AEDV 2023 Highlights

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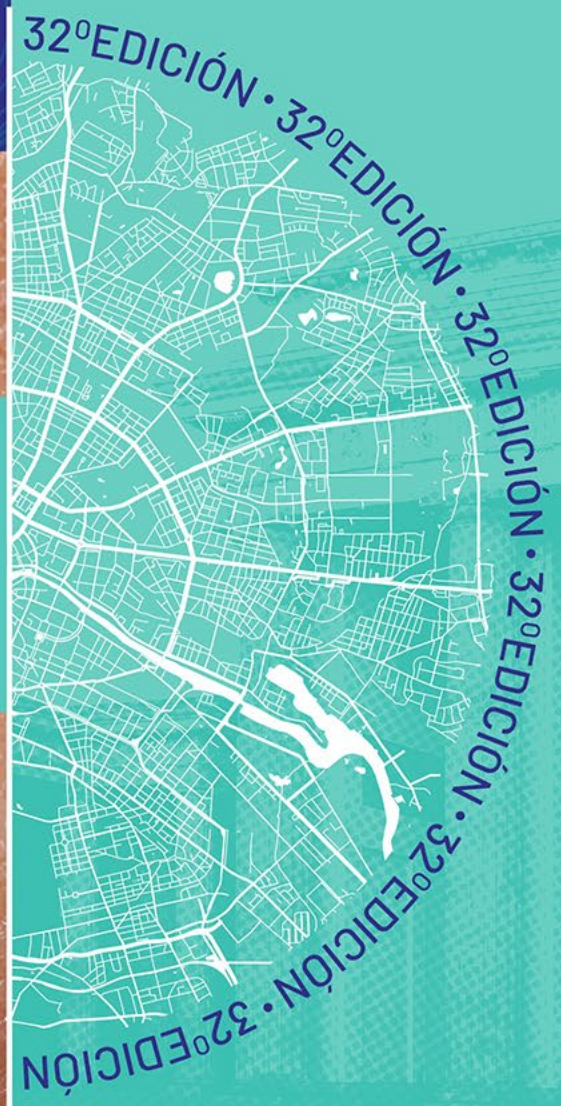


BERLIN

11-14 OCTUBRE

Iniciativa científica de:

AEDV 1909

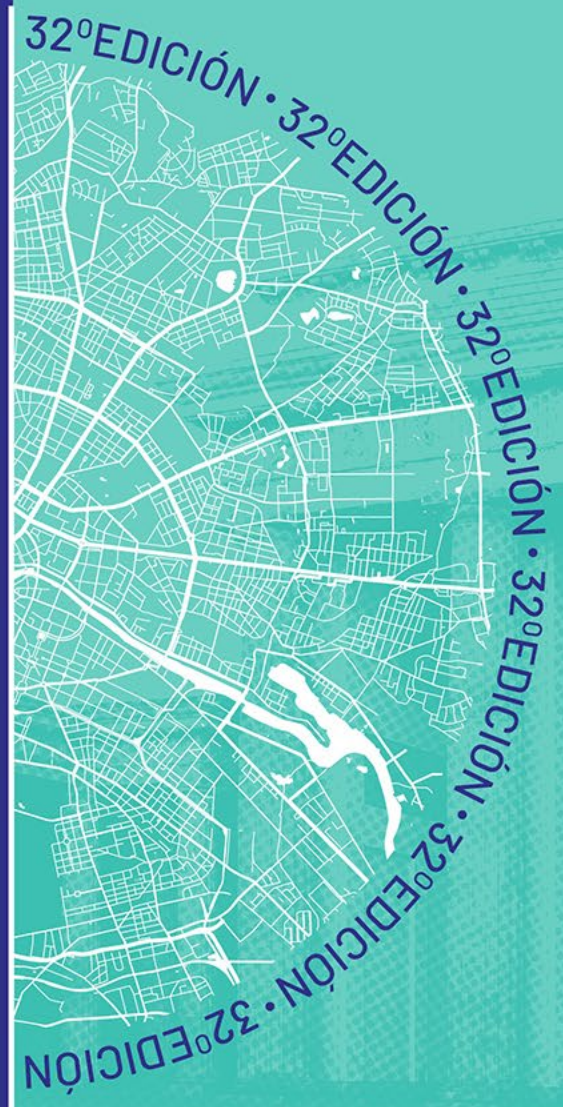
ACADEMIA ESPAÑOLA DE DERMATOLOGÍA Y VENEREOLOGÍA

DERMATITS ATOPICA E INMUNOALERGIA CUTANEA

Ariadna Ortiz Brugués

Institut Universitaire du Cancer de Toulouse Oncopole

NO TENGO CONFLICTOS DE INTERÉS



BERLIN

11-14 OCTUBRE

“BENEATH THE TIP OF THE ICEBERG”

SUMMARY:

- ATOPIC DERMATITIS
- IMMEDIATE TYPE ALLERGIES
- CONTACT ECZEMA
- BULLOUS DISEASES

COMPARING THE TREATMENT EFFECTIVENESS AND SAFETY OF DUPILUMAB AND METHOTREXATE IN PAEDIATRIC AND ADULT ATOPIC DERMATITIS: RESULTS FROM THE A-STAR REGISTER (Pr. Flohr, UK)

