

 #WCD2019

AEDV

HIGHLIGHTS

24th World Congress of Dermatology (WCD)

10-15
JUNIO
2019

Milán



Patrocina:

janssen  Immunology
PHARMACEUTICAL COMPANIES OF 

Organiza:



AEDV

HIGHLIGHTS

24th World Congress of Dermatology (WCD)

10-15
JUNIO
2019

Milán



Systematic and autoimmune disease

Raquel Rivera

Dermatologia. HU 12 de Octubre. Madrid

Patrocina:

janssen  Immunology
PHARMACEUTICAL COMPANIES OF 

Organiza:



AEDV

HIGHLIGHTS

24th World Congress of Dermatology (WCD)

10-15
JUNIO
2019

Milán



WS: Management of the itching patient

Patrocina:



Organiza:



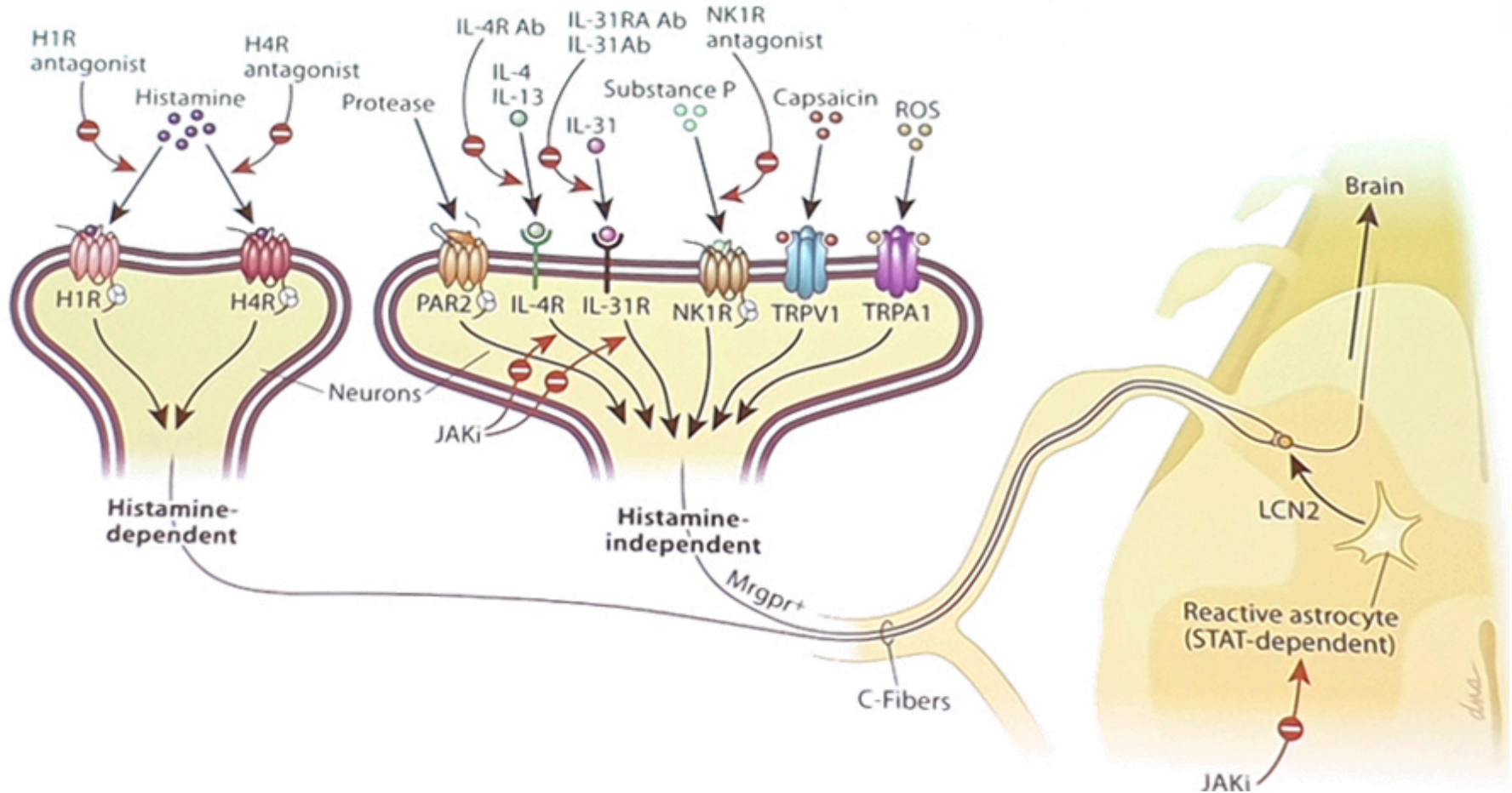
1. Peripheral mediators

Source	Mediators	Receptors
Mast cells	Histamine	H1, H4
	Kallikreins, tryptase, trypsin, cathepsins, and other endogenous/exogenous proteases	PAR-2,
Nerves	Substance P	NK-1R
	CGRP	
Eosinophils	Reactive oxygen	TRPA1 etc
Fibroblasts	Artemin	GFRalpha3
	Nerve growth factor	Nerve growth factor receptor, TrkA
Keratinocytes	Semaphorin 3A	Neuropilin-1 (NRP1)
	Small particles (air pollutants)	AhR (keratinocytes)
	TSLP	TSLP receptors
T cells	IL-2	IL-2 receptor
	IL-31	IL-31 receptor
Endothelial cells	Endothelin	ET1 (ET2)
	Acetylcholine	Ach receptor
Other	SLIGRL	MrgprC11
	beta-alanin	MrgprD

2. Central mediators

Mediators	Receptors
Enkephalin	
Morphine/opioid (such as endorphin)	m receptor (pruritogenic) k receptor (anti-pruritogenic)

Itch mediators



J Allergy Clin Immunol. 2017 Sep;140(3):633-643. doi: 10.1016/j.jaci.2017.07.006.

