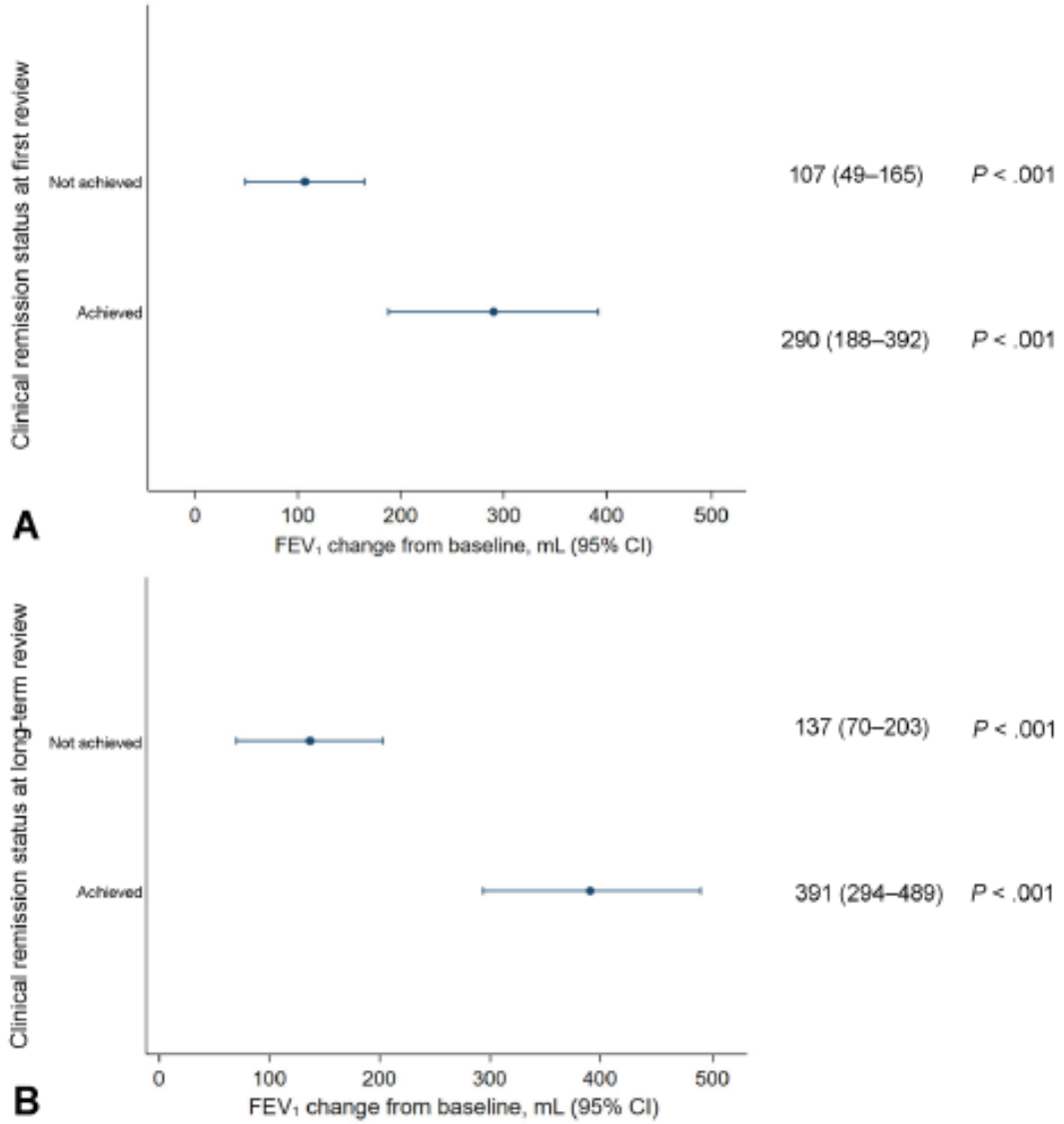


FIGURE 3. Changes in lung function between baseline and (A) first review and (B) long-term review.

- No longo prazo, a média do FEV1 previsto para quem atingiu a remissão chegou a **86,4%**, partindo de um baseline de 67,2%. Já o grupo sem remissão atingiu **72,3%** no mesmo período.

CONCLUSÃO

- Aumento progressivo das taxas de remissão
- Independência da troca de imunobiológicos
- Natureza dinâmica da remissão
- Fatores preditores e de barreira para remissão
- Importância do manejo de comorbidades
- Impacto na função pulmonar
- Limitações
  - Impacto da pandemia do COVID-19
  - Viés de seleção e ausência de dados
  - Representatividade dos imunobiológicos

Original Article

Comparative Effectiveness of Tezepelumab and Dupilumab in Asthma: A Multinational Retrospective Cohort Study

Chun-Tse Hung, MS, PharmD[a], Yu-Chien Hung, MD[b], Chen-Yen An, BPharm, RPh[c], and Chi-Won Suk, MD[d] *Ann Arbor, Mich; and Taipei, Taiwan*

METODOLOGIA

- Coorte retrospectiva multicêntrica
  - Dados de prontuários eletrônicos da rede global TriNetX
- Pacientes ≥ 18 anos que iniciaram uso do imunobiológico entre Dezembro/21 a Setembro/24.
- Incluídos apenas registro de pacientes sem resgistro de prescrição dos medicamentos no ano anterior a data da primeira prescrição
- Critérios de elegibilidade
  - Diagnóstico de asma
  - Histórico de exacerbação
  - Uso de corticoide inalatório associado a pelo menos outro medicamento de controle
- Desfechos
  - Primário: Tempo até a primeira exacerbação de asma
  - Secundário: Uso de corticoide sistêmico
- Acompanhamento por até 12 meses a partir da data de prescrição

RESULTADOS

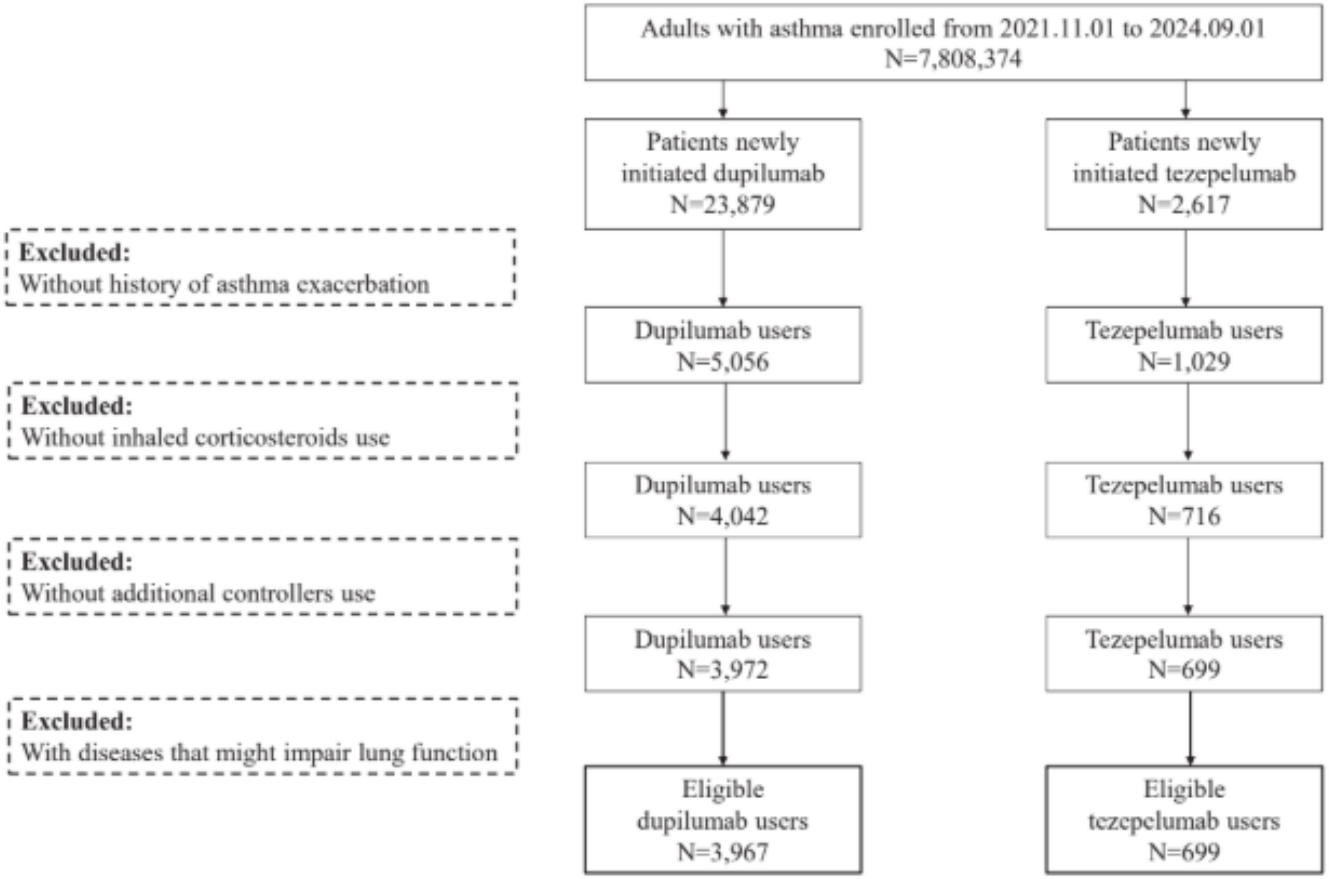


FIGURE 1. The selection of the study population.