- Prospective, multicenter register to compare the real-world clinical efficacy and safety profile of CyA, dupilumab and MTX in adult and paediatric AD (N=406)
- CyA and dupulimab were **more effective** than MTX in reducing physician-assessed EASI and patient-reported POEM and PP-NRS score, particularly in **severe disease**
- Similar incidence of adverse events
- The majority of patients on dupilumab will have received treatment with a first-line conventional systemic (CyA, MTX) → partially treated disease with less potential for improvement
- Future real-world studies need to compare dupilumab with other **novel biologics** and **Janus kinase** (JAKs) inhibitors
- Mechanistic studies are also needed to understand the factors underlying treatment responses, i.e., immune or microbiome-based **biomarkers** to allow for a more personalised approach

ATOPIC DERMATITIS
EFTAD – EUROPEAN TASK FORCE OF ATOPIC DERMATITS

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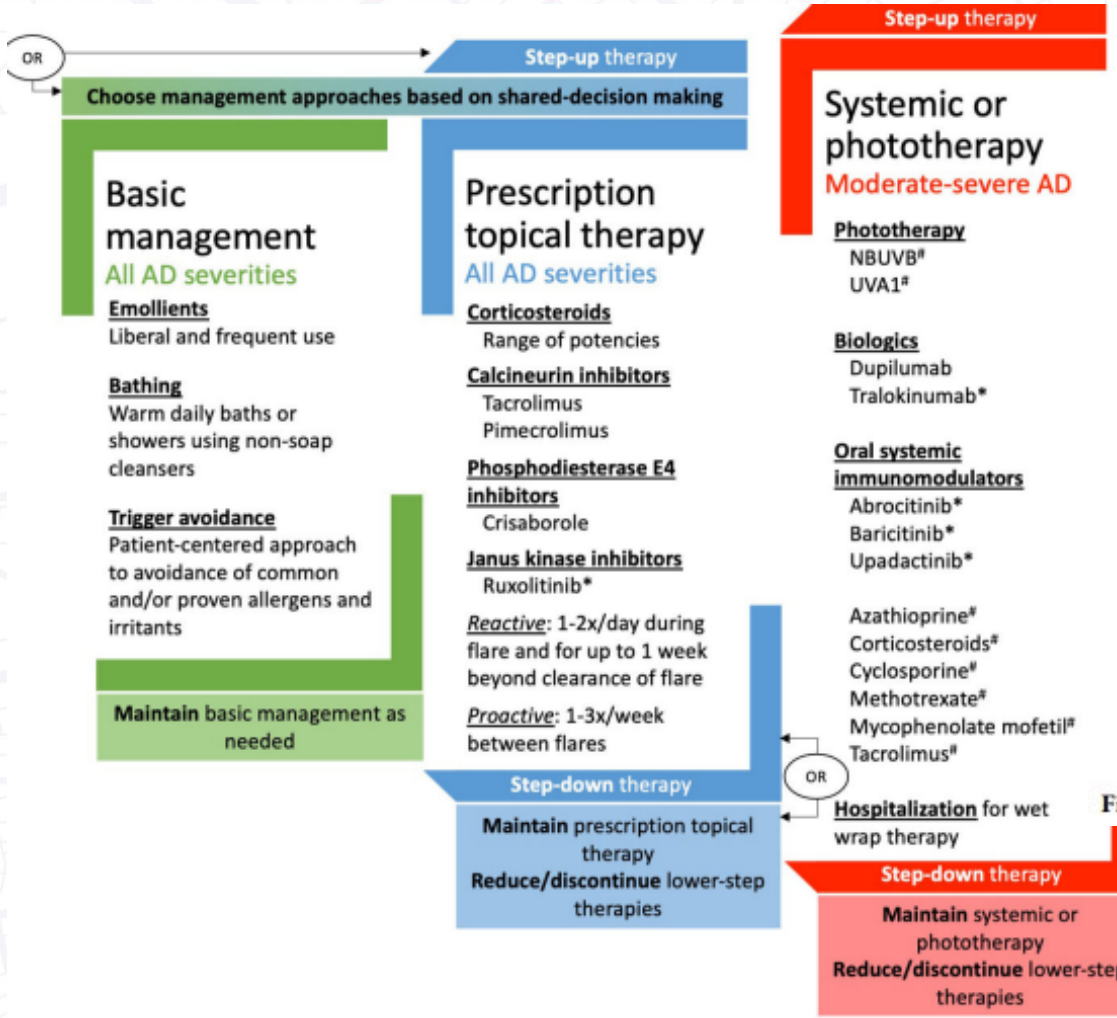
THE TREATgermany REGISTRY: ANALYSIS OF NON-RESPONDERS TO DUPILUMAB (Dr Heratizadeh, Germany)

- 1907 adults and 364 children and adolescents included
- Low-rate of non-responders to dupilumab (**7%)** until 34 weeks of treatment
- Rate of “late-responders” (week 20-34) is 5.5%
- **Later** disease **onset**, **lower** frequency of **asthma and rhinoconjuctivitis**, **less** frequent **family history** of AD in non-responders
- **Lower disease** scores at the beginning of the treatment
- Increased proportion of **smokers**
- Non-responders suffer more frequently from **arterial hypertension**