Therapeutic pipeline for atopic dermatitis: End of the drought?

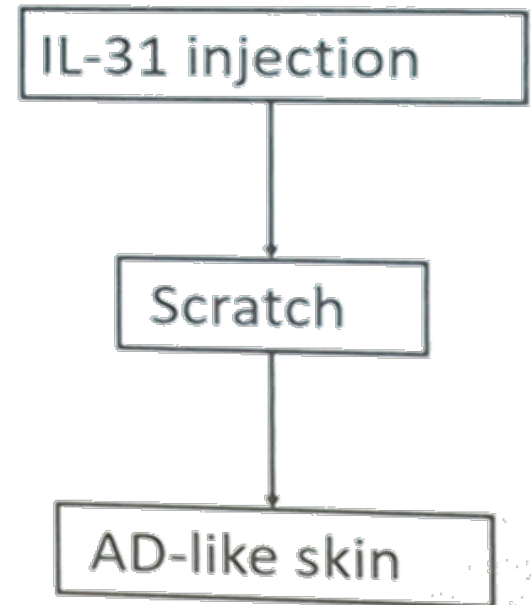
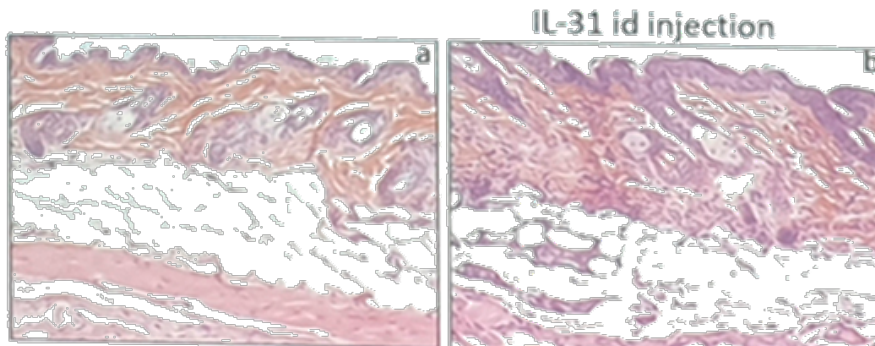
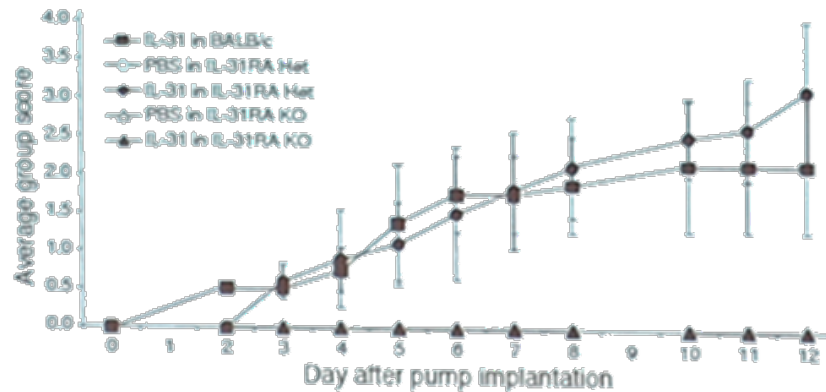
Paller AS¹, Kabashima K², Bieber T³.

Milan



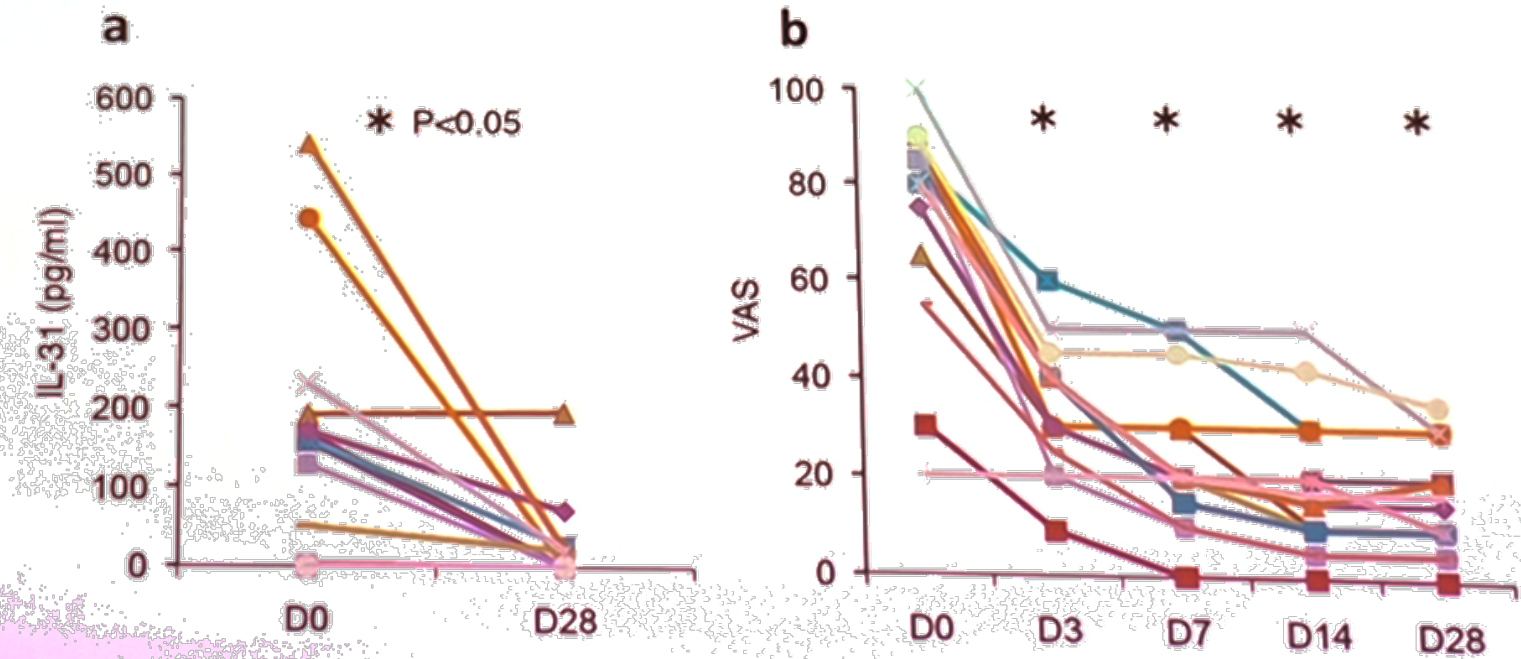
Interleukin 31, a cytokine produced by activated T cells, induces dermatitis in mice.