TABLE I. Baseline characteristics of the study population

	Before PSM (N = 4666)			After PSM (N = 1376)		
	Dupilumab users (N = 3967), n (%)	Tezepelumab users (N = 699), n (%)	aSMD	Dupilumab users (N = 688), n (%)	Tezepelumab users (N = 688), n (%)	aSMD
Demographics						
Age (y), mean (SD)	48.8 (17.3)	54.2 (15.8)	0.32	54.1 (16.4)	54.0 (15.8)	0.01
Female	2595 (65.4)	542 (77.5)	0.27	524 (76.2)	533 (77.5)	0.03
Race						
White	2437 (61.4)	458 (65.5)	0.09	452 (65.7)	448 (65.1)	0.01
Black or African American	910 (22.9)	132 (18.9)	0.10	124 (18.0)	131 (19.0)	0.03
Asian	147 (3.7)	30 (4.3)	0.03	34 (4.9)	30 (4.4)	0.03
Native Hawaiian or Other Pacific Islander	27 (0.7)	10 (1.4)	0.07	10 (1.5)	10 (1.5)	0
American Indian or Alaska Native	22 (0.6)	10 (1.4)	0.09	10 (1.5)	10 (1.5)	0
Other Race	176 (4.4)	25 (3.6)	0.04	24 (3.5)	25 (3.6)	0.01
Unknown Race	248 (6.3)	40 (5.7)	0.02	41 (6.0)	40 (5.8)	0.01
Current tobacco use	113 (2.8)	14 (2.0)	0.05	17 (2.5)	14 (2.0)	0.03
BMI (kg/m^2)						
<30	1545 (38.9)	278 (39.8)	0.02	269 (39.1)	272 (39.5)	0.01
≥30	1777 (44.8)	333 (47.6)	0.06	322 (46.8)	330 (48.0)	0.02
Unknown	645 (16.3)	88 (12.6)	0.01	97 (14.1)	86 (12.5)	0.02
Blood eosinophil counts (cells/μL)						
<150	1105 (27.9)	357 (51.1)	0.49	352 (51.2)	346 (50.3)	0.02
150 to <300	895 (22.6)	163 (23.3)	0.02	161 (23.4)	160 (23.3)	<0.01
≥300	1418 (35.7)	133 (19.0)	0.38	153 (22.2)	133 (19.3)	0.07
Unknown	549 (13.8)	46 (6.6)	0.14	22 (3.2)	49 (7.1)	0.07
Comorbidities						
Chronic obstructive pulmonary disease	648 (16.3)	182 (26.0)	0.24	180 (26.2)	174 (25.3)	0.02
Hypertension	1324 (33.4)	262 (37.5)	0.09	254 (36.9)	259 (37.6)	0.02
Hyperlipidemia	674 (17.0)	141 (20.2)	0.08	138 (20.1)	139 (20.2)	0.00
Type 2 diabetes mellitus	559 (14.1)	111 (15.9)	0.05	106 (15.4)	108 (15.7)	0.01
Acute myocardial infarction	61 (1.5)	13 (1.9)	0.02	10 (1.5)	12 (1.7)	0.02
Cerebral infarction	38 (1.0)	10 (1.4)	0.04	10 (1.5)	10 (1.5)	0
Depression	568 (14.3)	113 (16.2)	0.05	105 (15.3)	110 (16.0)	0.02
Gastroesophageal reflux disease	1340 (33.8)	299 (42.8)	0.19	298 (43.3)	291 (42.3)	0.02
Hypothyroidism	349 (8.8)	75 (10.7)	0.07	73 (10.6)	72 (10.5)	0
Sleep apnea	912 (23.0)	191 (27.3)	0.10	182 (26.5)	189 (27.5)	0.02
Allergic rhinitis	945 (23.8)	180 (25.8)	0.04	181 (26.3)	176 (25.6)	0.02
Allergic conjunctivitis	43 (1.1)	14 (2.0)	0.07	11 (1.6)	13 (1.9)	0.02
Food allergy	170 (4.3)	22 (3.1)	0.06	20 (2.9)	22 (3.2)	0.02
Urticaria	149 (3.8)	22 (3.1)	0.03	26 (3.8)	22 (3.2)	0.03
Chronic sinusitis	1077 (27.1)	121 (17.3)	0.24	104 (15.1)	119 (17.3)	0.06
Nasal polyp	805 (20.3)	18 (2.6)	0.58	11 (1.6)	18 (2.6)	0.07
Atopic dermatitis	457 (11.5)	17 (2.4)	0.36	15 (2.2)	17 (2.5)	0.02
Eosinophilic esophagitis	135 (3.4)	10 (1.4)	0.13	10 (1.5)	10 (1.5)	0
Hypereosinophilic syndrome	32 (0.8)	10 (1.4)	0.06	10 (1.5)	10 (1.5)	0
Concomitant medications						
Asthma medications						
Inhaled corticosteroids	3535 (89.1)	629 (90.0)	0.03	618 (89.8)	620 (90.1)	0.01
SABA or LABA	3528 (88.9)	638 (91.3)	0.08	632 (91.9)	627 (91.1)	0.03
Prednisone	3018 (76.1)	604 (86.4)	0.27	603 (87.6)	593 (86.2)	0.04
Leukotriene receptor antagonists	2089 (52.7)	413 (59.1)	0.13	419 (60.9)	406 (59.0)	0.04
Tiotropium	929 (23.4)	237 (33.9)	0.23	236 (34.3)	234 (34.0)	0.01
Umeclidinium	767 (19.3)	243 (34.8)	0.35	233 (33.9)	234 (34.0)	<0.01
Xanthines	73 (1.8)	16 (2.3)	0.03	22 (3.2)	16 (2.3)	0.05
Antihypertensives	284 (7.2)	63 (9.0)	0.07	61 (8.9)	61 (8.9)	0
Antihyperlipidemic agents	831 (20.9)	188 (26.9)	0.14	176 (25.6)	183 (26.6)	0.02
Antidiabetic agents	708 (17.8)	141 (20.2)	0.06	147 (21.4)	136 (19.8)	0.04
Nonsteroidal anti-inflammatory drug	1207 (30.4)	229 (32.8)	0.05	236 (34.3)	228 (33.1)	0.02
Proton pump inhibitors	1286 (32.4)	283 (40.5)	0.17	271 (39.4)	277 (40.3)	0.02

aSMD, Absolute standardized mean difference; *BMI*, body mass index; *LABA*, long-acting β_2-agonist; *PSM*, propensity score matching; *SABA*, short-acting β_2-agonist; *SD*, standard deviation.

RESULTADOS

	Number of events/total number of patients (%)		
	Dupilumab	Tezepelumab	HR (95% CI)
Main analysis	368/688 (53.5)	379/688 (55.1)	0.96 (0.83, 1.10)
Sensitivity analyses			
(1)- Change the follow-up period			
6 months	273/688 (39.7)	288/688 (41.9)	0.95 (0.80, 1.12)
15 months	390/688 (56.7)	399/688 (58.0)	0.96 (0.83, 1.10)
18 months	403/688 (58.6)	410/688 (59.6)	0.96 (0.84, 1.10)
(2)- Exclude patients with other indications for dupilumab	193/353 (54.7)	179/353 (50.7)	1.16 (0.95, 1.42)

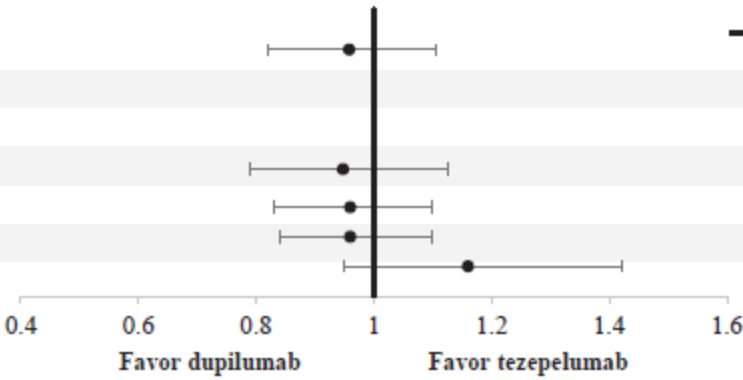


FIGURE 2. Comparative effectiveness in reducing asthma exacerbations among patients with asthma in the matched cohorts (main and sensitivity analyses). *CI*, Confidence interval; *HR*, hazard ratio.