ATOPIC DERMATITIS
JAK inhibitors (Pr Silverberg, USA)



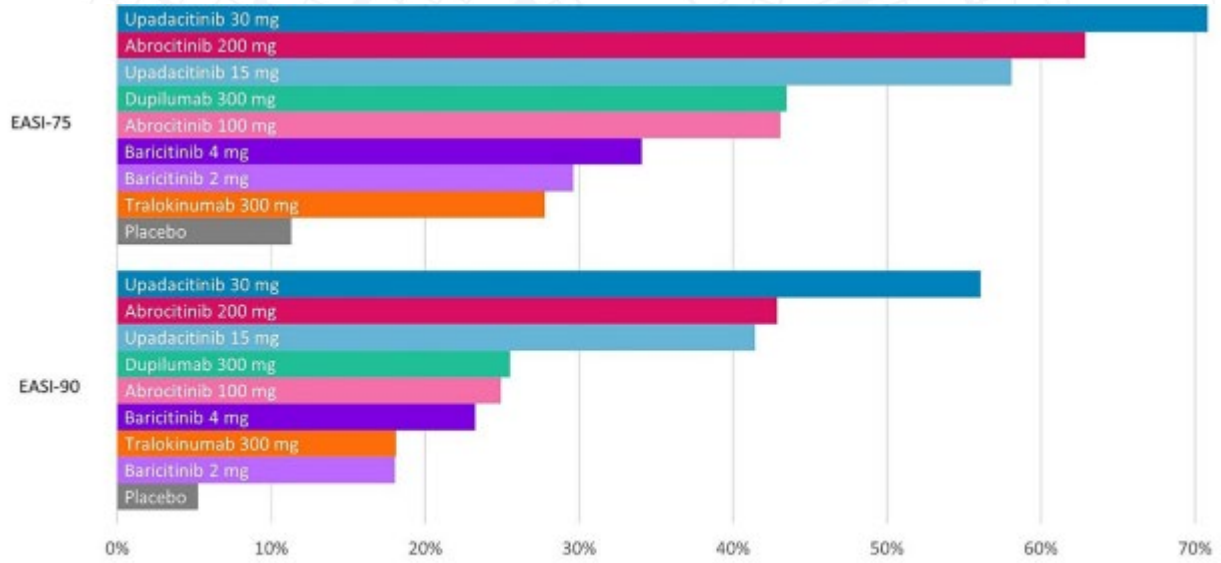


Fig. 3 EASI-75 and EASI-90 absolute response rate estimates for moderate to severe atopic dermatitis (primary endpoint

Raj Chovatiya, Jonathan I Silverberg. Iatrogenic Burden of Atopic Dermatitis. Dermatitis.2022;33(6S):S17-S23.

Jonathan I Silverberg 1, H Chih-Ho Hong 2 3, Jacob P Thyssen, et al. Comparative Efficacy of Targeted Systemic Therapies for Moderate to Severe Atopic Dermatitis without Topical Corticosteroids: Systematic Review and Network Meta-analysis. Dermatol Ther (Heidelb).2022;12(5):1181-1196.

ATOPIC DERMATITIS
JAK inhibitors (Pr Silverberg, USA)

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- All 3 JAK-inhibitors demonstrated efficacy for itch, pain, sleep disturbance, quality of life, symptoms of anxiety and/or depression
- Patients who responded showed good long-term maintenance
- Abrocitinib (JAK1): 100 or 200 mg
  - Recommended to start with 100 mg and if inadequate response increase to 200 mg
  - Use 100 mg in adolescents and seniors
- Upadacitinib (JAK1): 15 or 30 mg
  - Recommended to start with 15 mg and if inadequate response increase to 30 mg
  - Use 15 mg in adolescents and seniors
- Baricitibib (JAK1/2): 2 or 4 mg ex-USA