Dillon SR¹, Sprecher C, Hammond A, Bilsborough J, Rosenfeld-Franklin M, Presnell SR, Haugen HS, Maurer M, Harder B, Johnston J, Bert S, Mudri S, Kuilper JL, Bukowski T, Shea P, Dong DL, Dasovich M, Grant FJ, Lockwood L, Levin SD, LeCiel C, Waggie K, Day H, Topouzis S, Kramer J, Kuestner R, Chen Z, Foster D, Parrish-Novak J, Gross JA.



Effects of cyclosporine on pruritus and serum IL-31 levels in patients with atopic dermatitis.

Otsuka A, Tanioka M, Nakaqawa Y, Honda T, Ikoma A, Miyachi Y, Kabashima K.



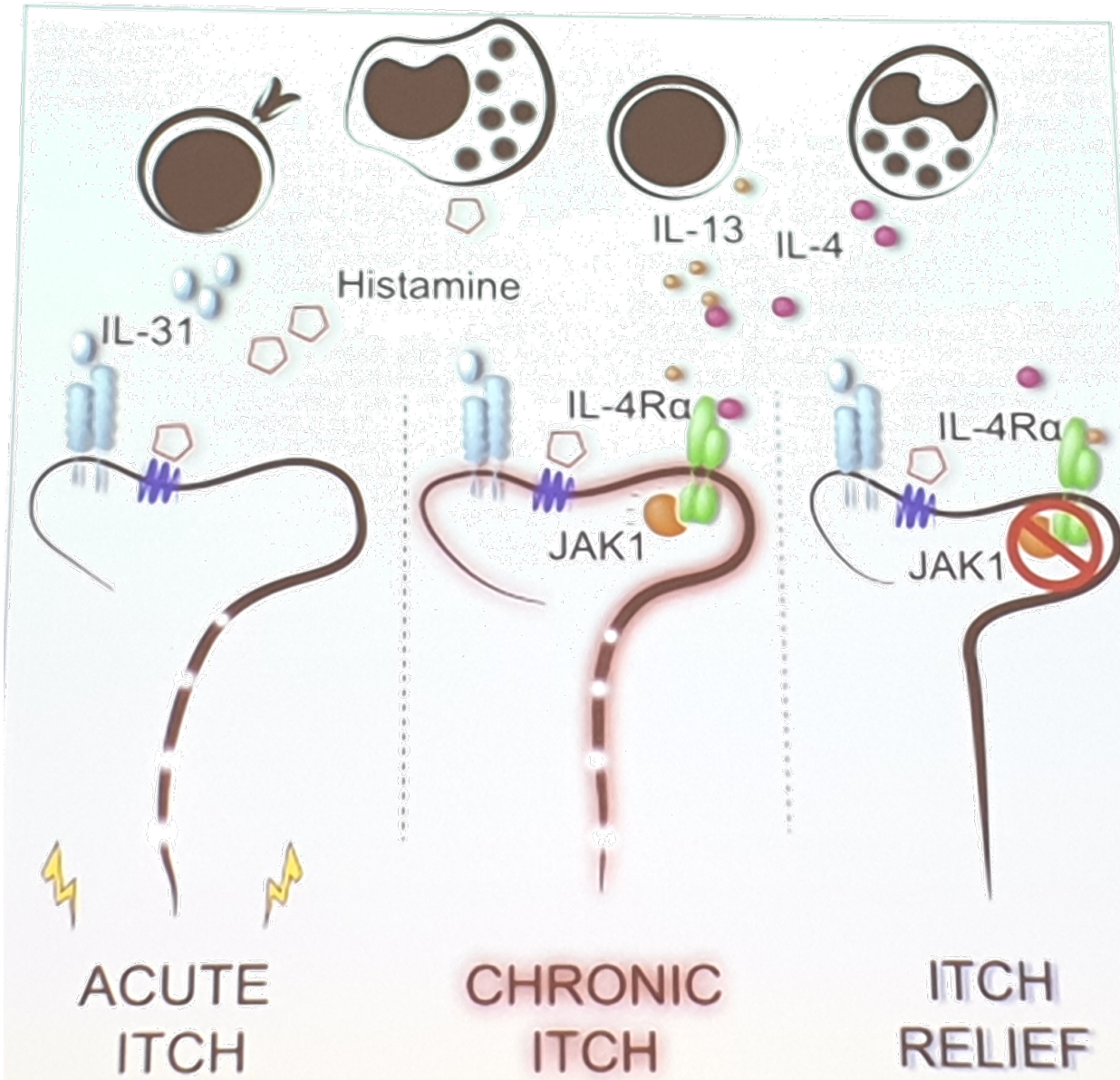
ORIGINAL ARTICLE

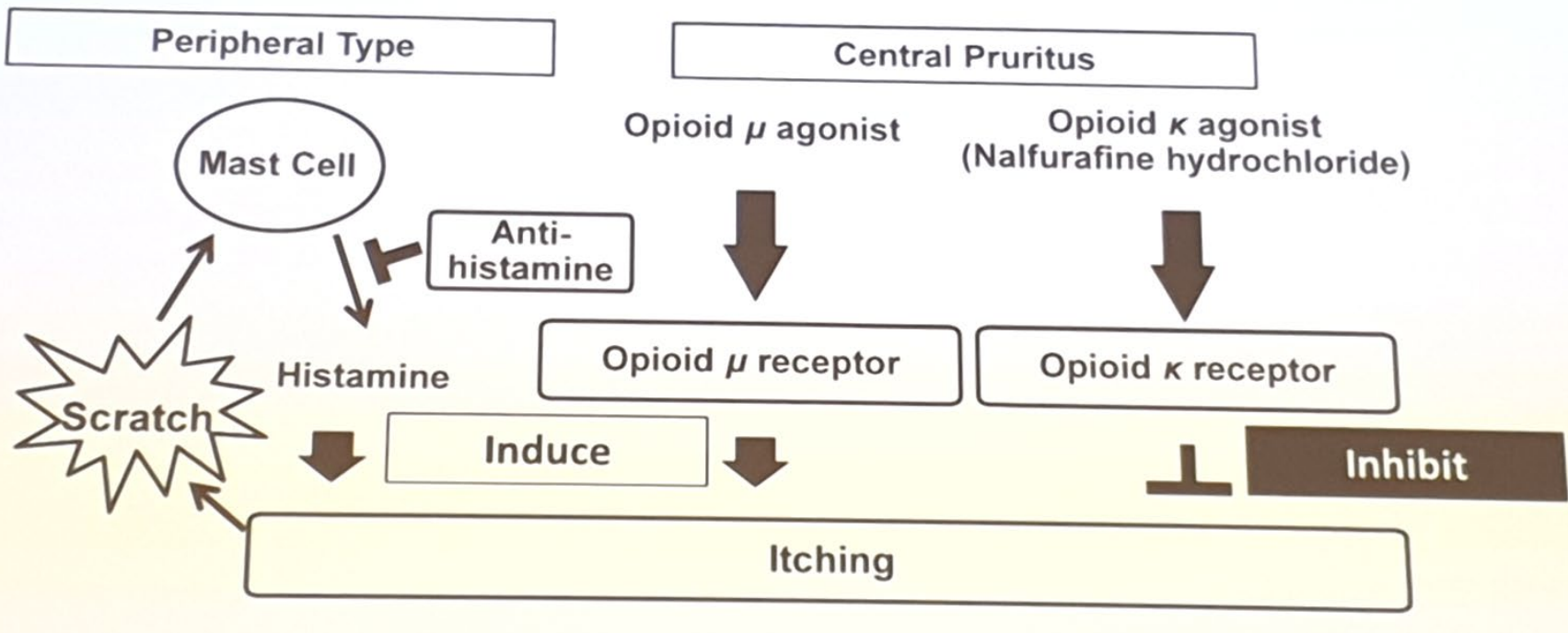
Anti–Interleukin-31 Receptor A Antibody for Atopic Dermatitis

Thomas Ruzicka, M.D., Jon M. Hanifin, M.D., Masataka Furue, M.D., Ph.D.,
Grazyna Pulka, M.D., Izabela Mlynarczyk, M.D., Andreas Wollenberg, M.D.,
Ryszard Galus, M.D., Ph.D., Takafumi Etoh, M.D., Ryosuke Mihara, M.S.,
Hiroki Yoshida, M.S., Jonathan Stewart, M.B., Ch.B.,
and **Kenji Kabashima, M.D., Ph.D.**, for the XCIMA Study Group*

CONCLUSIONS

In this phase 2 trial, nemolizumab at all monthly doses significantly improved pruritus in patients with moderate-to-severe atopic dermatitis, which showed the efficacy of targeting interleukin-31 receptor A. The limited size and length of the trial preclude conclusions regarding adverse events. (Funded by Chugai Pharmaceutical; XCIMA ClinicalTrials.gov number, NCT01986933.)