RESULTADO

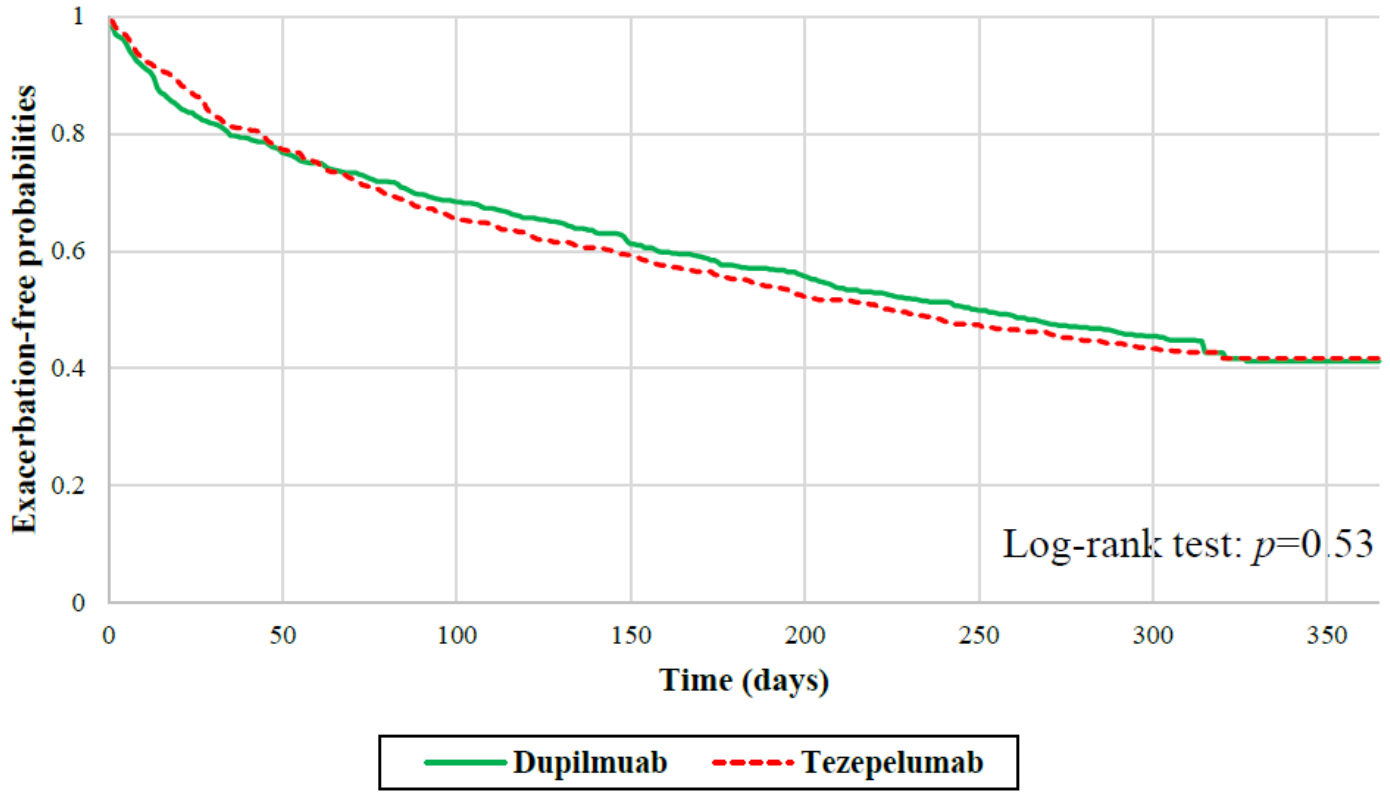


FIGURE E2. Comparisons of exacerbation-free probabilities of asthma exacerbations among patients with asthma in the matched cohorts: main analysis.

RESULTADO

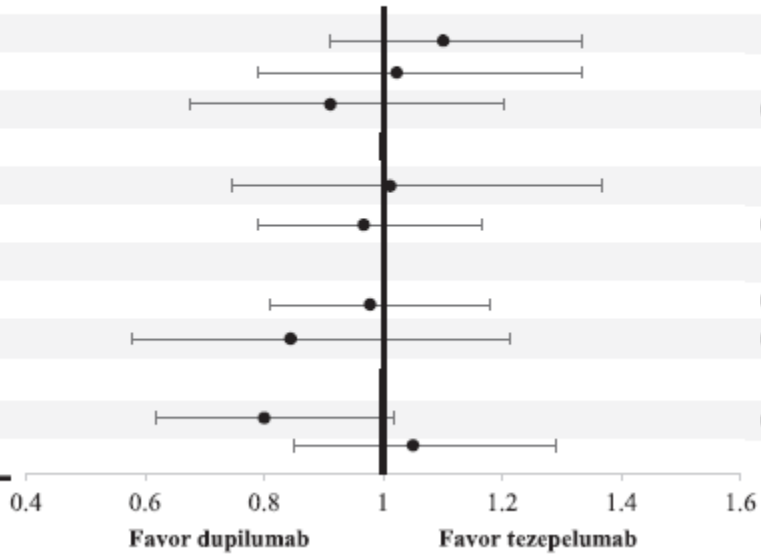
TABLE E5. Comparative effectiveness between dupilumab versus tezepelumab among patients with asthma: results from the Cox regression models (secondary outcome)

	Before PSM				After PSM			
Systemic corticosteroid use	No. of patients	No. of events (%)	Mean follow-up days (SD)	Unadjusted HR (95% CI)	No. of patients	No. of events (%)	Mean follow-up days (SD)	Adjusted HR (95% CI)
Dupilumab	3967	2464 (62.1)	346.8 (62.0)	0.74 (0.67, 0.81)	688	495 (71.9)	347.9 (60.4)	0.97 (0.85, 1.10)
Tezepelumab	699	515 (73.7)	347.2 (59.5)	Reference	688	504 (73.3)	346.9 (59.9)	Reference

CI, Confidence interval; *HR*, hazard ratio; *PSM*, propensity score matching; *SD*, standard deviation.

RESULTADOS

	Number of events/total number of patients (%)		
	Dupilumab	Tezepelumab	HR (95% CI)
(1)- Blood eosinophil counts (cells/µL)			
<150	250/423 (59.1)	240/423 (56.7)	1.09 (0.92, 1.30)
≥150–<300	130/224 (58.0)	134/224 (59.8)	1.02 (0.81, 1.30)
≥300	113/289 (39.1)	123/289 (42.6)	0.92 (0.71, 1.18)
(2)- Presence of COPD			
With COPD	99/170 (58.2)	104/170 (61.2)	1.01 (0.77, 1.33)
Without COPD	258/499 (51.7)	264/499 (52.9)	0.97 (0.81, 1.15)
(3)- Prior biologics use			
Biologics-naïve	276/534 (51.7)	286/534 (53.6)	0.98 (0.83, 1.16)
Biologics-experienced	67/131 (51.1)	77/131 (58.8)	0.86 (0.62, 1.19)
(4)- Obesity (BMI, kg/m^2)			
<30	114/248 (46.0)	139/248 (56.0)	0.80 (0.62, 1.02)
≥30	173/308 (56.2)	173/308 (56.2)	1.05 (0.85, 1.29)



CONCLUSÃO

- Não há diferença significativa no risco de exacerbações de asma
- Consistência em subgrupos
- Risco de uso de corticoide sistêmico foi semelhante
- Alinhamento com evidências prévias
- Limitações
  - Natureza retrospectiva
  - Potencial de classificação incorreta
  - Dados baseado em registros de prescrição
  - Ausência de dados
  - Viés de canalização
    - Tezepelumabe é mais novo

Theme Editorial

The Next Frontier Is Here: Targeted Systemic Therapies for Allergic and Immunologic Diseases

Tara F. Carr, MD[a,b], and Peck Y. Ong, MD[c,d] *Tucson, Ariz; and Los Angeles, Calif*

PRINCIPAIS TÓPICOS

- Necessidade de terapias sistêmicas
  - Tratamento tópicos têm eficácia limitada em doenças graves ou complexas
- Avanços na biologia molecular
- Novas aplicações e alvos terapêuticos
  - Reutilização de medicamentos existentes para novas indicações
  - Novos alvos terapêuticos
- Perspectivas futuras

Clinical Management Review

Systemic Treatments for Chronic Spontaneous Urticaria: Anti-IgE and Beyond

Florence Ida Hsu, MD[a], Jonathan A. Bernstein, MD[b], Krishan D. Chhiba, MD, PhD[c,d], and Sarbjit S. Saini, MD[e] *New Haven, Conn; Cincinnati, Ohio; Chicago, Ill; and Baltimore, Md*

INTRODUÇÃO

- Presença de lesões urticariformes, associadas ou não com angioedema, que ocorrem na maioria dos dias por mais de 6 semanas
- Urticária crônica espontânea X Urticária crônica induzida
- Tratamento atual e limitações
- Patogênese
  - Autoalérgico (Tipo I) X autoimune (Tipo II)
  - Ativação do receptor de IgE de alta afinidade
  - Liberação de histamina
- Necessidade de novas terapias

