ACNE ferrara 2017

14° Meeting di aggiornamento su acne e dermatosi

La sapete l'ultima:

Terapia Topica: quale approccio

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Disclosures: Galderma; La Roche Posay

Rosacea

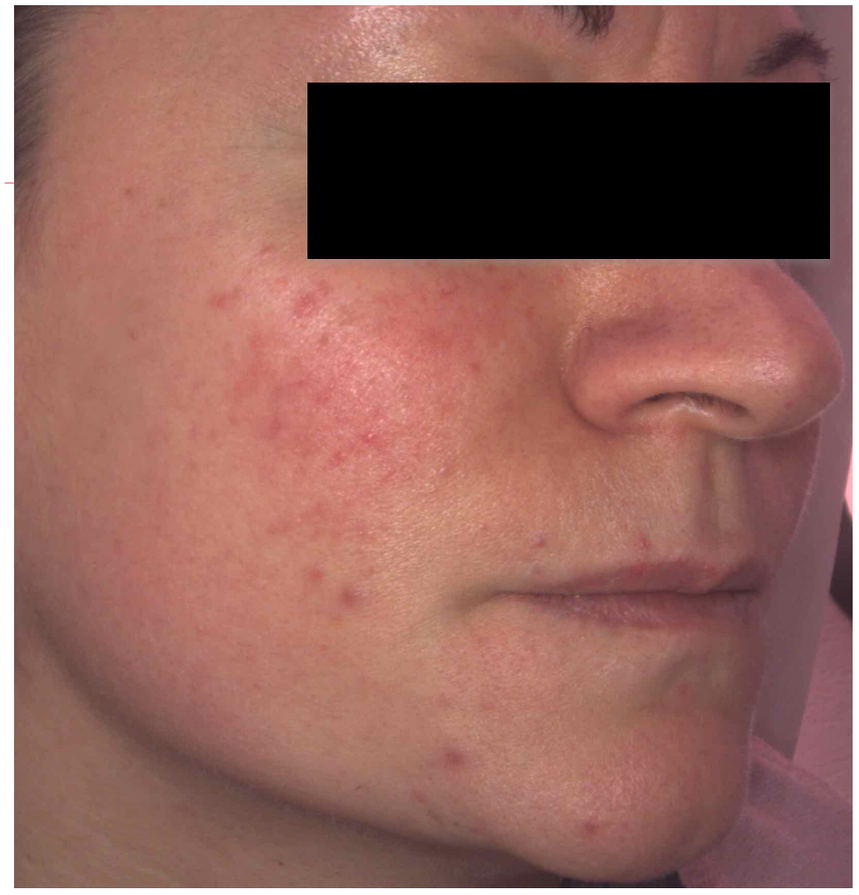
- Rosacea is a common centrofacial skin disease

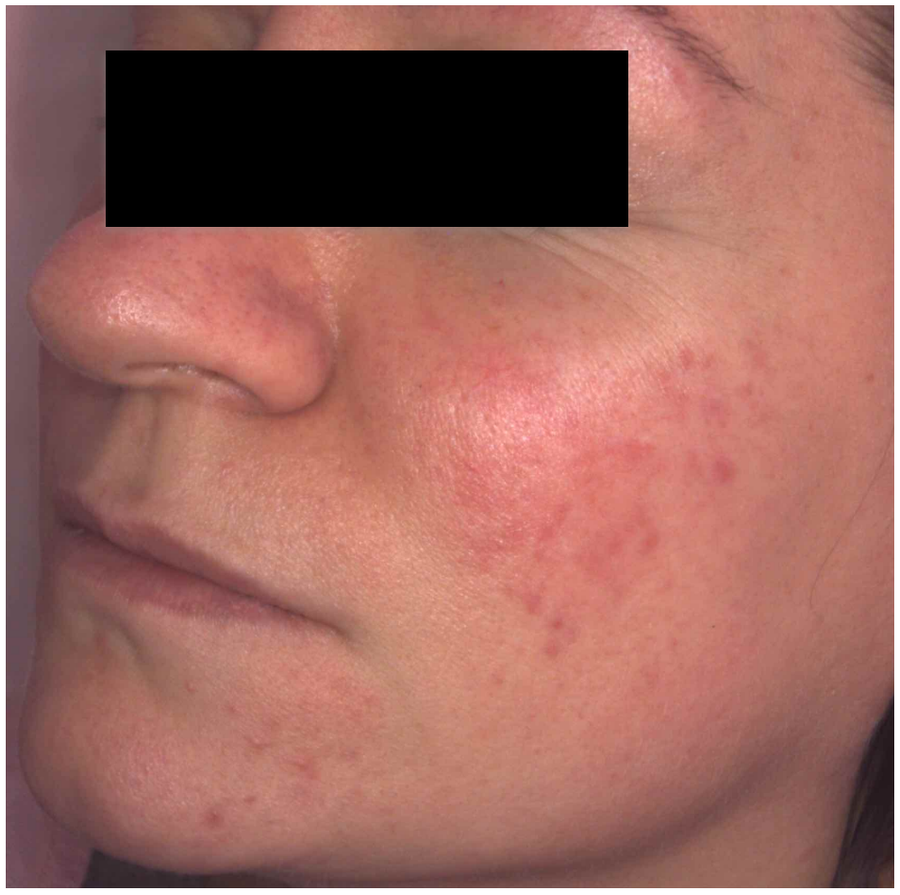
- In the past: starts as flush-like temporary dilation of capillaries and fleeting erythema, subsequently telangiectasias develop and persisting erythematous macules; in severe cases, development of pustules and disfiguring growth of hyperplastic sebaceous glands on the nose and other facial regions occurs

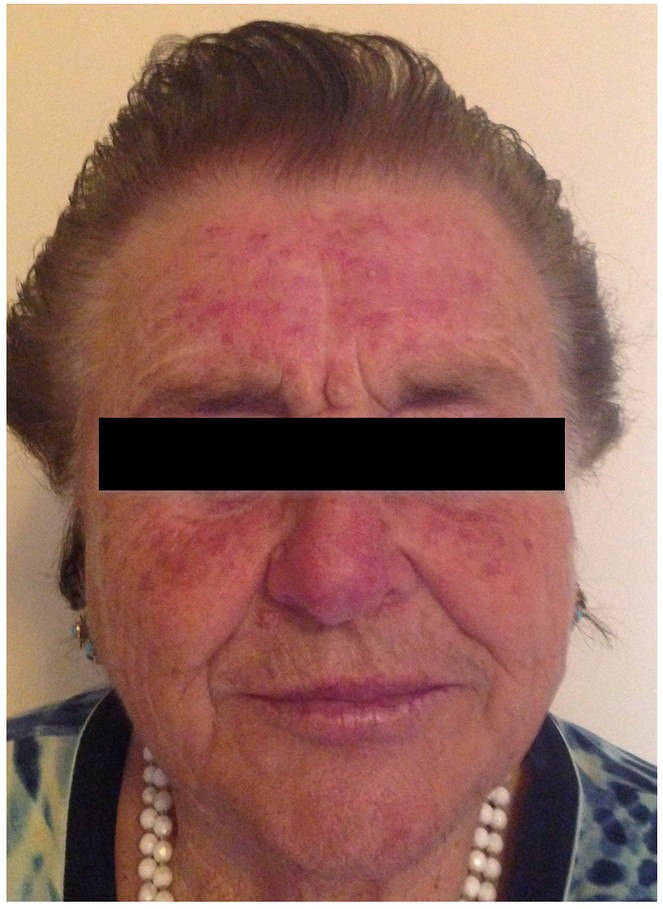
- Incidence: 165/100 000 person/year,[1] prevalence varies greatly between countries from 1% to 22%; persons with fair skin type have an increased risk of rosacea