Kappa agonist for central itch

Long-term efficacy and safety of **nalfurafine** hydrochloride on **pruritus** in chronic liver disease patients: Patient-reported outcome based analyses.

Kamimura K, Yokoo T, Kamimura H, Sakamaki A, Abe S, Tsuchiya A, Takamura M, Kawai H, Yamagiwa S, Terai S.

PLoS One. 2017 Jun 12;12(6):e0178991. doi: 10.1371/journal.pone.0178991. eCollection 2017.

PMID: 28604788 **Free PMC Article**

1. Is patient-reported outcome improved by **nalfurafine** hydrochloride in patients with primary biliary cholangitis and refractory pruritus? A post-marketing, single-arm, prospective study.

Yagi M, Tanaka A, Namisaki T, Takahashi A, Abe M, Honda A, Matsuzaki Y, Ohira H, Yoshiji H, Takikawa H; Japan PBC Study Group (JPBCSG).

J Gastroenterol. 2018 Oct;53(10):1151-1158. doi: 10.1007/s00535-018-1465-z. Epub 2018 Apr 16.

PMID: 29663077

Similar articles

Prevalence and Severity of Itching in Patients with End-Stage Renal Disease: Treatment with **Nalfurafine** Hydrochloride.

Nakamoto H, Kobayashi T, Noguchi T, Kusano T, Ashitani K, Imaeda H, Maezono M.

Blood Purif. 2019;47 Suppl 2:45-49. doi: 10.1159/000496637. Epub 2019 Apr 3.