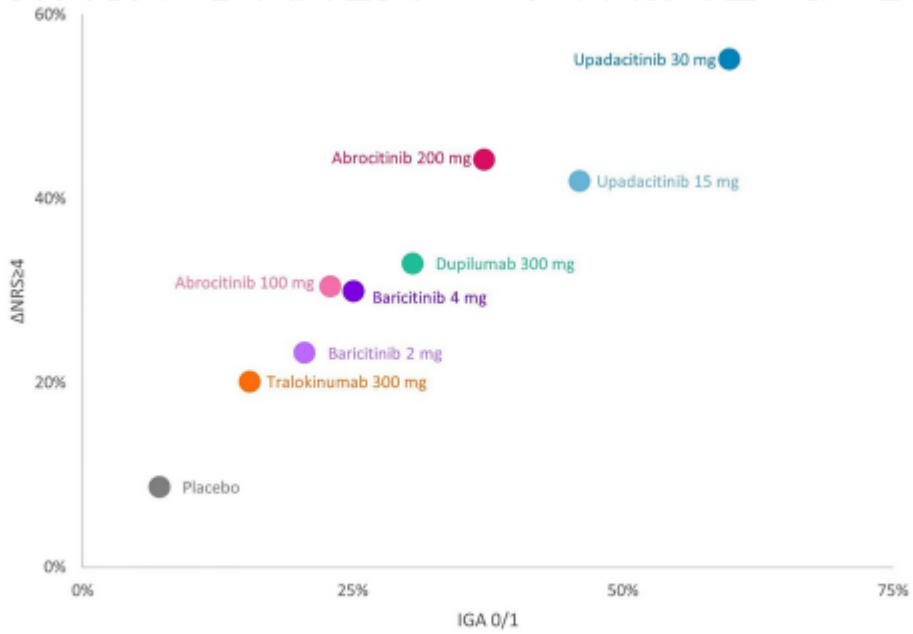

Fig. 2 IGA 0/1 versus ΔNRS ≥ 4 absolute response rate estimates for moderate to severe atopic dermatitis (primary endpoint, timepoint). *ΔNRS* ≥ *4* Pruritus Numerical Rating Scale reduction of ≥ 4 points from baseline, *IGA* Investigator Global Assessment for Atopic Dermatitis

Jonathan I Silverberg 1, H Chih-Ho Hong 2 3, Jacob P Thyssen, et al. Comparative Efficacy of Targeted Systemic Therapies for Moderate to Severe Atopic Dermatitis without Topical Corticosteroids: Systematic Review and Network Meta-analysis. Dermatol Ther (Heidelb).2022;12(5):1181-1196.

ATOPIC DERMATITIS
JAK inhibitors (Pr Silverberg, USA)

AEDV2023 Highlights BERLIN

- Overall, comparably safety profiles
- Abrocitinib more nausea / upadacitinib more acne
- HZ incidence / prevalence were relatively low and comparable with other indications
- Of note, studies excluded patients with disseminated HZ / VHS, recurrent HZ, history of eczema herpeticum → rates of HZ are expected to be higher if those patients were treated with JAKi's
- Consider vaccinating higher risk patients for HZ prior to initiating JAKi's
  - Recombinant (non-live) HZ vaccine may be administered while on JAKi's, but the impact on safety and vaccine efficacy is unknown
  - Live attenuated zoster vaccine is contraindicated and should be administered 4 weeks prior to initiating JAKi's

ATOPIC DERMATITIS
JAK inhibitors (Pr Silverberg, USA)

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History	Baseline	Week 4	Week 12	Week >12
Venous thromboembolism	+	+/-	+/-	Every 6-12 months
Infections	+	+/-	+/-	Every 6-12 months
Tuberculosis	+	+/-	+/-	Every 6-12 months
Risk factors for hepatitis B or C	+	+/-	+/-	Every 6-12 months
Cardiovascular risk factors	+	+/-	+/-	Every 6-12 months
Malignancy	+	+/-	+/-	Every 6-12 months
Concomitant medications				
Cox-2 inhibitors	+	+/-	+/-	Every 6-12 months
Prednisone or immunosuppressants	+	+/-	+/-	Every 6-12 months
Oral contraceptives	+	+/-	+/-	Every 6-12 months
Vaccination status, particularly HZ	+	+/-	+/-	Every 6-12 months
Pregnant of family planning	+	+/-	+/-	Every 6-12 months
Skin check for NMSC	+	+/-	+/-	+ Annually

ATOPIC DERMATITIS
JAK inhibitors (Pr Silverberg, USA)

Risk for venous thromboembolism with JAKi's:

- Prior venous thromboembolism
- Age > 65 years
- Obesity
- Prolonged immobility
- Hereditary and acquired thrombophilia
- Cox-2 inhibitor therapy
- Prednisone
- Major surgical interventions

Use of contraception pills may not be an optimal form of contraception (risk for venous thromboembolism)

ATOPIC DERMATITIS
JAK inhibitors (Pr Silverberg, USA)

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Laboratory / imaging	Baseline	Week 4	Week 12	Week >12
Complete blood count	+	+	+/-	+ for dose increase +/- if previous abnormal value
Liver enzimes	+	+	+/-	+ for dose increase +/- if previous abnormal value
Renal function	+	+	+/-	+ for dose increase +/- if previous abnormal value
Hepatitis B and C	+	+/-	+/-	+/- No more tan annually if routine
Quantiferon or Mantoux	+	+/-	+/-	+/- No more tan annually if routine
VIH	+/-	+/-	+/-	+/- No more tan annually if routine
Lipids	+	-	+/-	+/- No more tan annually if routine
CPK	-	-	-	-
Pregnancy test	+/-	+/-	+/-	+/-
Chest X-ray for TBC	+/-	-	-	+/- No more tan annually if routine