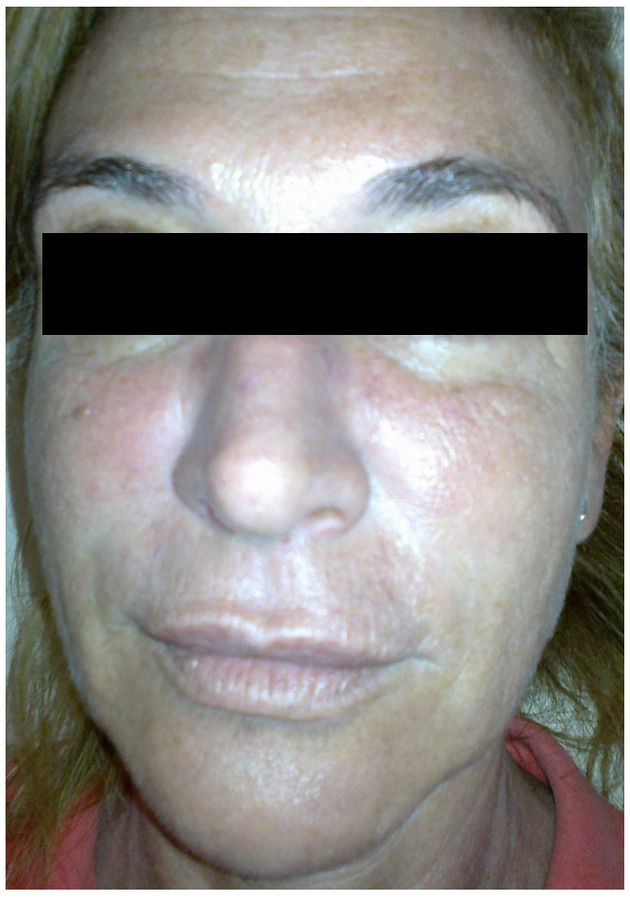
- "… While recently, an expert panel of dermatologists and ophthalmologists has agreed on a **phenotype-based classification** (transient and persistent erythema, telangiectasias, inflammatory papules or pustules, and phyma),[14] the most commonly used classification refers to **subtype** …"

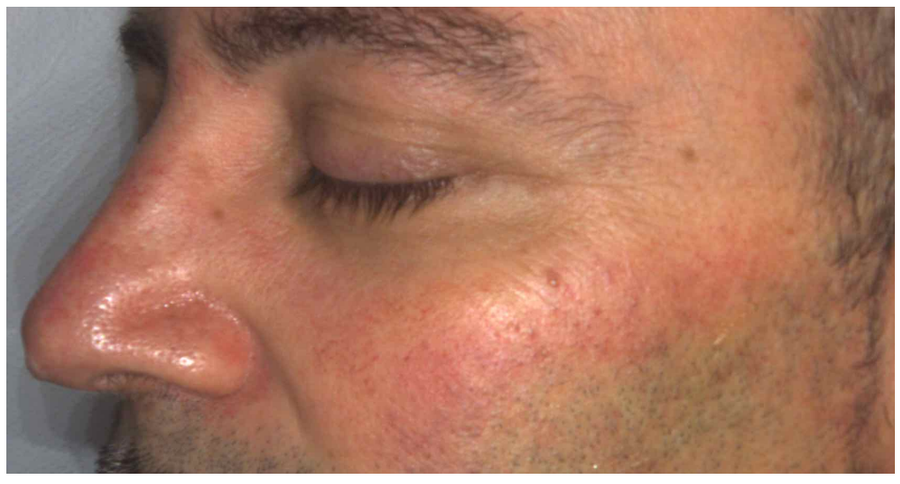
Swiss S1 guideline for the treatment of rosacea JEADV 2017, 31, 1775–1791