PMID: 30943482





European Dermatology Forum

European S2k Guideline on Chronic Pruritus

In cooperation with the European Dermatology Forum (EDF) and the European Academy of Dermatology and Venereology (EADV)

Elke WEISSHAAR¹, Jacek C. SZEPIETOWSKI², Florence DALGARD^{3,4}, Simone GARCOVICH⁵, Uwe GIELER⁶, Ana GIMENEZ-ARNAU⁷, Julien LAMBERT⁸, Tabi LESLIE⁹, Thomas METTANG¹⁰, Laurent MISERY¹¹, Ekin SAVK¹², Markus STREIT¹³, Erwin TSCHACHLER¹⁴, Joanna WALLENGREN¹⁵ and Sonja STANDER¹⁶

¹Department of Clinical Social Medicine, Environmental and Occupational Dermatology, Ruprecht-Karls-University, Heidelberg, ²Department of Dermatology, Venereology and Allergology, Wrocław Medical University, Wrocław, Poland, ³Department of Dermatology and Venereology, Skåne University Hospital, Lund University, Malmö, Sweden, ⁴National Centre for Dual Diagnosis, Innlandet Hospital Trust, Brønnøysund, Norway, ⁵Institute of Dermatology, F. Policlinico Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy, ⁶Department of Psychosomatic Dermatology, Clinic for Psychosomatic Medicine, University of Giessen, Giessen, Germany, ⁷Department of Dermatology, Hospital del Mar – Institut Mar d'Investigacions Mèdiques (IMIM), Universitat Autònoma de Barcelona (UAB), Barcelona, Spain, Departments of Dermatology: ⁸University Hospital of Antwerp, University of Antwerp, Belgium, ⁹Royal Free Hospital, London, UK, ¹⁰DKD Helios, Wiesbaden, Germany, ¹¹University Hospital Brest, France, ¹²Adnan Menderes University, Aydin, Turkey, ¹³Kantonsspital, Aarau, Switzerland and ¹⁴Medical University, Vienna, Austria, ¹⁵Department of Clinical Sciences Lund, Dermatology and Venereology, Lund University, Skåne University Hospital, Lund, Sweden, and ¹⁶Center for Chronic Pruritus, Department of Dermatology, University Hospital Muenster, Germany

Corr: Elke Weisshaar, MD, Occupational Dermatology, Department of Dermatology, Ruprecht-Karls University Heidelberg, Voßstr. 2, DE-69115 Heidelberg, Germany. E-mail: elke.weisshaar@med.uni-heidelberg.de



European Guideline on Chronic Pruritus

In cooperation with the European Dermatology Forum (EDF) and the European Academy of Dermatology and Venereology (EADV)

Dr. VERAPOVA, J. & M. KAMBOURIS, C. (2013). J. Am. Acad. Dermatol. 68(5), 911-922. doi:10.1016/j.jaad.2012.08.047. PMID: 22988331.