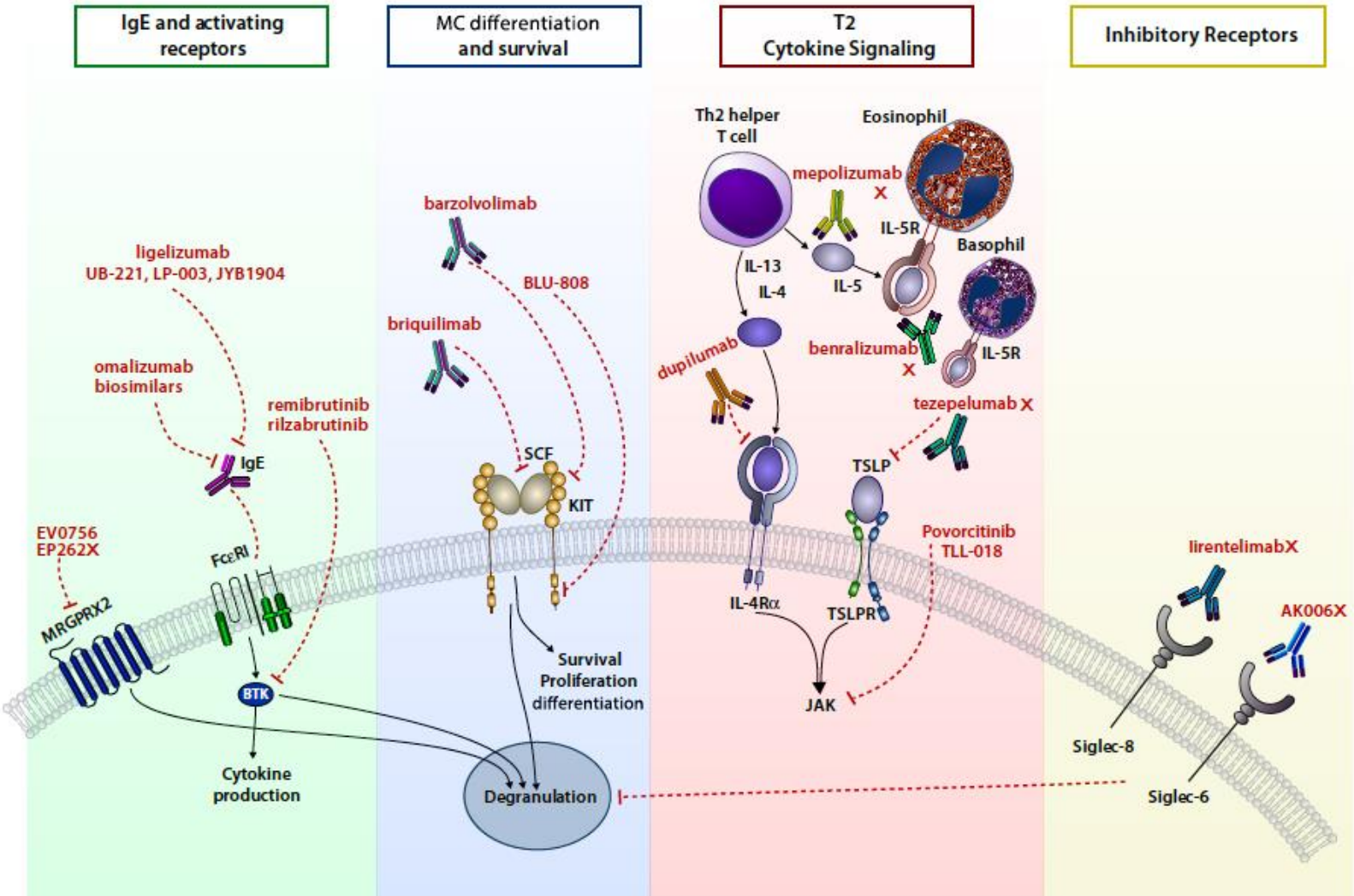


FIGURE 1. Targeted pathways and receptors in chronic urticaria. *BTK*, Bruton's tyrosine kinase; *FcεRI*, high-affinity IgE receptor; *JAK*, Janus kinase; *MC*, mast cell; *SCF*, stem cell factor; *TSLP*, thymic stromal lymphopoietin. *X*, failed or discontinued in clinical trials. Reproduced from Chhiba and Saini,[22] with permission.

TABLE I Summary of therapeutic targets approved or emerging in refractory CSU

Therapy	Target	Biopredictors	Side effects/monitoring	Patient profiles	Dosing
Omalizumab	Free IgE	Negative: • Low IgE • Basopenia • CU index positive • High BMI	Side effects: • Anaphylaxis 0.2%, epinephrine autoinjector advised • Injection site reactions • Headache • Arthralgias Monitoring: first 3 doses in office	• Age ≥12 years • Pregnant or planning pregnancy • Concomitant food allergy, asthma, or CRSwNP	Subcutaneous: 150-300 mg every 4 weeks, updose or shorten interval if partial response after 12 weeks
Cyclosporine (off-label use)	Inhibits IgE pathway of MCs/ basophils/ T-cell activation	Positive: ASST or CU index positive	Side effects: • Hypertension • Headache • Nausea/vomiting/abdominal pain • Tremors • Paresthesia • Renal dysfunction Monitoring: • Renal function • Blood pressure • CBC/ lipids • CYP3A4 caution	Omalizumab-refractory	Oral: 1-5 mg/kg/d
Remibrutinib	BTK	None identified: effective across IgE levels, omalizumab-refractory, positive CU index	Side effects: • URIs • Headache • Nausea/abdominal pain • Bleeding (petechiae) • Stop pre- and post-surgery • Avoid if hepatic impairment • Avoid live virus vaccines; for nonlive vaccines, consider discontinuing therapy for 3 weeks with vaccine administration performed 1 week after stopping Monitoring: • None required • Consider baseline CBC and LFTs • CYP3A4 caution	• Age ≥18 years • Omalizumab-refractory, possible CIndU benefits • Low IgE • CU index positive • Caution in pregnancy • Caution in mild, moderate, or severe hepatic impairment (Child-Pugh Class A, B, and C)	Oral: 25 mg twice daily
Dupilumab	IL-4 receptor alpha	Effective in low- and high-IgE patients	Side effects: • Injection site reactions • Conjunctivitis, facial dermatitis, headache, URIs, arthralgias • Eosinophilia Monitoring: none	• Age ≥12 years • Omalizumab naïve • Atopic comorbidities (atopic dermatitis, prurigo nodularis, EoE, Asthma, or CRSwNP)	Subcutaneous: 600 mg once, then 300 mg every 2 weeks
Barzolvolimab	c-Kit inhibitor	Under investigation	Side effects: • Hair and skin pigment changes (lightening) • Taste alteration • Neutropenia • Effects on spermatogenesis Monitoring: • CBC • Fertility counseling	• Phase 3 ongoing in CSU • Potential efficacy in CIndU	Subcutaneous: 300 mg once, then 150 mg every 4 weeks, or 450 mg once, then 300 mg every 8 weeks

ASST, Autologous serum skin test; *BMI*, body mass index; *BTK*, Bruton's tyrosine kinase; *CBC*, complete blood count; *CIndU*, chronic inducible urticaria; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *CSU*, chronic spontaneous urticaria; *CU*, chronic urticaria; *CU index*, chronic urticaria index; *EoE*, eosinophilic esophagitis; *LFT*, liver function test; *MC*, mast cell; *URI*, upper respiratory infection.

CONCLUSÃO

- Novas opções terapêuticas imediatas
  - Aprovação do biossimilar do omalizumabe (CT-P39), do dupilumabe e do remibrutinibe
- Superação da resistência ao omalizumabe
  - Terapias que visam sinalizações abaixo do receptor de IgE conseguiram obter sucesso
- Eficácia da depleção de mastócitos
  - Inibidores de c-Kit demonstraram que a depleção física dos mastócitos é altamente eficaz e pode induzir remissão duradoura
- Aprendizado com falhas terapêuticas
  - Terapias voltadas apenas para eosinófilos ou receptores inibitórios isolados sugere que o bloqueio funcional por ser insuficiente, se os mastócitos permanecem na pele puderem ser ativados por vias alternativas
- Transição para a medicina de precisão
- Necessidade de dados de longo prazo

Clinical Management Review

Systemic Therapy for Atopic Dermatitis: Choosing Biologics or Janus Kinase Inhibitors for Children and Adults

Irene M. Scholl, MD[a], Aaron M. Drucker, MD, PhD[b,c], Carsten Flohr, MD, PhD[d], and Louise A.A. Gerbens, MD, PhD[a]

Amsterdam, The Netherlands; Toronto, Ontario, Canada; and London, United Kingdom

ALVOS IMUNOLÓGICOS DAS TERAPIAS SISTÊMICAS

- Interação complexa entre elementos genéticos, imunológicos e ambientais
  - Quebra da barreira epitelial e desequilíbrio do sistema imuno tipo 2
- Principais alvos
  - Predomínio de células Th2
  - Interleucinas Il-4, IL-13 (suprime expressão da filagrina) e IL-31 contribuem para inflamação e prurido
  - Via de sinalização JAK-STAT
    - JAK1 - sinalização de citocinas que impulsionam o prurido
    - JAK 2 – Utilizada pela IL-5, que é responsável pela ativação de eosinófilos
  - Outras vias inflamatórias - TH22 e TH1/TH17