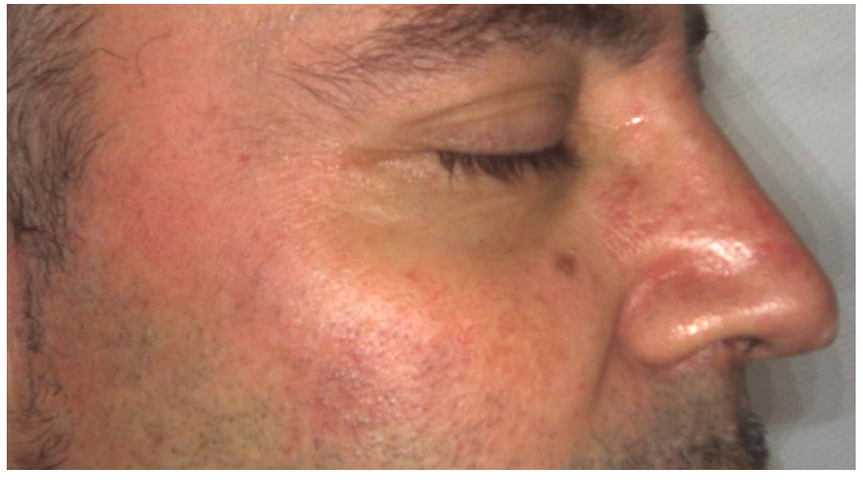






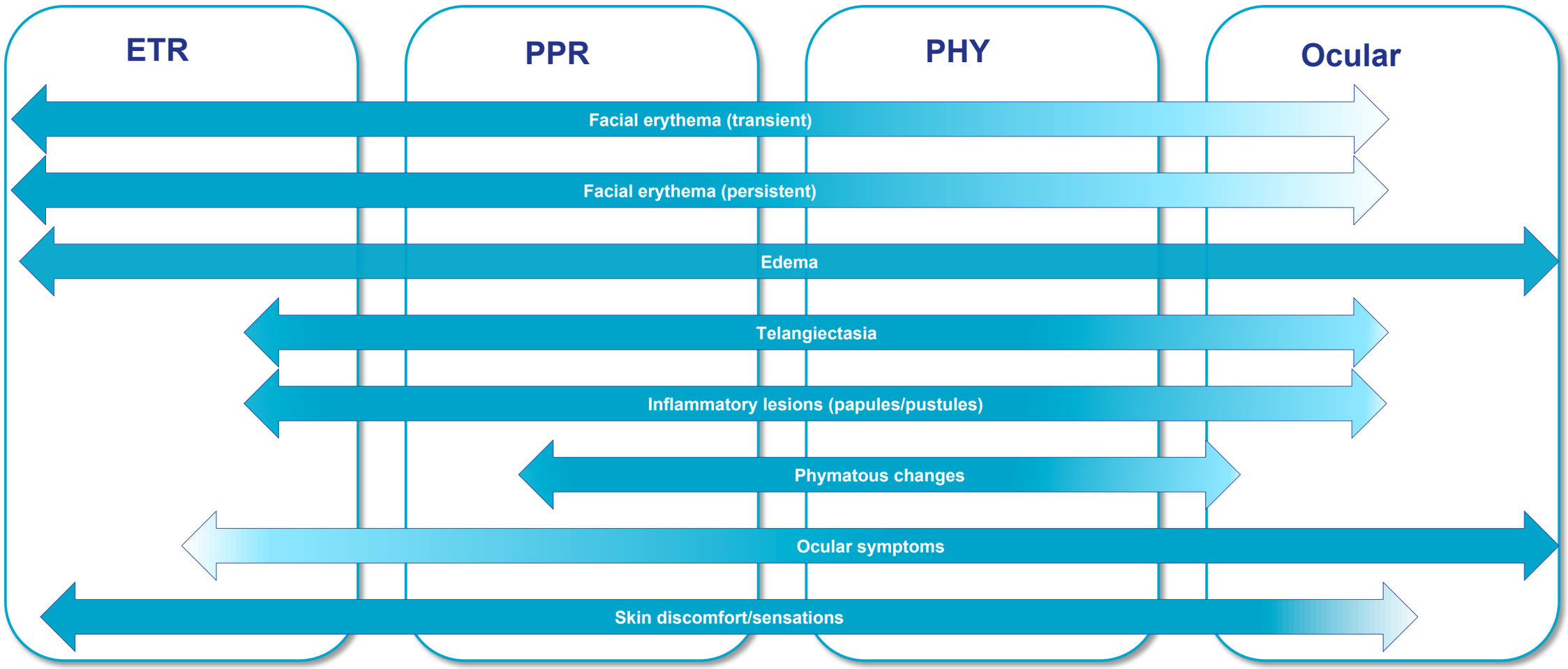






Sub-Type⟷Pheno-Type

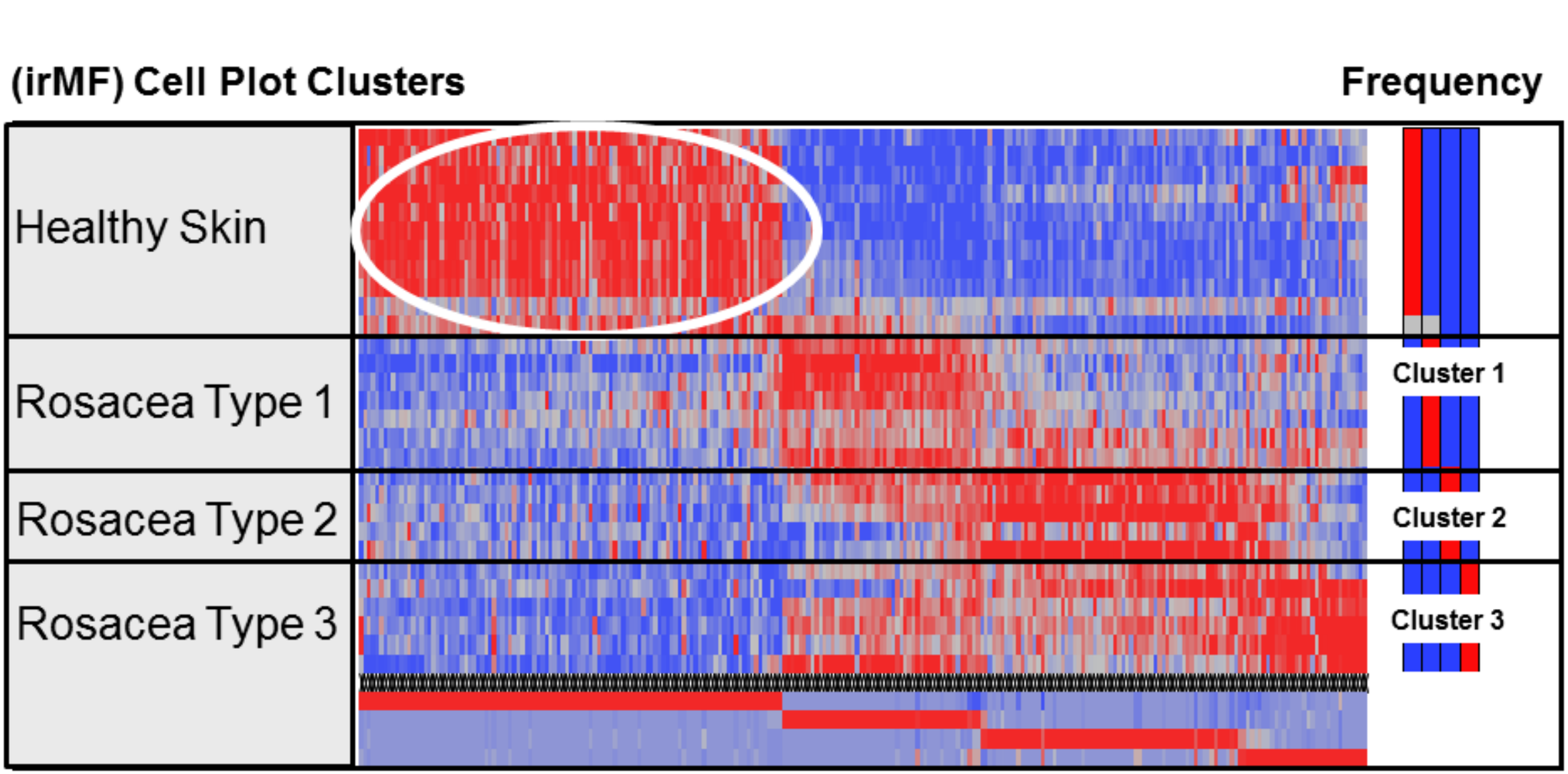
- In clinical practice, pt often present with a range of symptoms that include *more than one of these defined subtypes*[1]



Important to focus on individual treatment strategies and treating the individual symptoms for the benefit of the patient

Tan J, et al. Br J Dermatol 2013;169(3):555–62; Br J Dermatol. 2016 Oct 8. doi: 10.1111/bjd.15122

Gene Arrays: Molecular Characterization of Rosacea subtypes



Regulation of more than 313 known genes as compared with controls

Steinhoff M, **Buddenkotte J**. J Investig Dermatol Symp Proc. 2011 Dec;15(1):2-11

Tailored therapies

J Dtsch Dermatol Ges. 2016 Dec;14 Suppl 6:4-15. doi: 10.1111/ddg.13139.