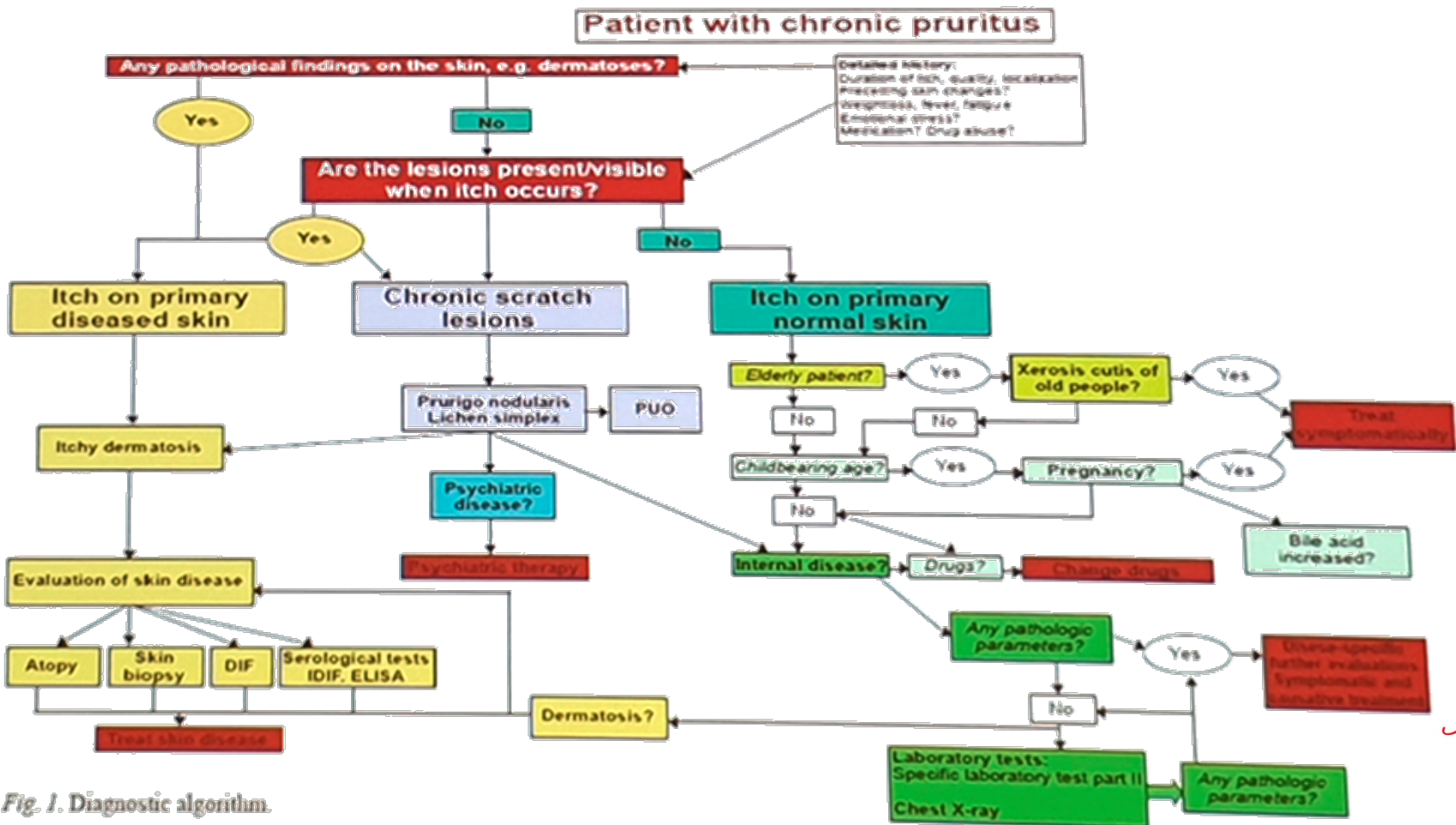


Fig. 1. Diagnostic algorithm.



European Guideline on Chronic Pruritus

In cooperation with the European Dermatology Forum (EDF) and the European Academy of Dermatology and Venereology (EADV)

Elke WEISSHAAR¹, Jacek C. SZEPietowski², Ulf DARSONW³, Laurent MISERY⁴, Joanna WALLENGREN⁵, Thomas METZANG⁶, Uwe GIELER⁷, Tomilla LOTTI⁸, Julian LAMBERT⁹, Peter MAISEL¹⁰, Markus STREIT¹¹, Malcolm W. GREAVES¹², Andrew CARMICHAEL¹³, Erwin TSCHACHLER¹⁴, Johannes RING¹⁵ and Senta STÄNDER¹⁶

Expert recommendation: SSRIs can be recommended for the treatment of somatoform pruritus, paraneoplastic CP, PUO and cholestatic pruritus. Mirtazapine can be recommended in CP of AD.

Weisshaar E et al. Acta Derm Venereol 2012;92: 563-581



European Prurigo Project (EPP)

35 member, 18 countries



- Terminology
- Definition of a clinical profile
- Expert consensus on diagnostics and therapy



Pereira M, Ständer S. *Exp Dermatol*. 2019 May 18. doi: 10.1111/exd.13972.

Pereira M et al. *J Eur Acad Dermatol Venereol*. 2019 Feb;33(2):263-266.

Pereira M et al. *J Eur Acad Dermatol Venereol*. 2018 Dec;32(12):2224-2229.

Pereira M et al. *J Eur Acad Dermatol Venereol*. 2018 Jul;32(7):1059-1065.

Milano



Subtypes of Chronic Prurigo

Chronic prurigo

as an umbrella term for a range of clinical manifestations



Papular prurigo



Nodular Prurigo



Plaque Prurigo



Umbilicated Prurigo



Linear Prurigo

Pereira M et al. J Eur Acad Dermatol Venereol. 2018 Jul;32(7):1059-1065.

Differences between subtypes?

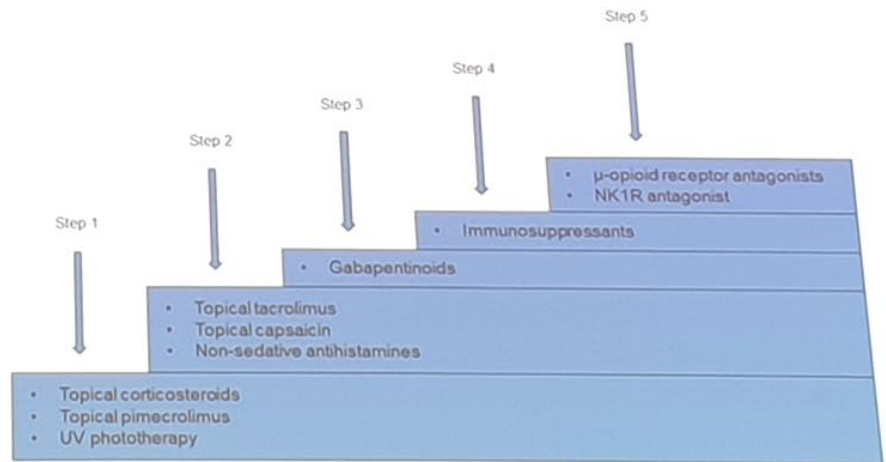
NO

Current Guidelines & Reviews

- Evidence and experience driven recommendations^{1,2}:
 - treatment ladder³

- Treat the underlying disease if possible
- In cases of psychological factors add paroxetine, amitriptyline or mirtazapine
- In cases of severe inflammation add topical steroids
- In cases of remained single nodules inject corticosteroid-triamcinolone intralesional

- Few RCT available⁴:
 - topical steroids
 - topical calcipotriol
 - topical pimecrolimus
 - PUVA, excimer



European Guideline: Acta Derm Venereol. 2019 Apr 1;99(5):469-506;
German Guideline: J Dtsch Dermatol Ges. 2017 Aug;15(8):860-872
Zeidler C, Yosipovitch G, Ständer S. Dermatol Clin. 2018; 36:189-197;
Qureshi AA et al. J Am Acad Dermatol. 2019; 80:756-764