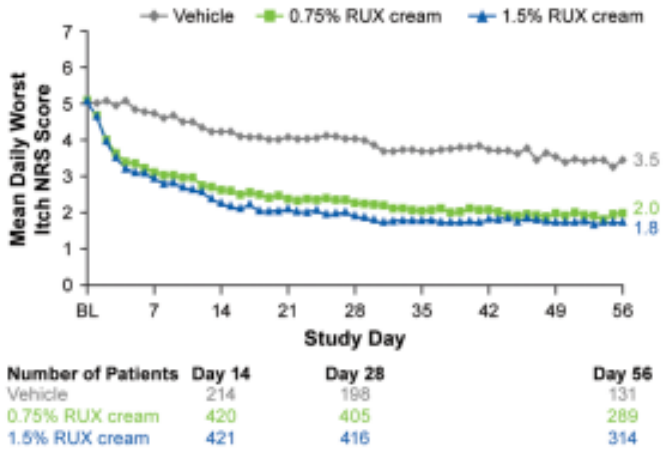
ATOPIC DERMATITIS
JAK inhibitors (Pr Silverberg, USA)

AEDV2023 Highlights BERLIN

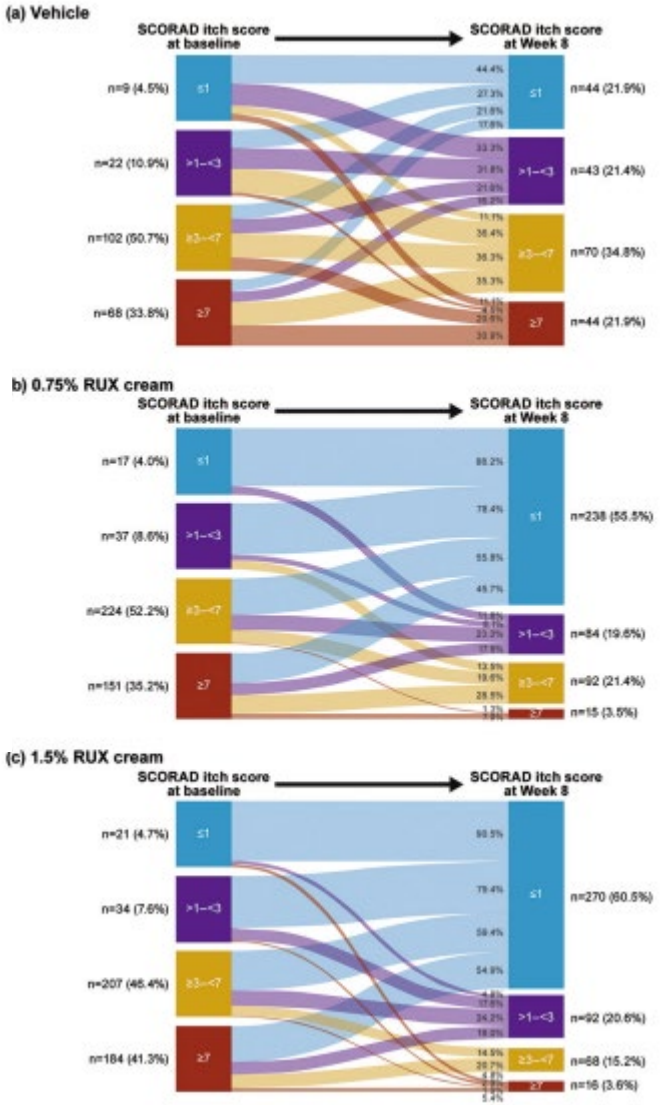
Ruxolitinib (topical JAK 1/2 inhibitor): TRuE-AD1 & TRuE-AD2

- Phase III, RCT (3 arms)
- 12-70 years with active AD
- AD duration > 2 years
- IGA 2/3 (Mild - Moderate)
- BSA 3-20% excluding scalp
- 8 weeks of treatment

Lab screening (serious infection, mortality, malignancy, lymphoproliferative disorders, NMSC)



Number of Patients	Day 14	Day 28	Day 56
Vehicle	214	198	131
0.75% RUX cream	420	405	289
1.5% RUX cream	421	416	314



Ruxolitinib, delgocitinib, brepocitinib: efficacy comparable to or better than mid-potency topical corticosteroids