Pathogenesis and clinical presentation of rosacea as a key for a symptom-oriented therapy.

Reinholz M[1], Ruzicka T[1], Steinhoff M[2], Schaller M[3], Gieler U[4], Schöfer H[5], Homey B[6], Lehmann P[7], Luger TA[8].

Author information

Abstract

Rosacea is a common chronic inflammatory skin disorder that typically occurs in adults and affects the face. Synonyms of rosacea include "acne rosacea", "couperose" and "facial erythrosis", in German also "Kupferfinne" and "Rotfinne". The disorder is characterised by a chronic and flaring course and is caused by a genetically predisposed, multifactorial process. A higher incidence is seen in people with fair skin and a positive family history. The characteristic rosacea symptoms manifest primarily, but not exclusively centrofacially, with forehead, nose, chin and cheeks significantly affected. Based on the various main symptoms a classification of the individual clinical pictures can be performed. However, a classification often does not reflect the clinical reality, since the various symptoms commonly coexist. The present review provides an introduction on pathogenesis and clinical manifestations of rosacea and prefers a symptom-oriented therapy approach.

J Dtsch Dermatol Ges. 2016 Dec;14 Suppl 6:17-27. doi: 10.1111/ddg.13143.

Rosacea Management: Update on general measures and topical treatment options.

Schaller M[1], Schöfer H[2], Homey B[3], Hofmann M[4], Gieler U[5], Lehmann P[6], Luger TA[7], Ruzicka T[8], Steinhoff M[9].

Author information

Abstract

Although there is presently no cure for rosacea, there are several recommended treatment options available to control many of the symptoms and to prevent them from getting worse. In addition to self-help measures like avoidance of trigger factors and proper skin care, rosacea management should include topical medications as one of the first-line choices for patients with erythematous and mild to severe papulopustular rosacea. Since mixed forms of characteristic rosacea symptoms are more common, medical treatment must be symptom-tailored for each individual case and will often involve a combination therapy. Approved topical agents for the major symptoms of rosacea encompass brimonidine for erythema and ivermectin, metronidazole or azelaic acid for inflammatory lesions, all of which have shown their efficacy in numerous valid, well-controlled trials. In addition, there are several other, not approved topical treatments which are possible options that require further validation in larger well-controlled studies.

	Flushing/ Transient Erythema	Persistant Erythema	Teleangi-ectasia	Inflammatory Lesions	Connective Tissue/ Sebaceous Hyperplasia	Ocular Rosacea
	General Measures: Patient education, avoidance of triggers, sun-protection, skincare, doctor-patient relationship, etc.					
MEDICINAL – approved		**Topical therapy:** – Brimonidine 3 mg/g (++++)		**Topical therapy:** – Ivermectin 10 mg/g (++++) – Azelaic acid 150 mg/g (++++) – Metronidazole 7,5 mg/g (+++)	**Topical therapy:** – Ivermectin 10 mg/g (++++) **Systemic therapy:** – Low-dose, modified-release doxycycline 40 mg (++++) **In severe and/or treatment-resistant rosacea:** Combination of topical and/or systemic anti-inflammatory therapy	
MEDICINAL – off label	**Systemic therapy:** Beta blockers, e.g. Carvedilol	**Systemic therapy:** Beta blockers, e.g. Carvedilol		**Topical therapy:** – Permethrin – Benzyl benzoate – Retinoids – Calcineurin-inhibitors **Systemic therapy:** – Low-dose Isotretinoin (++++) – Doxycycline (++++) – Tetracycline (+++) – Azithromycin (+) **In severe and/or treatment-resistant rosacea:** Combination of topical and/or systemic anti-inflammatory therapy	**Systemic therapy:** – Low-dose Isotretinoin	**Systemic therapy:** – Doxycycline: low-dose (40 mg) or conventional dose – Low-dose Isotretinoin **Topical therapy:** – Cyclosporin A (++) – Azithromycin – Tetracycline – Steroids

Severity

Luger TA, Ruzicka T, Steinhoff M. JDDG | 1610-0379/2016/14 (Suppl. 6) 17–27

Swiss recommendationons for Rosacea

	Rosacea grade (classical)	I		II	III	IV
	Rosacea grade (new)	**Erythema**	**Telangiectasias**	**Papules/Pustules**	**Phyma**	**Ocular Rosacea**
Topical drugs	Azelaic acid	+	No data	+++	No data	(+)
	Botulinum toxin	–	No effect	No data	No data	No data
	BPO/Clindamycin	No data	No data	++	No data	No data
	Brimonidine	+++	No effect	No data	No data	No data
	Dapsone	No data	No data	Not available in CH	No data	No data
	Erythromycin	No data	No data	++	No data	No data
	Ivermectin	No data	No data	+++	No data	+
	Metronidazole	+	No data	+++	No data	++
	Permethrin	No data	No data	+	No data	No data
	Pimecrolimus	+	No data	++	No data	No data
	Retinoids	No data	No data	++	No data	No data
	Steroids	–	–	–	–	+
	Tacrolimus	+	No data	–	No data	+

JEADV 2017, 31, 1775–1791

Rosacea treatment update: recommendations from the ROSCO Panel

		Inflammatory papules/pustules				Phyma	
Transient erythema[a]	Persistent erythema[b]	Mild	Moderate	Severe	Telangiectasia	Clinically inflamed	Clinically noninflamed
α-adrenergics (topical)	Brimonidine (topical)	Azelaic acid (topical)	Azelaic acid (topical)	Ivermectin (topical)	Electrodessication	Doxycycline (oral)[c]	Physical modalities
Beta blockers (oral)	IPL	Ivermectin (topical)	Ivermectin (topical)	Doxycycline (oral)[c]	IPL		
	PDL	Metronidazole (topical)	Metronidazole (topical)	Isotretinoin (oral)	Lasers		
		Doxycycline (oral)[c]	Doxycycline (oral)[c]			Isotretinoin (oral)	

General skincare (sun protection factor 30+, moisturizers, gentle cleansers, trigger avoidance).