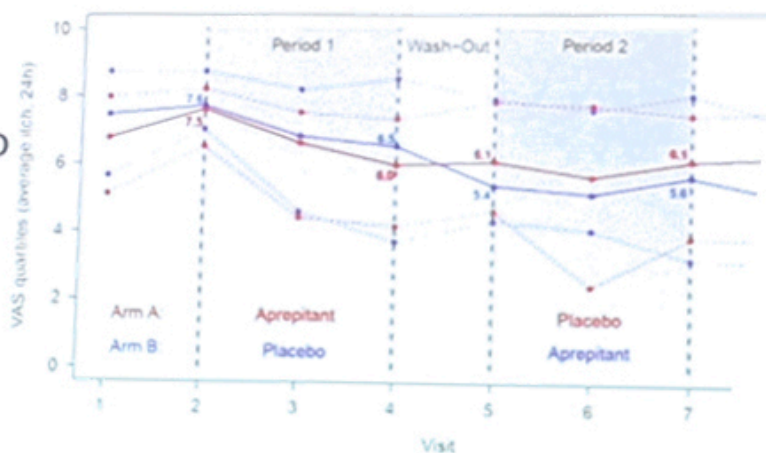


Future therapy chronic prurigo

- Until 2013 no clinical trials for systemic substances
- Randomized controlled trials
 - NK1 antagonist (phase III ongoing)
 - Opioid receptor modulators (phase III ongoing)
 - Interleukin 31 antagonist (phase II terminated)

Aprepitant in Chronic Nodular Prurigo

- 58 patients with prurigo nodularis
- 5 centers in Germany
- Two arms: 80 mg aprepitant / placebo
- No significant difference to placebo
- Side effects: mild to moderate
- Sample size: 19 patients per group
- Naïve population
- (negative or positive) expectations

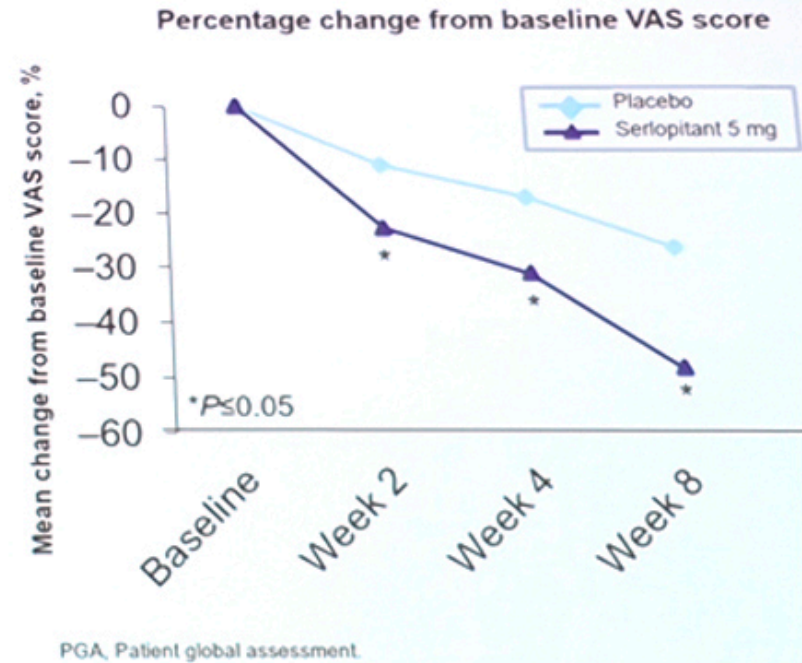


Line: 50 quartile;
Dashed line: 25 and 75 quartile



Serlopitant in Chronic Nodular Prurigo

- 127 patients with prurigo nodularis
- 15 centers in Germany
- Two arms: 5 mg serlopitant / placebo
- Significant difference to placebo
- Week 8, Visual Analogue Scale (VAS)
- Primary endpoint: -3.6 cm vs -1.9 cm VAS
- 4 point decrease (Responder): 54% vs. 25%
- Side effects: mild to moderate

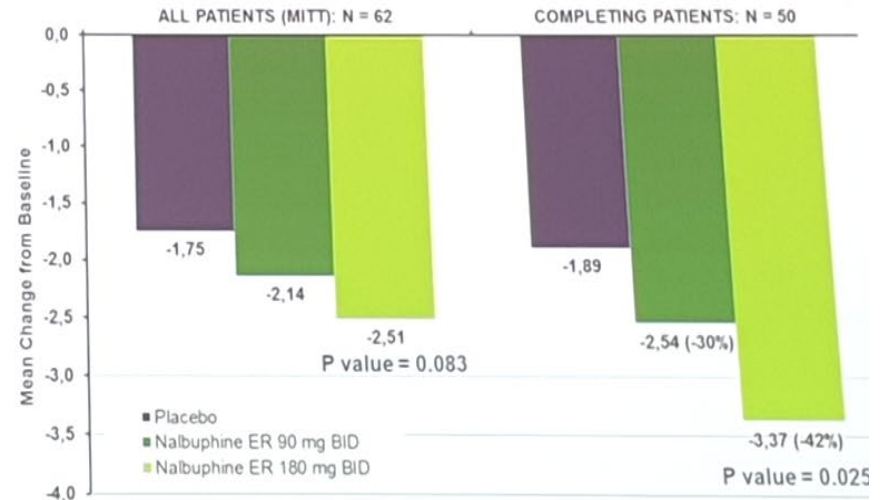


Ständer et al. J Am Acad Dermatol. 2019; 80: 1395-1402



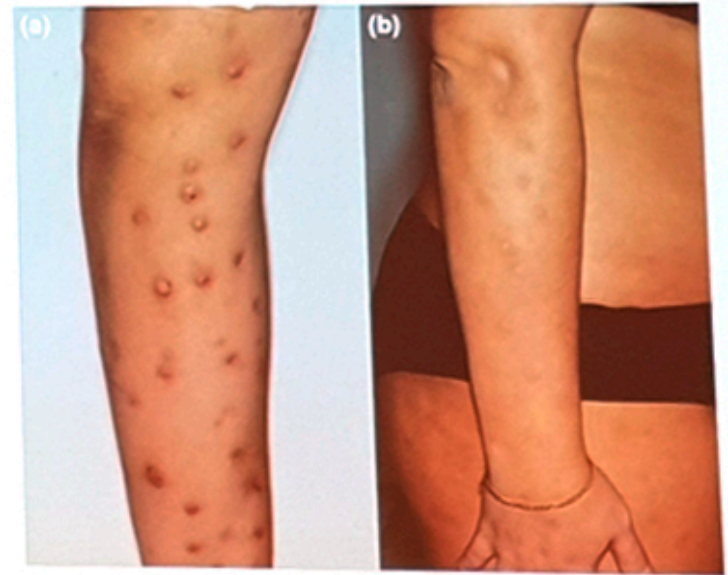
Nalbuphine in Chronic Nodular Prurigo

- 62 patients with prurigo nodularis
- Three arms: 180/360 mg nalbuphine/ placebo
- Significant difference to placebo in completers
Week 10, NRS
Primary endpoint: -3.4 cm vs -1.9 cm VAS
- Side effects: moderate