ALGORITMO PARA TRATAMENTO SISTÊMICO

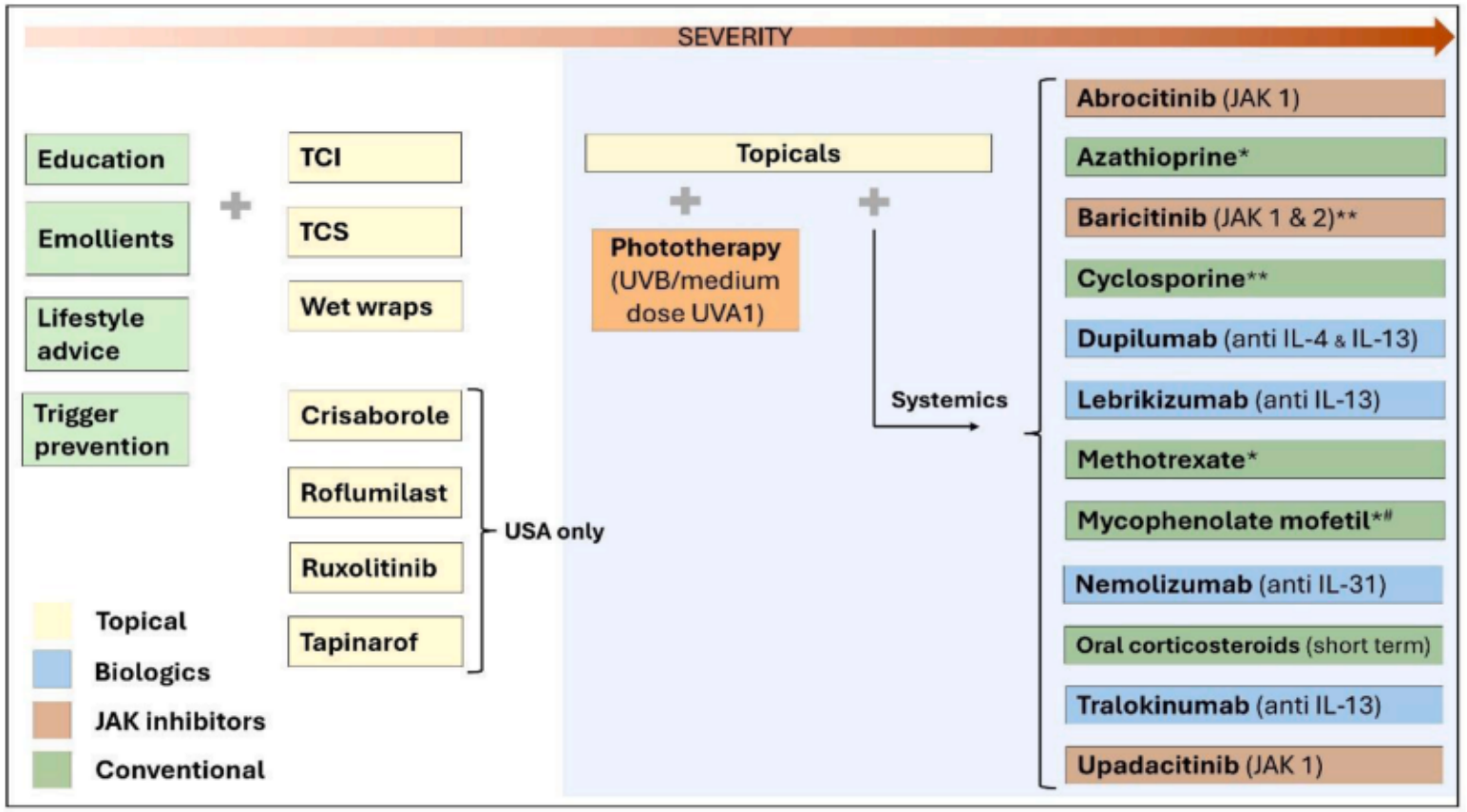


FIGURE 2. Stepped-care plan for adults with atopic dermatitis (AD). All treatment options are listed in alphabetical order. For children, systemic options include abrocitinib, cyclosporine, dupilumab, lebrikizumab, methotrexate, and upadacitinib. Dupilumab is approved from age 6 months and older in the United States and, in Europe only for severe AD (otherwise from age 12 years on). Baricitinib is approved only in Europe but, like cyclosporine and methotrexate, may be used from age 2 years on. Abrocitinib, lebrikizumab, and upadacitinib are approved from 12 years on. Nemolizumab is approved from age 12 years and older in the United States and the United Kingdom, but in the rest of Europe from age 18 on, whereas tralokinumab is approved from age 12 years in Europe and age 18 years in the United States. *TCI*, topical calcineurin inhibitors; *TCS*, topical corticosteroids. *Off-label; **on-label in Europe; #rarely used currently.

TABLE I. Option grid: Comparison of targeted systemic treatment options for atopic dermatitis[4,13,23]

	Biologics				Janus kinase inhibitors		
	Dupilumab	Lebrikizumab	Nemolizumab	Tralokinumab	Abrocitinib	Baricitinib	Upadacitinib
Best efficacy short-term (Eczema Area and Severity Index)†	■	■			■		■
Comorbidities							
Asthma, chronic rhinosinusitis with nasal polyps, eosinophilic esophagitis, chronic spontaneous urticaria, prurigo nodularis	■		■ Only prurigo nodularis				
Rheumatoid arthritis, uveitis, psoriatic arthritis, axial spondylarthritis, inflammatory bowel disease, polyarticular juvenile idiopathic arthritis, giant cell arteritis					□ Potential effect but not approved	■ Rheumatoid arthritis, juvenile idiopathic arthritis	■
Alopecia areata	□ Potential effect in case of elevated IgE but not approved					■	
Active malignancy	□	□	□	□	■	■	■

(continued)

TABLE I. *(Continued)*

	Biologics				Janus kinase inhibitors		
	Dupilumab	Lebrikizumab	Nemolizumab	Tralokinumab	Abrocitinib	Baricitinib	Upadacitinib
At risk for developing malignancy (including malignancy in medical history apart from non-melanoma skin cancer)	☐	☐	☐	☐	🟧	🟧	🟧
Serious infections	☐	☐	☐	☐	🟥	🟥	🟥
At risk for serious infections	☐	☐	☐	☐	🟧	🟧	🟧
Recurrent herpes zoster infections in medical history (unless vaccination)	☐	☐	☐	☐	🟧	🟧	🟧
Untreated (latent) tuberculosis	☐	☐	☐	☐	🟥	🟥	🟥
History of atherosclerotic cardiovascular disease or at risk (including smoking)	☐	☐	☐	☐	🟧	🟧	🟧
History of gastrointestinal perforation or diverticulitis	☐	☐	☐	☐	🟧	🟧	🟧

Severe kidney failure (estimated glomerular filtration rate >15 and >30 mL/min)							
Severe liver cirrhosis							
Moderate to severe ocular surface disease							
Pregnancy							
Active pregnancy							
Breastfeeding							
Other characteristics							
Age >65 y							
Children							

(continued)

TABLE I. *(Continued)*

	Biologics				Janus kinase inhibitors		
	Dupilumab	Lebrikizumab	Nemolizumab	Tralokinumab	Abrocitinib	Baricitinib	Upadacitinib
Adolescents	■	■	■*	■**	■	■**	■
Fast time of onset					□	□	□
Intermittent or short treatment					□	□	□
Less monitoring	□	□	□	□	■	■	■
Fear of needles	■	■	■	■			
Recent or planned vaccination with live vaccine	□	□	□	□	■	■	■

■ very favorable, □ favorable, ■ less favorable, ■ uncertain, ■ not favorable.

*Only in the United States.
**Only in Europe.
†Based on surface under the cumulative ranking curve values at 16 wk of treatment.

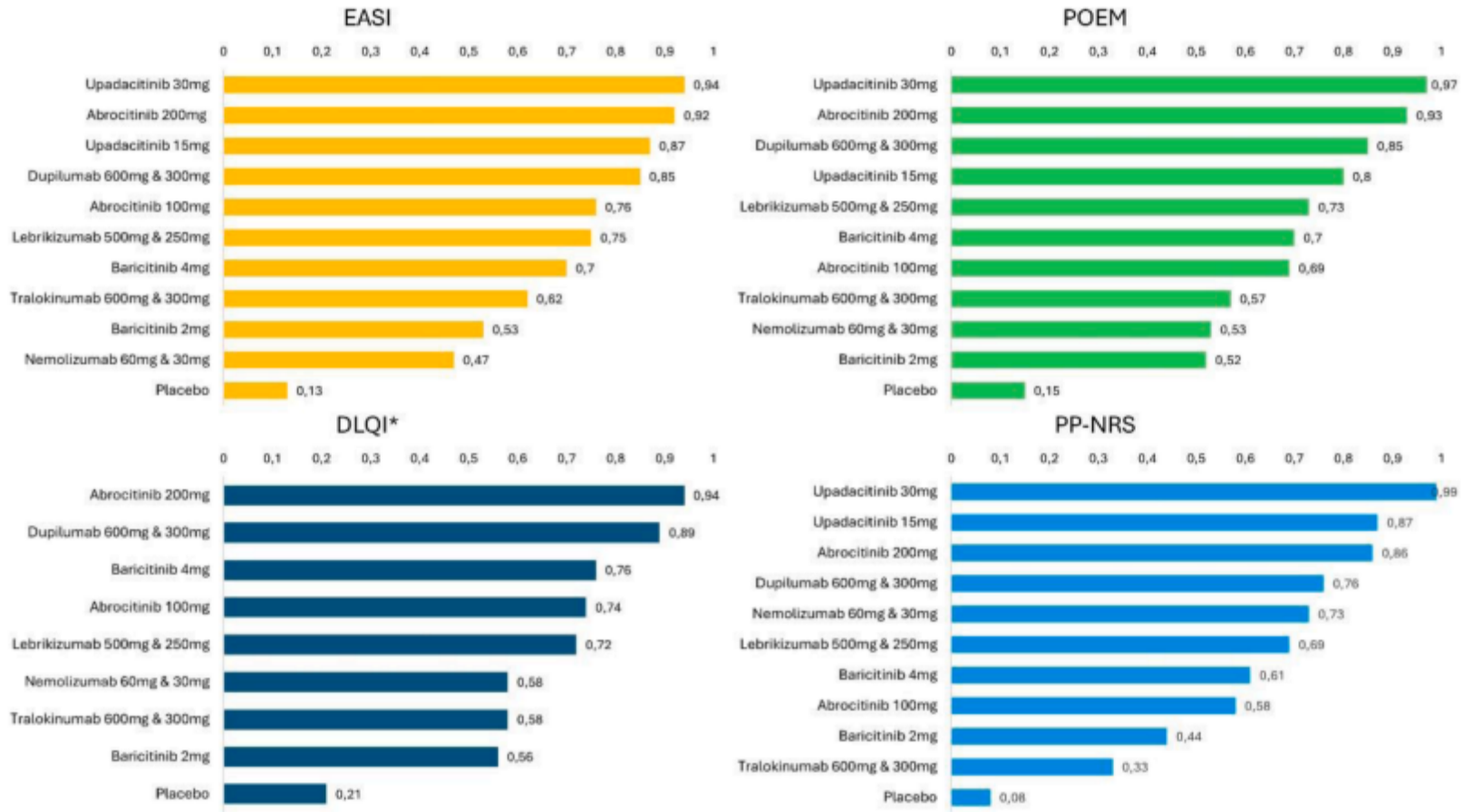


FIGURE 3. Surface under the cumulative ranking curve values on short-term indirect efficacy of biologics and Janus kinase (JAK) inhibitors based on the results from a network meta-analysis.[24] *DLQI*, Dermatology Life Quality Index; *EASI*, Eczema Area and Severity Index; *POEM*, Patient-Oriented Eczema Measure; *PP-NRS*, Peak Pruritus Numerical Rating Scale.