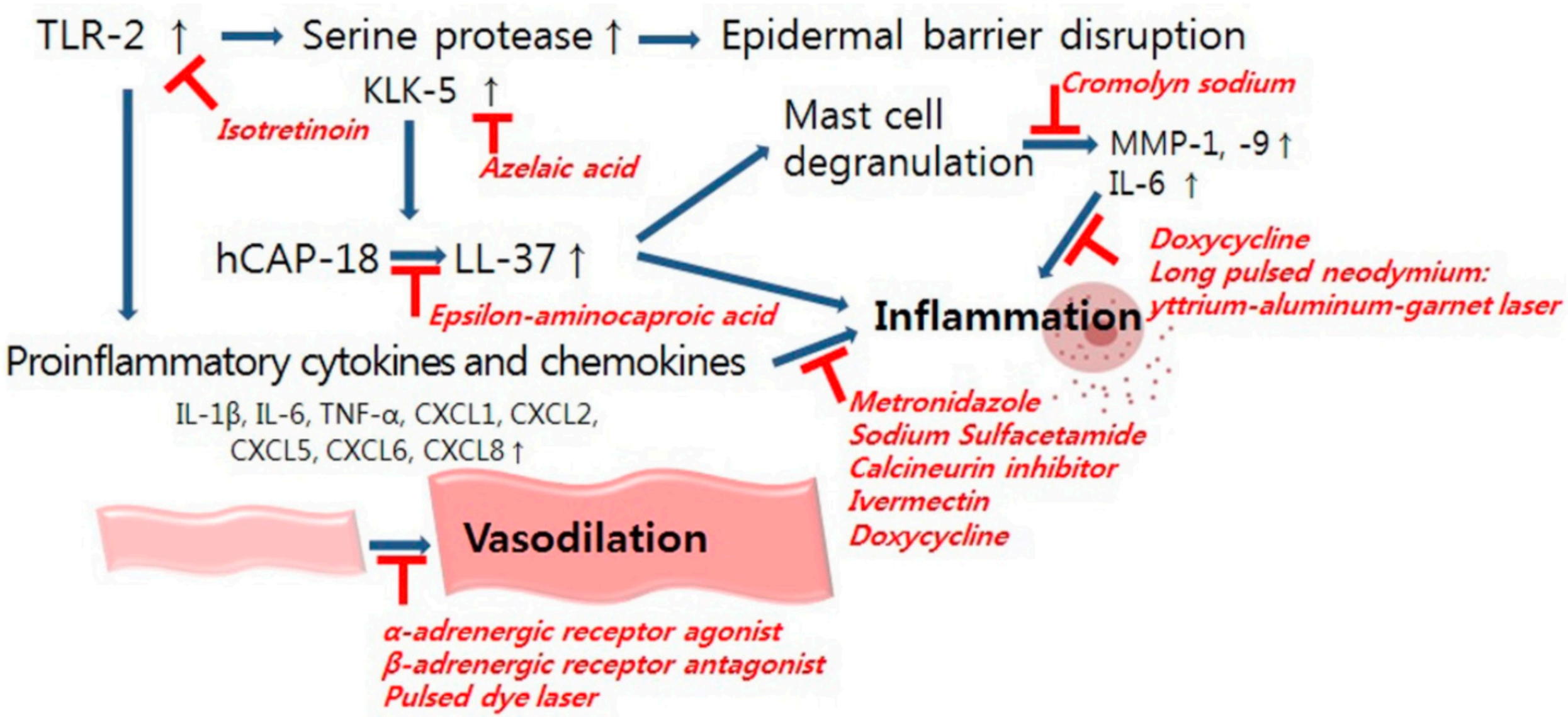
Not all products or indications are licensed in every country and may be subject to further local variations. For specific product information the local label should always be consulted. Doxy, doxycycline; IPL intense pulsed light; PDL, pulsed-dye laser. [a]There is no high-quality evidence for flushing treatments; consensus on this statement is based on case reports and clinical evidence. [b]Persistent centrofacial erythema associated with periodic intensification by potential trigger factors. [c]Doxycycline 40 mg superior to placebo; doxycycline 40 mg noninferior to doxycycline 100 mg. No inference possible from indirect comparison.

Phenotype-led treatment algorithm drawn from the consensus statements relating to major cutaneous features,

The treatments listed in the table are considered first-choice options for the treatment of each rosacea feature.