Dupilumab

- 8 patients
 - Calugareanu: n=1
 - Beck: n=3
 - Mollanazar: n=4
- Quick relief of itch and nodules



Calugareanu A et al.

¹Calugareanu A et al. J Eur Acad Dermatol Venereol. 2019. doi: 10.1111/jdv.15584

²Beck KM et al. JAMA Dermatol. 2019; 155: 118-120.

³Mollanazar NK et al. JAMA Dermatol. 2018 doi: 10.1001/jamadermatol.2018.3906

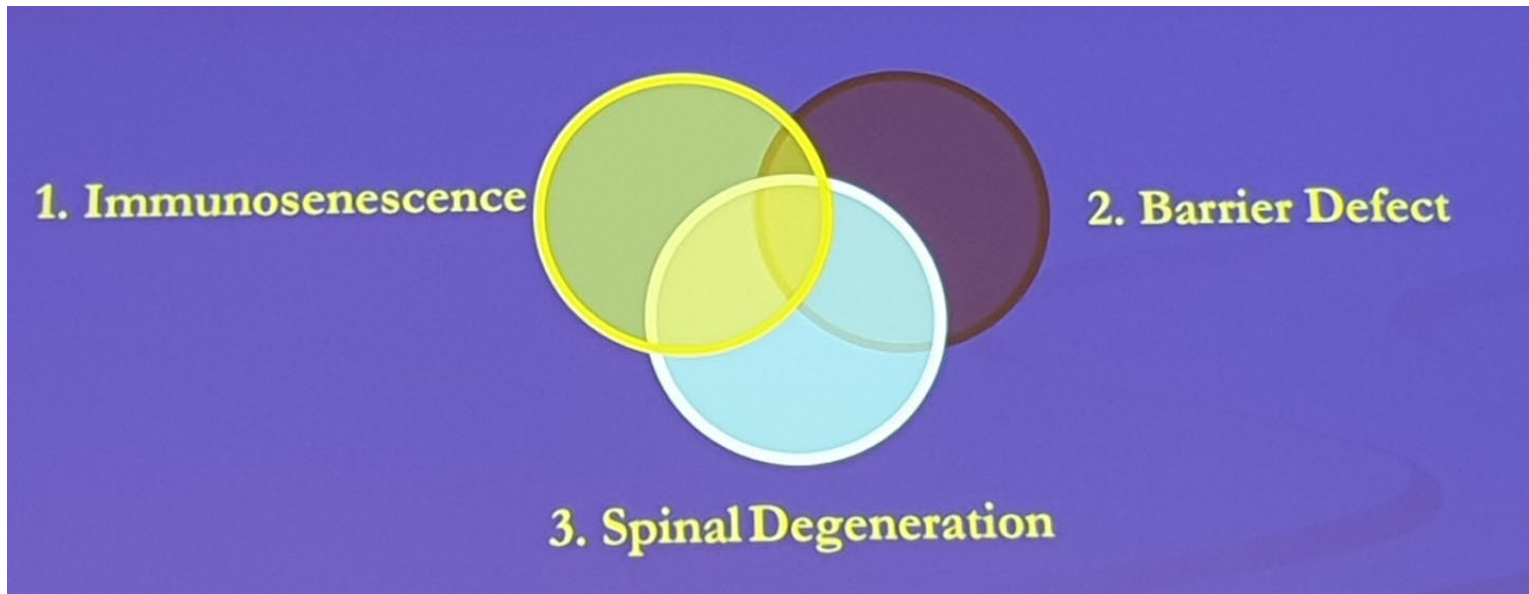
Itch in the elderly

- Scabies
- Drugs: Calcium Channel Blockers can cause eczematous dermatitis (eczema can start up 14 years after starting tt^o and last up to one year after stopping)



Why are the elderly more itchy?

- Skin barrier
- Immune System : Immunosenescence
- Nervous System: Neuropathy/Degenerative spine disease



- Most elderly patients with severe, chronic pruritus have an inflammatory dermatosis
- Elderly itchy patients often have MULTIPLE causes for their pruritus
- The elderly patient with eczema DOES NOT have atopic dermatitis, they usually have contact dermatitis, numular eczema, bullous pemphigoid, drug eruption or MF

Diagnostic workup

- Biopsy and DIF
- Based on morphology and history: patch testing, photo-testing/ELISA for BP antigen/T cell Gene Rearrangements
- If this is all negative and the patient does not respond to treatment, AND the itch is >7 , start a work up for cancer:CT, T cell subsets.

Antihistamines

1st generation: Hydroxyzine

2nd generation:

Fexofenodine, Loratadine,
Ceterizine

Neural Agents

Gabapentin/Pregabalin

Doxepin

Mirtazipine

Amitriptyline (TCA's)

Mexilitine

Aprepitant

Duloxetine

Cannabinoids

Marinol (THC)

Opiate Pathway

Naltrexone

Butorphanol

Kappa-Agonist
(Nalfurefine)

Photo- Therapy

nb-UVB

bb-UVB (renal)

PUVA