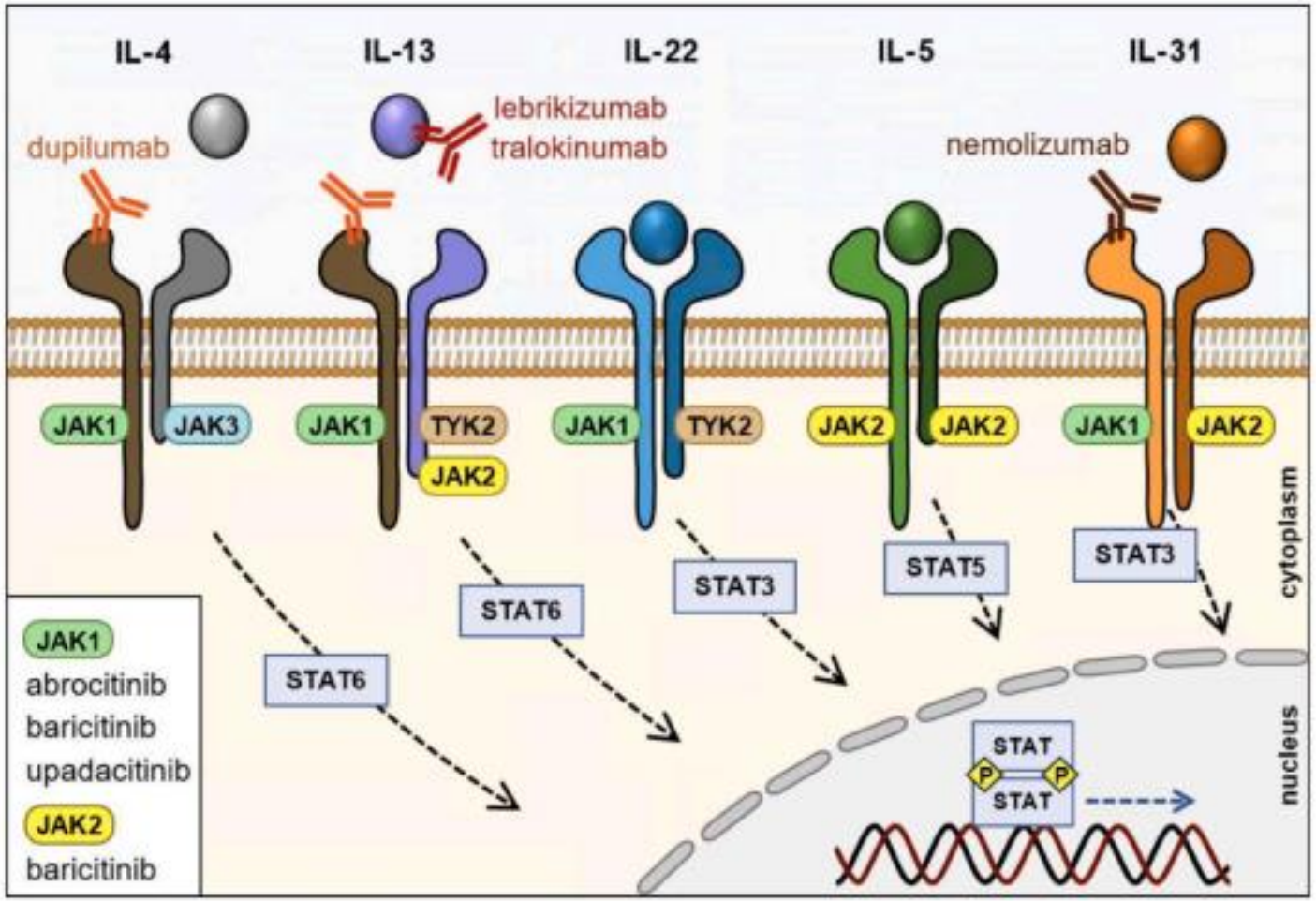


FIGURE 1. Mechanism of action of biologics and Janus kinase (JAK) inhibitors. Created by Dr Marcel B.M. Teunissen (Amsterdam UMC, Location AMC, Amsterdam), 2025. Created with Microsoft Powerpoint, Adobe Illustrator, and Adobe Acrobat.

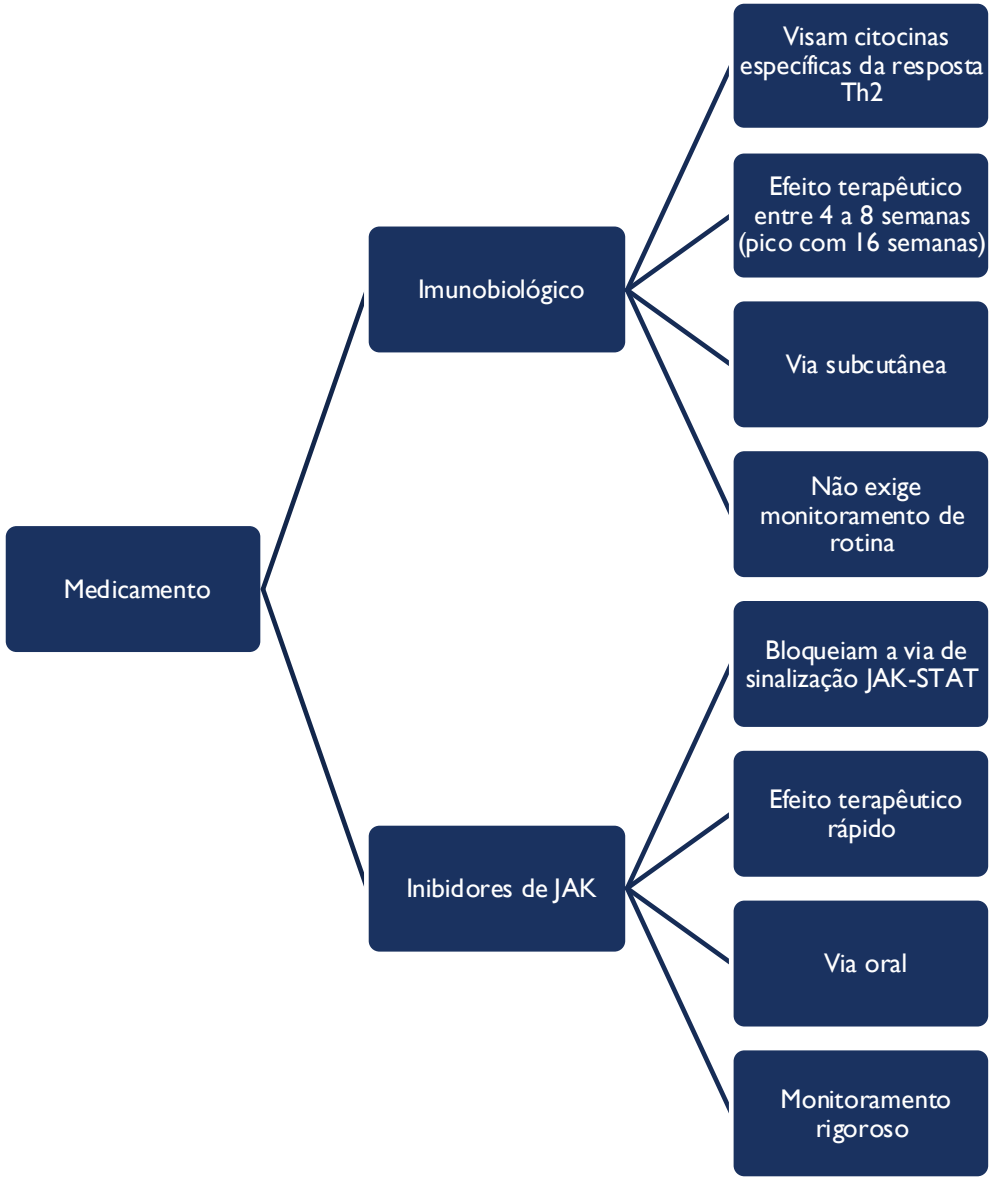

Medicamento
Imunobiológico
Visam citocinas específicas da resposta Th2
Efeito terapêutico entre 4 a 8 semanas (pico com 16 semanas)
Via subcutânea
Não exige monitoramento de rotina
Inibidores de JAK
Bloqueiam a via de sinalização JAK-STAT
Efeito terapêutico rápido
Via oral
Monitoramento rigoroso

TABLE II. Recommended laboratory monitoring[4,20,23]

	Before initiation	At wk 4	At wk 12	Every 3-6 mo
Biologics				
Not required*				
Janus kinase inhibitors				
Complete blood count	X	X	X	X
Alanine aminotransferase	X	X	X	X
Renal function	O	O	O	O
Lipid profile (cholesterol (high-density lipoprotein, low-density lipoprotein, and total) and triglycerides)	O	X†	X‡	O
Creatine kinase§	(O)	(O)	(O)	(O)
Hepatitis B and C, HIV, and tuberculosis	X			
Pregnancy	X*			

(), optional; *O,* only in Europe; *X,* in both the United States and Europe.

Clinically significant values are typically much higher, with levels exceeding 10,000, usually indicating possible rhabdomyolysis or myositis. An elevated creatine kinase level rarely necessitates discontinuation of the medication.[23]

*Only when indicated (eg, risk factors for serious infections).

†Only for abrocitinib in the United States.

‡Only for upadacitinib in the United States.