M. Schaller, J. Tan . British Journal of Dermatology (2017) 176, pp465–471

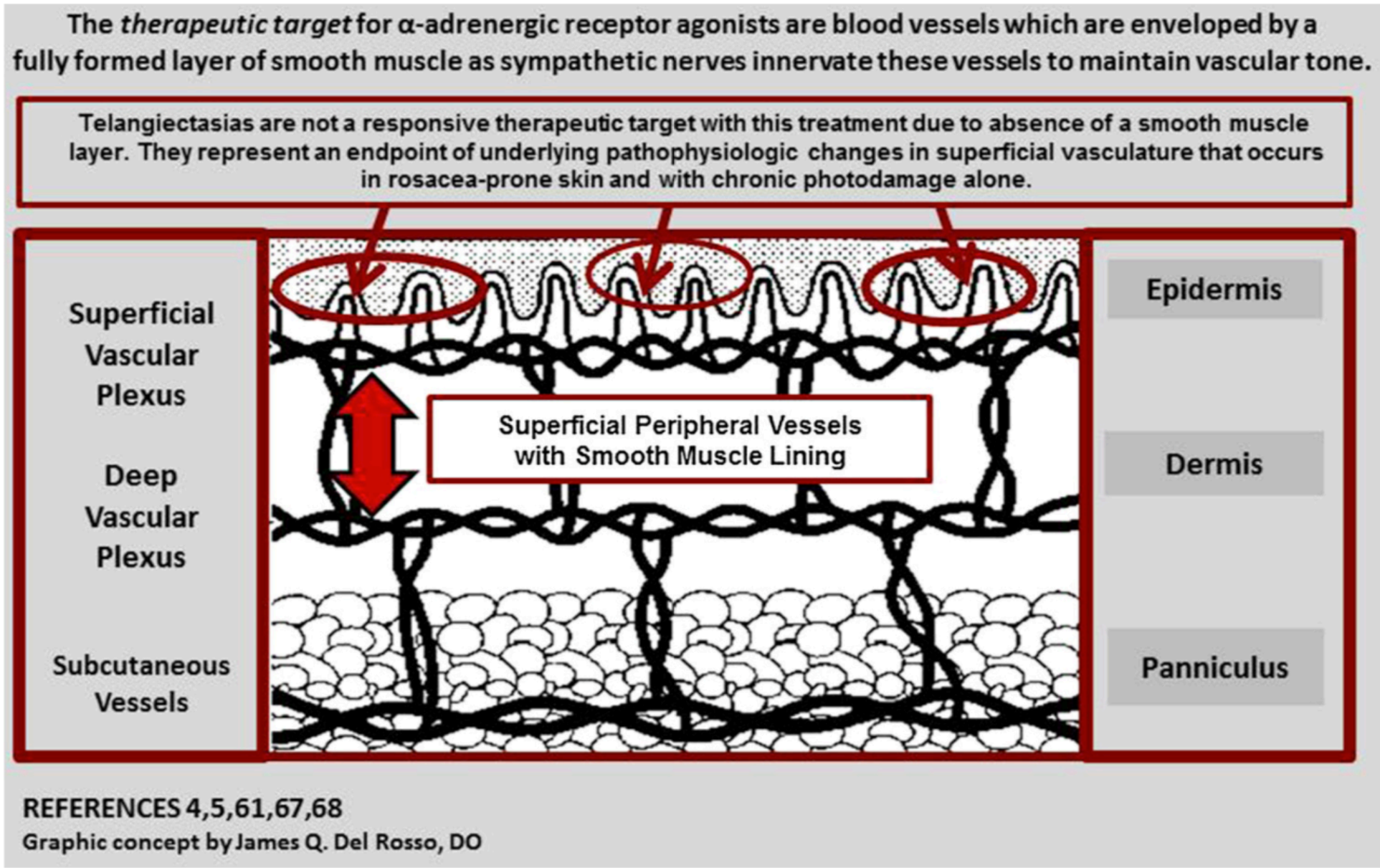
Rosacea treatment update: MoA



Int. J. Mol. Sci. **2016**, *17*, 1562

α-adrenergics

Modulation of cutaneous vasculature by a-adrenergic receptor agonists

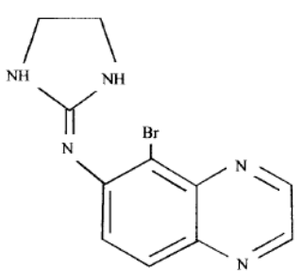


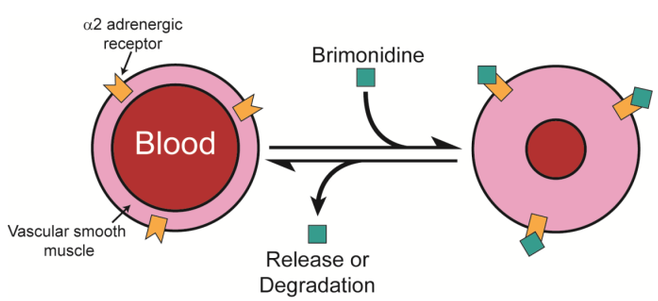
JQ Del Rosso. J Am Acad Dermatol 2013;69:S44-56

α-adrenergics

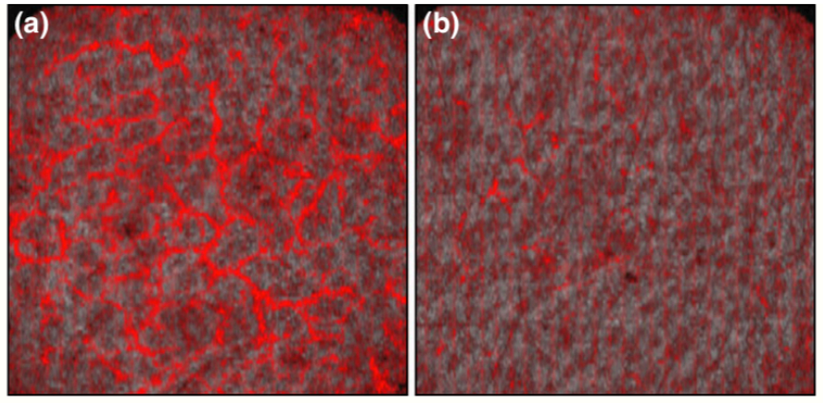
Brimonidine α-2 receptor agonist

Brimonidine gel





Brimonidine is a highly specific alpha$_2$−adrenergic receptor agonist



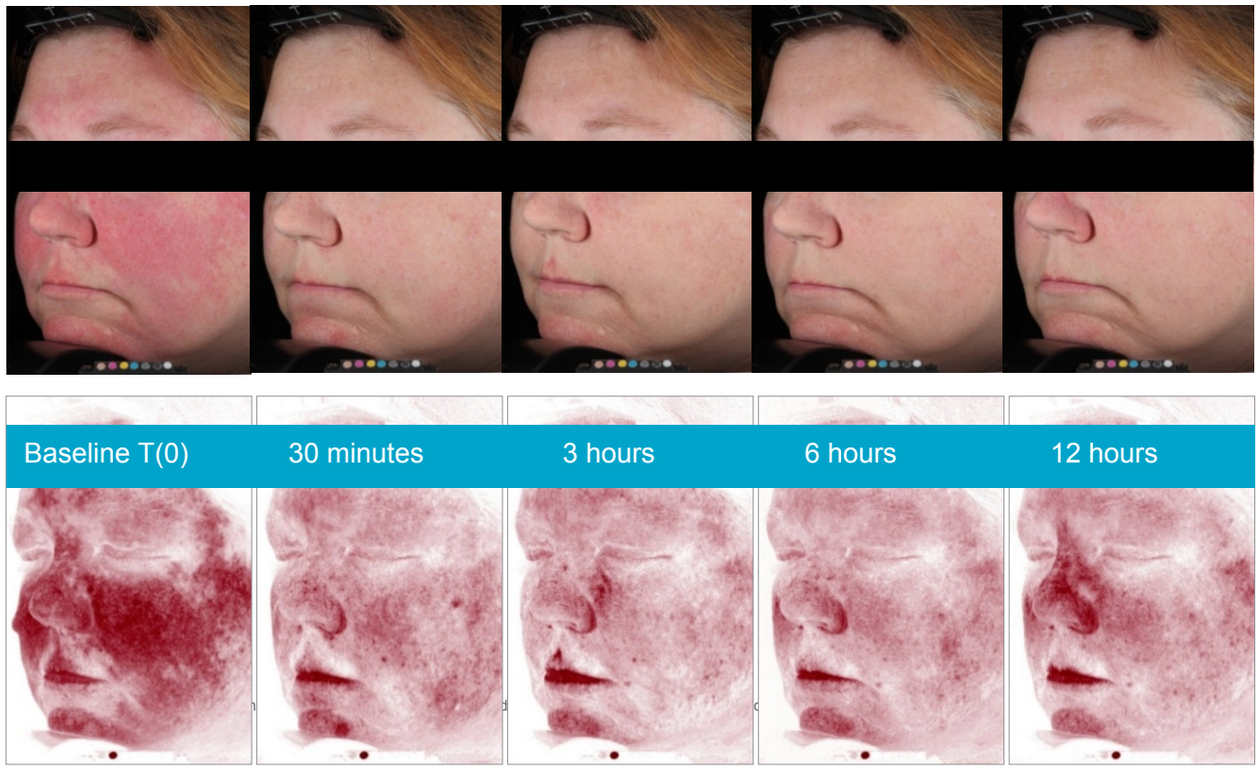
Dynamic OCT image, en face view, of normal skin located on the cheek before [image (a)] and 60 min after application of topical brimonidine [image (b)]. Image (a) shows a conspicuous network of blood vessels. In image (b) the application of brimonidine has led to an almost complete clearance of visible vessels