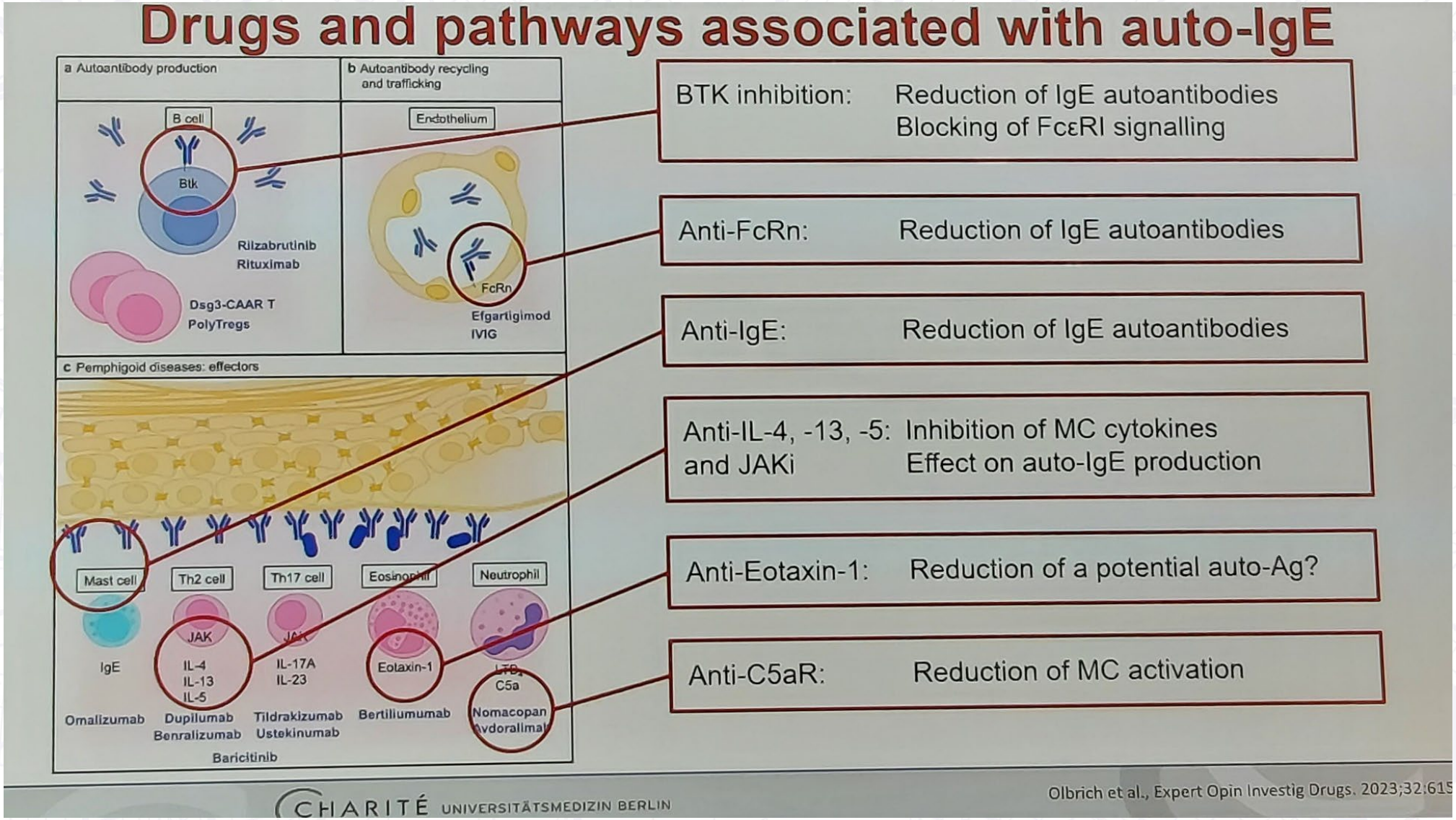
Andrew Blauvelt 1, Leon Kircik 2, Kim A Papp, et al. Rapid pruritus reduction with ruxolitinib cream treatment in patients with atopic dermatitis. J Eur Acad Dermatol Venereol. 2023;37(1):137-146

IMMEDIATE TYPE ALLERGIES
Auto-allergy: a new concept in skin diseases (Pr Maurer, Germany)

- Auto-allergy: autoimmunity mediated by **immunoglobulin E** (IgE) **autoantibodies**
- Systemic lupus erythematosus, bullous pemphigoid (BP), chronic urticaria (spontaneous and inducible)
- Type I autoimmune (“autoallergic”) chronic spontaneous urticarial (CSU)
- Most of the IgE reactivity in CSU patients is against self
- Autoallergic CSU patients have **elevated total IgE**
- CSU patients often have **IgE-anti-thyreoperoxidase** (TPO)
- IgE-antiTPO + CSU patients benefit from **omalizumab**

Marcus Maurer, Sabine Altrichter, Oliver Schmetzer, Jörg Scheffel, Martin K Church, Martin Metz. Immunoglobulin E-Mediated Autoimmunity. Front Immunol.2018;9:9:689

IMMEDIATE TYPE ALLERGIES
Auto-allergy: a new concept in skin diseases (Pr Maurer, Germany)



CONTACT ECZEMA
New allergens during COVID-pandemic (Pr Giménez-Arnau, Spain)

AEDV2023 Highlights BERLIN

Contact dermatitis caused by PPE:

- Mask wearing
- Surgical mask
- N95/KN95 respirators
- Cloth masks
- Gloves
- Clothing
- Protective googles
- Face shields

TABLE 1 The main materials, potential allergens, sites of skin lesions and symptoms caused by PPE.

PPE		Material	Allergen	Body regions	ASR
Masks	Surgical mask	Soft absorbent sheets, Polypropylene barriers, Melt-blown non-woven fabric	Formaldehyde, 2-bromo-2-nitropropane-1,3-diol, Coco-propylenediamine-guanidinium diacetate, Dibromodicyanobutane Vulcanization promoters, Antioxidants, Nickel, Cobalt	Nasal, Bridge, Ears, Cheeks, Perioral, Chin	Redness, Itching, Dryness
	N95/KN95 respirator	Skin-friendly layer, Structural support filter layer, Hydrophobic coating layer	Formaldehyde, Thiurams, Dithiocarbamates, Mercaptobenzothiazole		Redness, Itching
	Cloth mask	Cotton, Polyester	Formaldehyde, Formaldehyde textile resins, Formaldehyde releasers, Disperse dyes, P-aminobenzene, P-phenylenediamine		Erythema, Scaling
Gloves		Latex, Nitrile rubber, Plastic	Latex, Carba mix, Mercaptobenzothiazole (MBT), Thiuram mix	Hands	Dryness, Rash, Itching
Protective clothing		Polypropylene melt-blown cloth, Polyester fiber	Vinyl, Rubber materials	Limbs, Trunk	Dryness, Pruritus
Protective goggles		Polycarbonate, Optical resin, Polymethyl methacrylate	Not available at present	Nasal bridge	Pressure, Sores, Rash
Face shields		Elastic, Headband, Polycarbonate	Not available at present	Forehead	Abrasions, Itching