§Usually asymptomatic and commonly associated with physical exercise.[13]

CONCLUSÃO

- Abordagem personalizada
- Tomada de decisão compartilhada
- Biológicos
  - Segurança superior a longo prazo
  - Ausência de necessidade de monitoramento de rotina
  - Eficácia estabelecida na modulação da resposta Th2
- Inibidores de JAK
  - Ação rápida e alta eficácia
- Intervenção precoce
- Avaliação clínica regular

Clinical Commentary Review

Emerging Systemic Treatments for Asthma and Allergic Diseases: New Tricks, Same Dog?

Alessandra Tomasello, MD[a], Stanley J. Szefler, MD[b], and Katherine N. Cahill, MD[a] *Nashville, Tenn; and Aurora, Colo*

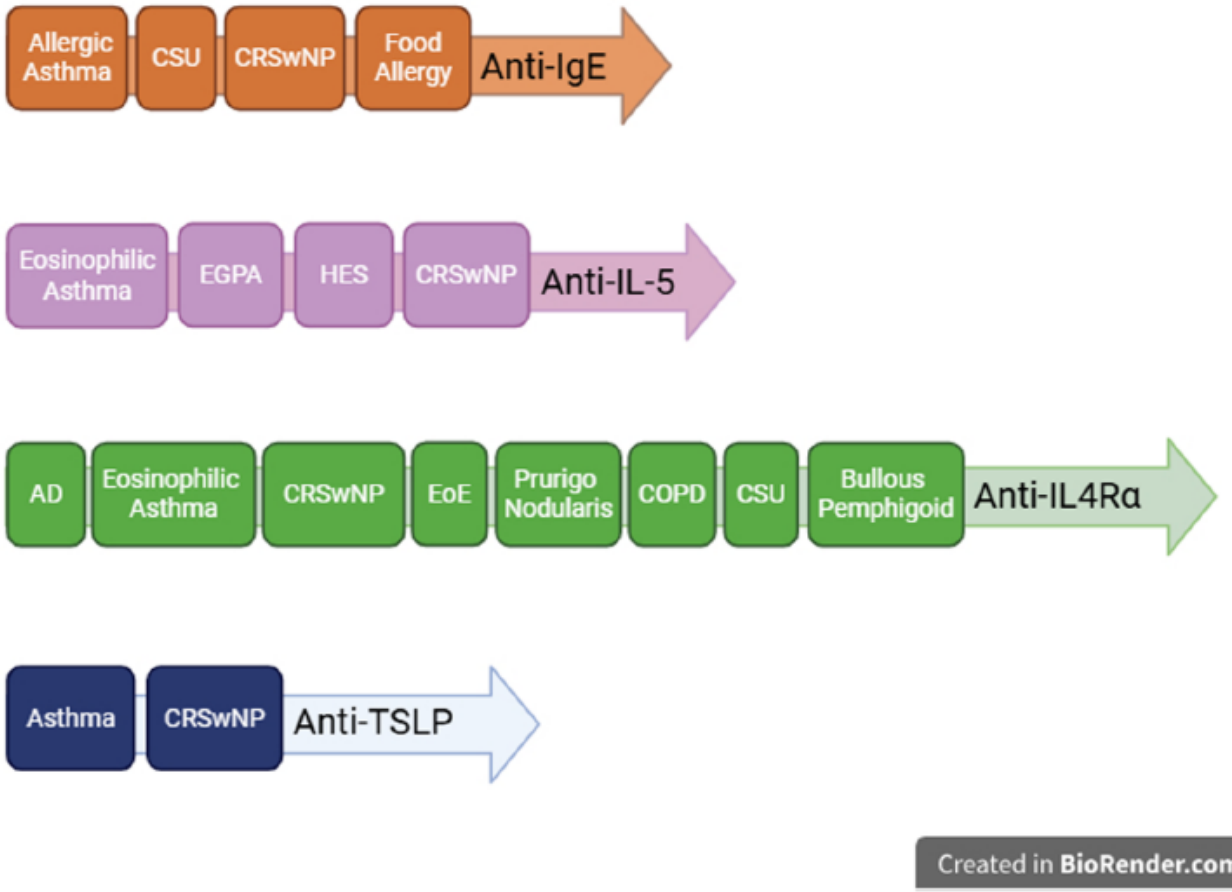


FIGURE 1. Chronologic trajectory of indication expansion and therapeutic repurposing for currently approved biologics in asthma and related allergic diseases. The progression of clinical approvals across multiple indications reflects the shared immunopathologic mechanisms targeted by existing therapies. This model highlights how cross-disease repurposing has already been employed and suggests a scalable framework for future biomarker-driven indication expansion. *AD*, Atopic dermatitis; *COPD*, chronic obstructive pulmonary disease; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *CSU*, chronic spontaneous urticaria; *EGPA*, eosinophilic granulomatosis with polyangiitis; *EoE*, eosinophilic esophagitis; *HES*, hypereosinophilic syndrome; *IL4Rα*, IL4 receptor α chain; *TSLP*, thymic stromal lymphopoietin.

INIBIDORES DE CITOCINAS T2

Terapias de ação ultraprolongada

- Anti-LI5 - Depemokimab
- Via SC a cada 6 meses
- Bom resultado em paciente com fenótipo eosinofílico

Terapias direcionadas à IL-13

- Tralokinumabe e Lebrikizumabe
- Resultados mistos na asma

Anticorpos Bi e Triespecíficos

- Bloqueio simultâneo de múltiplos alvos inflamatórios

TABLE I. Overview of therapeutic products targeting type 2 cytokines

Product/target in development	Current evidence	Ongoing RCTs	Unique strengths	Unique limitations	References
Depemokimab: IL-5	Phase 3 Asthma (SWIFT-1, SWIFT-2) Phase 3 CRSwNP (ANCHOR-1, ANCHOR-2)	Asthma: Phase 3 NCT04718389 (NIMBLE) NCT05243680 (AGILE) NCT06979323 (IMAGINE) HES: Phase 3 NCT05334368 EGPA: Phase 3 NCT05263934 COPD: Phase 3 NCT06959095 (ENDURA-1), NCT06961214 (ENDURA-2)	Long half-life; may be considered in pediatric use/for population older than 11 years	Pathway with existing therapy	15-19
Lebrikizumab: IL-13	Phase 3 Asthma (LA VOLTA 1, LA VOLTA 2, ACOUSTICS) Phase 3 Atopic dermatitis (ADvocate1, ADvocate1)	Perennial allergic rhinitis: Phase 3 NCT06339008 (PREPARED-1) CRSwNP: Phase 3 NCT06338995 (CONTRAST-NP)	Potential exacerbation reduction in subgroup of patients with high-T2 biomarkers and frequent exacerbators	Did not consistently show benefit over placebo in patients with uncontrolled asthma	20-24
PF-07275315: IL-13, IL-4, TSLP	Phase 1 NCT05411588	Asthma: Phase 2 NCT06977581 AD: Phase 2 NCT05995964	May offer more complete disease suppression	Limited data	25
PF-07264660: IL-13, IL-4, IL-33	Phase 1 NCT05496738	AD: Phase 2 NCT05995964	May offer more complete disease suppression	Limited data	25
Lunsekimig: IL-13, TSLP	Phase 1	Asthma: Phase 2 NCT06102005 (AIRCULES) NCT06609239 (AIRPHRODITE) NCT06676319 (AIRLYMPUS) AD: Phase 2 NCT06790121 CRSwNP: Phase 2 NCT06914908, NCT06454240	May offer more complete disease suppression	Limited data	26

AD, Atopic dermatitis; *COPD*, chronic obstructive pulmonary disease; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *EGPA*, eosinophilic granulomatosis with polyangiitis; *HES*, hypereosinophilic syndrome; *RCT*, randomized controlled trial; *TSLP*, thymic stromal lymphopoietin.

BLOQUEADORES DE ALARMINAS (TLSP, IL-33 E IL-25)

Via da TSLP

- Tezepelumabe (aprovado)
- Verekitug – Atua contra o receptor de TLSP
- Meia vida estendida
- Dose a cada 24 semanas

Eixo IL-33/ST2

- Apaga a IL-33 ou seu receptor (ST2)
- Eficaz em ambos os fenótipos
- Tozorakimab – anti IL-33
- Astegolimab – direcionado ao receptor ST2

TABLE II. Overview of therapeutic products targeting alarmins

Product/target in development	Current evidence	Ongoing RCTs	Unique strengths	Unique limitations	References
Tezepelumab: TSLP	Phase 3 Asthma (NAVIGATOR, WAYFINDER, DESTINATION, SOURCE) Phase 2 Asthma (CASCADE) Phase 3 CRSwNP (WAYPOINT)	Food allergy: Phase 2 NCT07015996 EoE: Phase 3 NCT05583227 EGPA: Phase 2b NCT06230354 COPD: Phase 3 NCT06883305, NCT06878261 Asthma age 5-<12 years: Phase 3 NCT06023589	May be considered in pediatric use	Inconsistent and modest efficacy for AD in phase 2b terminated early by sponsor	38-43
Verekitug: TSLP-R	Phase 1 trials (including asthma patients) Phase 1b asthma study	Asthma: Phase 2 NCT06196879 (VALIANT), NCT06966479 CRSwNP : Phase 2 NCT06164704 (VIBRANT) COPD: Phase 2b NCT06981078	Long half-life; durable T2 suppression	No clinical efficacy data yet available; overlapping mechanisms with existing therapy	44
Itepekimab: IL-33	Phase 2 asthma Phase 2 AD Phase 2a COPD	COPD: Phase 3 NCT04701983 (AERIFY-1), NCT04751487 (AERIFY-2), NCT06208306 (AERIFY-4) Phase 2 NCT05326412 (AERIFY-3) CRSwNP: Phase 3 NCT06834347 (CEREN1), NCT06834360 (CEREN2) Phase 2 NCT06691113	Novel therapeutic pathway; improves asthma control and lung function; attenuates IL-4R–induced eosinophilia (potential safety advantage); potential benefit in former smokers with COPD	No additional benefit over anti–IL-4R in asthma; no added benefit in combination therapy; no benefit across asthma phenotypes spectrum; no benefit in AD; variable COPD response	45,46
Tozorakimab: IL-33	Phase 2a adults with early-onset, moderate-to-severe asthma (FRONTIER-3)	Asthma: Phase 2b NCT06932263 COPD: Phase 3 NCT05166889 (OBERON), NCT05158387 (TITANIA), NCT05742802 (PROSPERO), NCT06040086 (MIRANDA), NCT06897748 (COMETA) no US but Russian federation	Novel therapeutic pathway; potential benefit for frequent exacerbators	Limited data; efficacy limited to selected subgroup	44,47,48
Astegolimab: ST2	Phase 2 Asthma (ZENYATTA) Phase 2 AD	COPD: Phase 3 NCT05878769, NCT05595642 Phase 2 NCT05037929	Targets the IL-33 receptor, offering a distinct mechanism; reduce exacerbations in eosinophil-low asthma	No efficacy in AD; COPD trials ongoing	49,50