JEADV 2016, 30, 974–979

Over a 4-week treatment period, once-daily topical Brimonidine Gel was significantly more effective at reducing erythema than vehicle gel over 12 hours

1-grade improvement on clinician and patient assessment provided a noticeable, clinically relevant effect

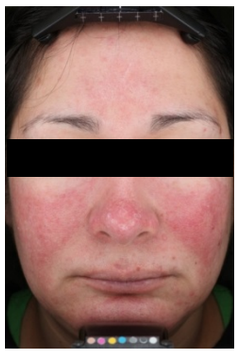
2-grade improvement on clinician and patient assessment required for regulatory approval



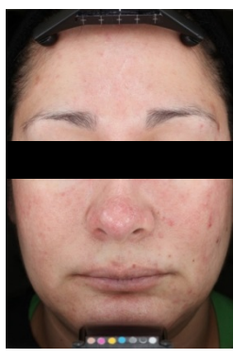
Fowler J, *et al. J Drugs Dermatol* 2013;12(6):650–6. **2.** Jackson JM, *et al. J Drugs Dermatol* 2014;13(6):699–704.

Long term (1-year) safety study

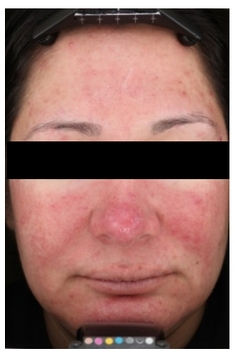
Patient with inflammatory lesions treated with Brimonidine Gel



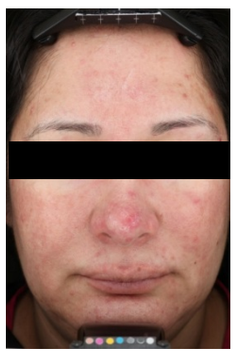
Baseline



3 hours

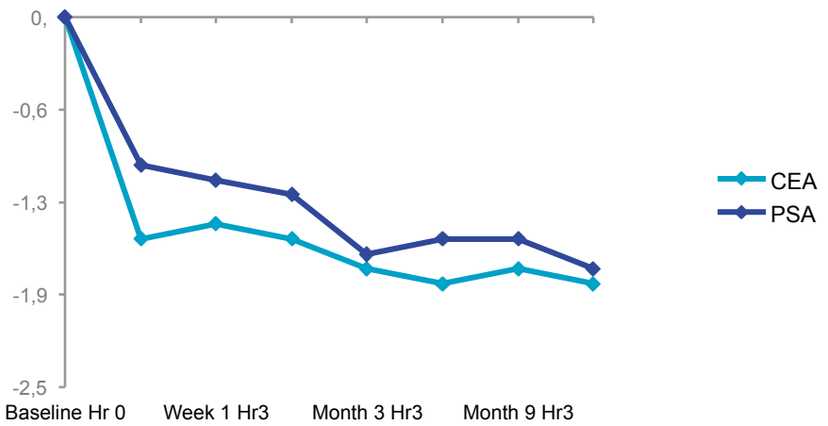


Month 12
0 hours



Month 12
3 hours

Mean change in CEA and PSA from baseline over 12 months

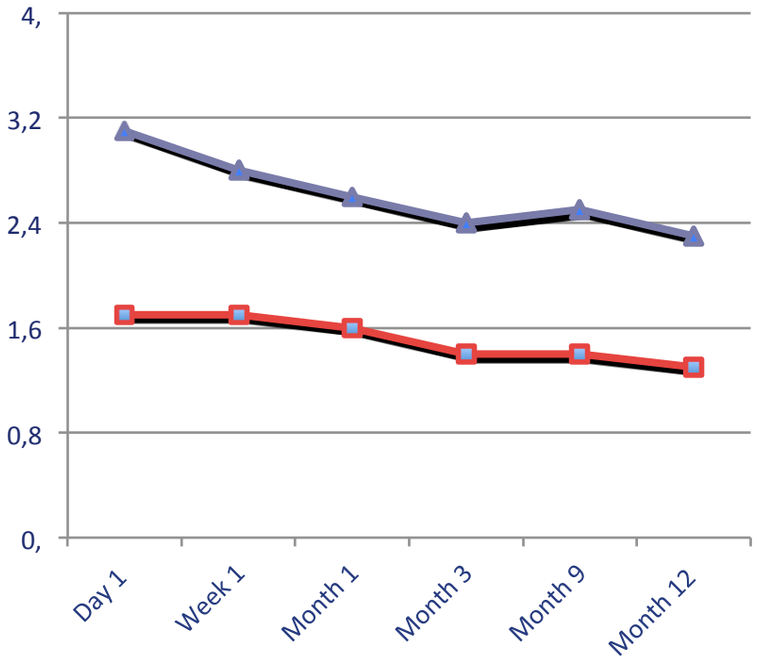


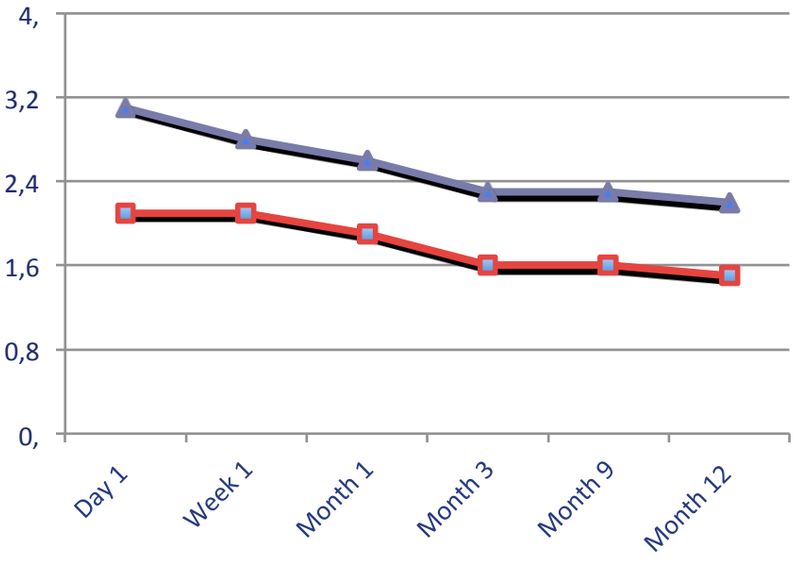
- Efficacy measures (CEA and PSA) improved on Day 1 of treatment
  - Initial reduction in erythema grade from Hours 0 to 3
  - Subsequent visits showed a similar or better level of improvement vs. Hour 0

CEA, Clinician's Erythema Assessment; PSA, Patient's Self Assessment

Moore A, *et al. J Drugs Dermatol* 2014;13(1):56–61. Patient ID:8047-00.2 **2**
Galderma Laboratories, L.P. Clinical study report. RD.06.SRE.18142 (December 2012).