Huimiao Tang, Hao Wang, Michael R Hamblin, et al. Contact dermatitis caused by prevention measures during the COVID-19 pandemic: a narrative review. Front Public Health. 2023 Jul 20:11:1189190.

CONTACT ECZEMA
New allergens during COVID-pandemic (Pr Giménez-Arnau, Spain)

AEDV2023 Highlights BERLIN

Contact dermatitis caused by disinfectant:

- Hand higiene products
- Environmental disinfectants
- Disinfectants for clothing

TABLE 2 Active ingredients, allergens and hand ASRs of different hand hygiene products.

Hand hygiene products	Dominant sector	Sensitizer	ASR
ABHS	Ethanol, Isopropanol, Hydrogen, Peroxide, Glycerol	Ethanol, Isopropanol, Preservative agent, Quaternary ammonium chloride, Chlorhexidine, Triclosan, Chlorocresol, Phenoxyethanol, Myristool, Benzalkonium chloride	Dryness, Peeling, Itching
AFHS	Chlorides, Iodides, Peroxides, Phenols, Biguanide	Benzalkonium chloride, Cetroamide, Chlorocresol, Chlorhexidine, Triclosan, Sodium hypochlorite, Povidone-iodine	Dryness, Peeling, Skin color change
Soap	Surfactant, Emulsifier, Moisturizer, Fragrance, Coloring agent	Spice, Tocopherol, Polyethylene glycol, Ethylhexyl glycerol, Quaternary ammonium salts, Sezolinone, Sodium benzoate, Phenoxyethanol, Chlorocresol, Polyethylene glycol, Triclosan, Chlorhexidine gluconate, Iodophor, Povidone iodine	Dryness, Peeling, Eczema

Huimiao Tang, Hao Wang, Michael R Hamblin, et al. Contact dermatitis caused by prevention measures during the COVID-19 pandemic: a narrative review. Front Public Health. 2023 Jul 20:11:1189190.

CONTACT ECZEMA
New allergens during COVID-pandemic (Pr Giménez-Arnau, Spain)

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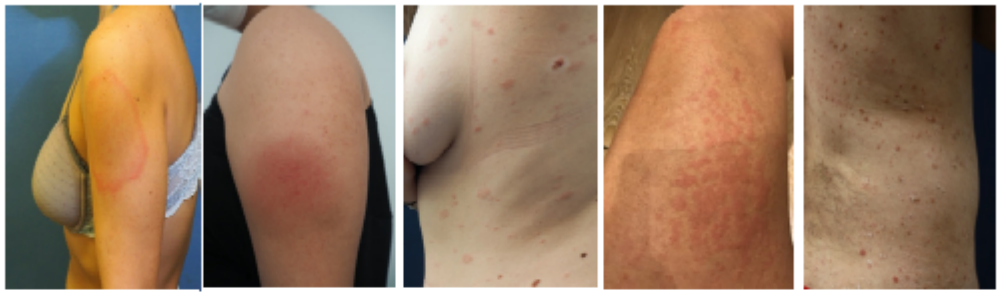
- Study to evaluate the role of skin testing excipients in delayed skin reactions due to mRNA COVID-19 vaccines
- Patch testing and intradermal testing with PEG-400, PEG-2000, trometamol, 1,2-dimyristoyl-sn-glycero-3-phosphocholine
- 31/4315 experienced cutaneous adverse vaccine reactions

David Pesqué, Ramon Maria Pujol, Orianna Marcantonio, et al. Study of Excipients in Delayed Skin Reactions to mRNA Vaccines: Positive Delayed Intradermal Reactions to Polyethylene Glycol Provide New Insights for COVID-19 Arm. Vaccines (Basel). 2022 Nov 30;10(12):2048

Table 1. Demographic baseline and clinical characterization of skin reactions due to mRNA COVID-19 vaccines.