AD, Atopic dermatitis; *COPD*, chronic obstructive pulmonary disease; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *EGPA*, eosinophilic granulomatosis with polyangiitis; *EoE*, eosinophilic esophagitis; *IL-4R*, IL-4 receptor; *RCT*, randomized controlled trial; *TSLP*, thymic stromal lymphopoietin; *TSLP-R*, thymic stromal lymphopoietin receptor.

CÉLULAS EFETORAS

Eosinófilos

- Dexpramipexol
- Inibe a maturação de eosinófilos na medula óssea

Mastócitos

- Inibidores de tirosina quinase
- Imatinibe
- Masitinibe

BTK

- Rilzabrutinibe
- Remibrutinibe

TABLE III. Overview of therapeutic products targeting effector cells

Product/target in development	Current evidence	Ongoing RCTs	Unique strengths	Unique limitations	References
Dexpramipexole: Eosinophils	Phase 2 asthma (EXHALE-1) Phase 2 CRSwNP	Asthma: Phase 3 NCT05763121 (EXHALE-2), NCT05813288 (EXHALE-3), NCT05748600 (EXHALE-4), NCT06388889 (EXHALE-5) COPD: Phase 2 NCT06533553	Oral eosinophil-depleting agent May be considered in pediatric use/for population older than 11 years	Clinical efficacy to be proven	58,59
Imatinib: KIT	Phase 2 asthma (KIA)	Asthma: Phase 2 NCT04129931 (PrecISE)	Novel cell target	Limited data; lack of predictive biomarker	60
Masitinib: KIT and PDGFR	Phase 3 asthma	–	Novel cell target	Risk/benefit assessments Lack of predictive biomarker	61
Rilzabrutinib: BTK	Phase 2 asthma Phase 2 CSU (RILECSU)	–	Broader immunomodulatory roles	Limited data Risk/benefit assessments Lack of predictive biomarker	62,63

BTK, Bruton's tyrosine kinase; *COPD*, chronic obstructive pulmonary disease; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *CSU*, chronic spontaneous urticaria; *PDGFR*, platelet-derived growth factor receptor; *RCT*, randomized controlled trial.

ALVOS NÃO CONVENCIONAIS, IMUNOMODULAÇÃO AMPLA E VIAS DE INFLAMAÇÃO NÃO T2

Modulação de vias de coestimulação de células T

- Amlitelimab
- Impede diferenciação e sobrevivência de subconjuntos de células T efetoras

Intervenções metabólicas

- Agonista do receptor de GLP-1
- Metformina

Modulação nutricional

- Triglicerídeos de cadeia média (MCTs)

TABLE IV. Overview of therapeutic products targeting unconventional, broad immune, and non-T2 inflammation targets

Product/target in development	Current evidence	Ongoing RCTs	Unique strengths	Unique limitations	References
Amlitelimab: OX40 ligand	Phase 2 AD	Asthma: Phase 2 NCT05421598, NCT06033833	Broad immunomodulatory effects	Limited data; long-term safety of broad immune modulation	67
Semaglutide: GLP-1 receptor agonist	Preclinical studies; observational studies in diabetes with comorbid asthma and COPD	Asthma: Phase 2 NCT05254314 (GATA-3)	Potential for addressing airway T2 and immunometabolic inflammation May be considered in pediatric use/for population older than 11 years	Clinical validation; lack of predictive biomarker; overweight and obese patients	68-72
Metformin	Observational studies in diabetes	Asthma: Phase 2 NCT06273072 (MINA)	Addressing immunometabolic inflammation May be considered in pediatric use/for population older than 11 years	Clinical validation; lack of predictive biomarker; overweight and obese patients	73,74
Medium chain triglycerides	Phase 2 Asthma	Asthma: Phase 2 NCT04129931 (PrecISE)	Nutritional modulation May be considered in pediatric use/for population older than 11 years	Limited data	75

AD, Atopic dermatitis; *COPD*, chronic obstructive pulmonary disease; *GLP-1*, glucagon-like peptide-1; *RCT*, randomized controlled trial.

CONCLUSÃO

- Expansão de indicações e reaproveitamento
- Necessidade de mais estudos
- Novos biomarcadores além do perfil Th2 alto
- Redefinição de desfechos clínicos
- Intervenção precoce

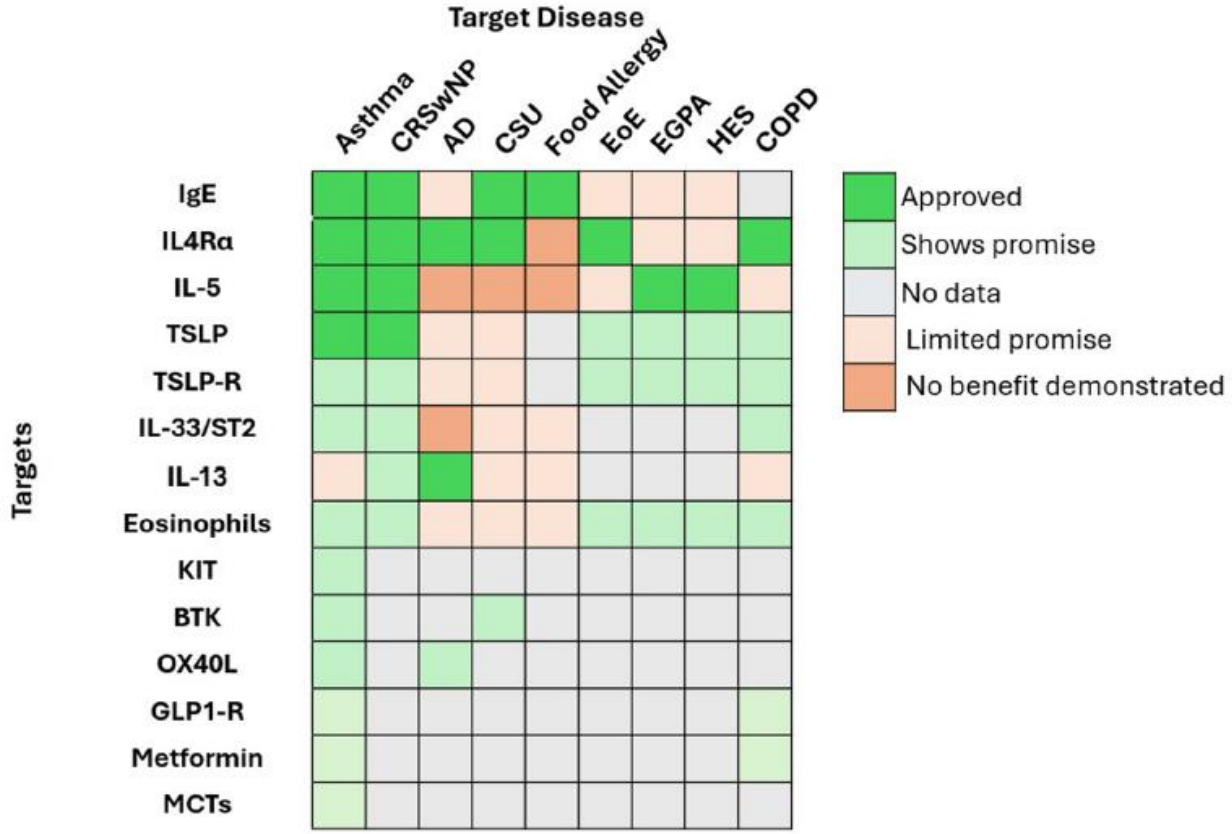


FIGURE 2. Cross-disease mapping of therapeutic targets illustrates potential for treatment expansion. Color coding reflects the strength of current clinical evidence. *AD*, Atopic dermatitis; *BTK*, Bruton's tyrosine kinase; *COPD*, chronic obstructive pulmonary disease; *CRSwNP*, chronic rhinosinusitis with nasal polyps; *CSU*, chronic spontaneous urticaria; *EGPA*, eosinophilic granulomatosis with polyangiitis; *EoE*, eosinophilic esophagitis; *GLP1-R*, glucagon-like peptide-1 receptor; *HES*, hypereosinophilic syndrome; *IL4Rα*, IL4 receptor α chain; *MCT*, medium-chain triglyceride; *OX40L*, OX40 ligand; *TSLP*, thymic stromal lymphopoietin; *TSLP-R*, TSLP receptor.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