Skin Reactions	DLLR	ILR	Morbilliform and Pityriasis Rosea-Like Rash	Urticariform Rash	Psoriasiform Rash	BMS
Clinical picture						No image $n = 1$
	$n = 18$	$n = 5$	$n = 4$	$n = 2$	$n = 1$	
Median age (IQR)	38.9 (47–30)	47.6 (61.5–34)	43.8 (59.5–28)	35.5	72	44
Sex, *n* (%) Women Men	 16 (88.9) 2	 5 None	 3 1	 2 None	 None 1	 1 None
Allergies, *n* (%)	11 (61.1)	1	2	1	1	1
Past anaphylaxis, *n*	2	None	None	None	None	None
Chronic skin disorder, *n* AD CSU	 3 3	 2 1	 None 1	 1 1	 None None	 None None
Median onset (days) (IQR)	8.1 (9–7)	2.4 (3.5–1.5)	6.8 (8.5–5)	6	10	1
Median duration (days) (IQR)	4.8 (7–3)	3 (4.5–1.5)	4.3 (6–2.5)	6.5	15	10
Vaccine, *n* (%) Moderna Pfizer	 16 (88.9) 2	 5 None	 1 3	 None 2	 1 None	 None 1
Dose, *n* (%) 1st 2nd	 13 (72.2) 5	 5 None	 3 1	 None 2	 None 1	 1 None
Relapse with 2nd dose, *n*	3	1	None	None	None	None
Local symptoms, *n* (%)	16 (88.9)	3	4	2	None	1
Response to treatment	All patients presented a good response to conventional treatments					
Vaccine discontinuation	No vaccine discontinuation was needed for any patient with the 2nd dose					

CONTACT ECZEMA
Hand dermatitis: new treatments (Pr Bauer, Germany)

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New systemic treatments

- Anti IL4/IL13: dupilumab 300 mg– LIBERTY AD HAFT
  - 40% of patients reached IGA0/1 at week 16
  - Improvement in modified Total Lesion Sign Score, Hand Eczema Severity Index (HECSI), Peak Pruritus NRS

- JAK inhibitors:
  - Abrocitinib 300 mg – phase III JADE DARE: vs dupilumab 300 mg + corticosteroids: proportion of patients achieving IGA 0/1 was greater in the abrocitinib group from week 2

  - Upadacitinib – phase III MEASURE UP 1&2: HECSI 75 % was achieved in 62% (15 mg) and 69-71% (30 mg) at week 16

CONTACT ECZEMA
Hand dermatitis: new treatments (Pr Bauer, Germany)

AEDV2023 Highlights BERLIN

Future systemic treatments

- Phase II study Oral Spleen Tyrosin Kynase (SYK)/JAK–inhibitor: **Gusacitinib**
  - Physician Global Assessment 0/1: 30% at week 16
  - Improvement in HECSI with gusacitinib 80 mg was comparable to upacitinib 15 and 30 mg and dupilumab 300 mg
  - Most common adverse events (>10%) were upper respiratory tract infections, headache and nausea

Pablo A Jimenez, Howard L Sofen, Robert Bissonnette, et al. Oral spleen tyrosine kinase/Janus Kinase inhibitor gusacitinib for the treatment of chronic hand eczema: Results of a randomized phase 2 study. J Am Acad Dermatol. 2023 Aug;89(2):235-242.

CONTACT ECZEMA
Hand dermatitis: new treatments (Pr Bauer, Germany)

Future topical treatments:

- **Delgocitinib** (pan JAK inhibitor): phase III DELTA 1
  - 20% IGA chronic hand eczema 0/1 at week 16
  - 50% improvement in HECSI 75 and 30% HECSI 90 at week 16
  - > 4 point improvement in DLQI at week 16
  - Safety profile similar to vehicle over 16 weeks
- Ruxolitinib (JAK1/2 inhibitor): phase II re-scheduled
- Roflumilast (PDE-4-inhibitor): studies completed (not published)
- AFX5931 (CCL2/CCL5 inhibitor): studies completed (not published)

Hand eczema core outcome set initiative (HECOS): establish a core outcome set to be measured in all hand eczema studies

BULLOUS DISEASES
When to screen for malignancy (Pr Horvath, Netherlands)

- Paraneoplastic pemphigus: erosive stomatitis & lichenoid dermatitis
- Bullous pemphigoid: associated with hematological malignancies
- Mucous membrane pemphigoid: 30% of patients with anti-laminine 332 develop solid malignancies
- Linear IgA dermatosis: higher risk of lymphoproliferative diseases

BULLOUS DISEASES
New drugs on the horizon
(Pr Schmidt, Germany)

Pemphigus vulgaris / foliaceous:

- CTLA4-based anti-CD80/86 antibody (Abatacept): phase IV
- Bruton's tyrosin kinase (BTK) inhibitor (Rilzabrutinib): phase III
- Neonatal Fc receptor inhibitor (**Efgartigimod**): phase III
- Immunoadsorption: phase II
- Desmoglein-3 specific nanoparticles: phase Ib
- Desmoglein-3 specific CAART cell therapy: phase Ib

Bullous pemphigod:

- IL5α receptor inhibitor (Benralizumab): phase III
- IL4α receptor inhibitor (**Dupilumab**): phase III
- Neonatal Fc receptor inhibitor (**Efgartigimod**): phase III
- C5a/LTB4 inhibitor (Nomacopan): phase III
- C5aR1 inhibitor (Avdoralimab): phase II
- Methotrexate: phase II

THANK YOU VERY MUCH FOR YOUR ATTENTION

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AEDV 1909 ACADEMIA ESPAÑOLA DE DERMATOLOGÍA Y VENEREOLOGÍA

La Academia Española de Dermatología y Venereología expresa su agradecimiento al patrocinador UCB, por su especial apoyo y contribución con la actividad formativa Highlights 2023.