Long term efficacy

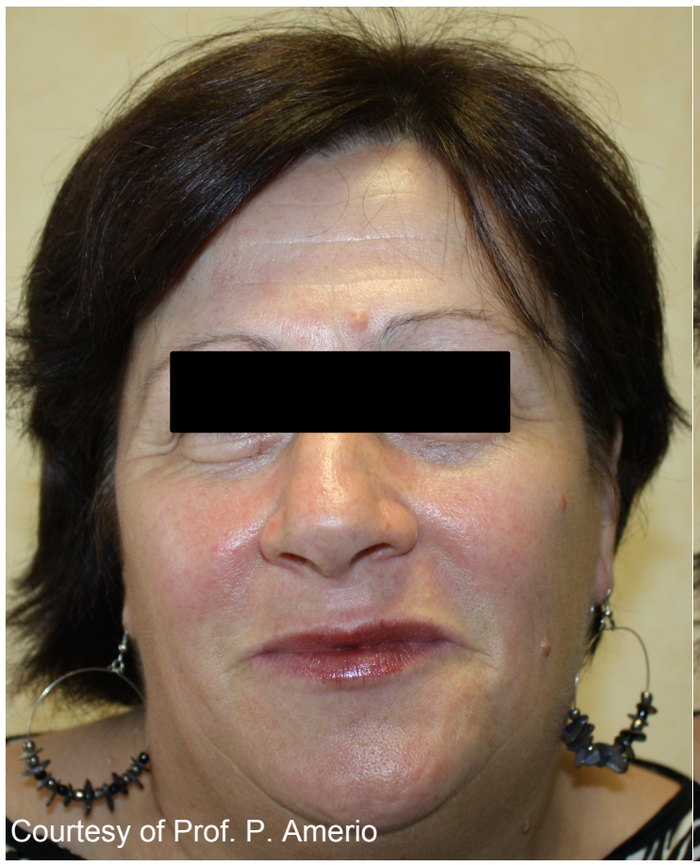




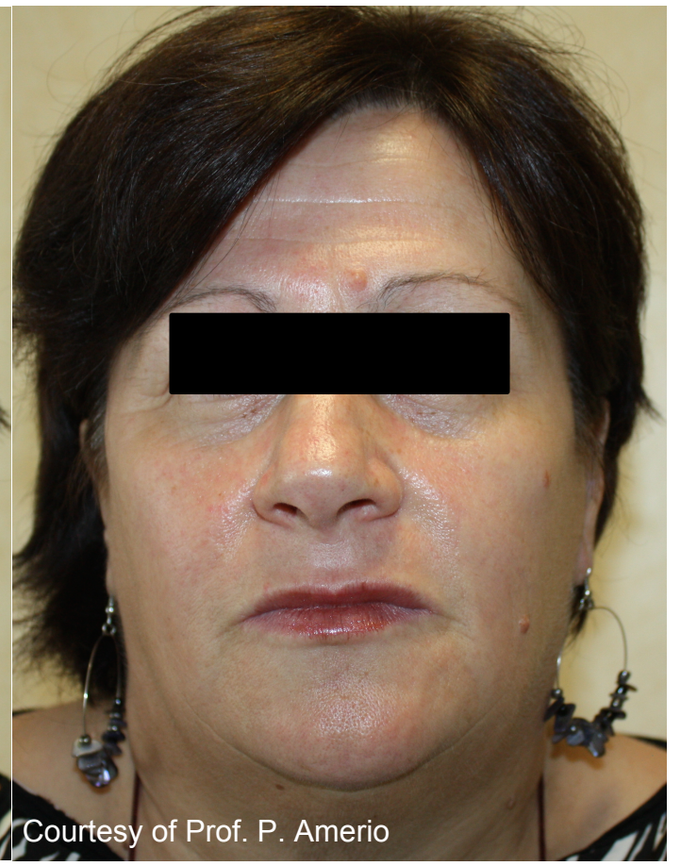
- Brimonidine 0.33 % (5mg/g), 12 months,
- 335 → 6 mesi
- 279 pz completed 12 months study
- possible concomitant treatment
- CEA/PSA, questionario HRQOL

No tachiphilaxys or loss of efficacy

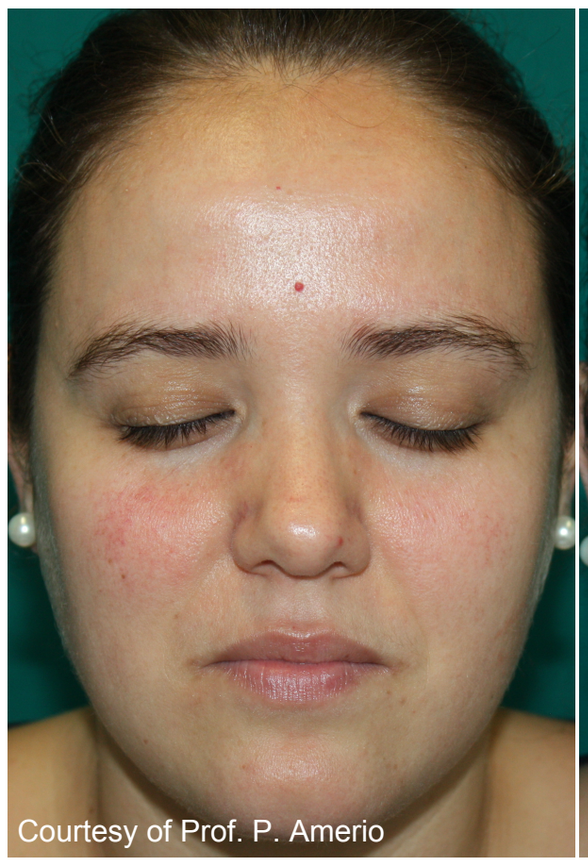
J Drug Dermatol 2014; 13(1): 56-61



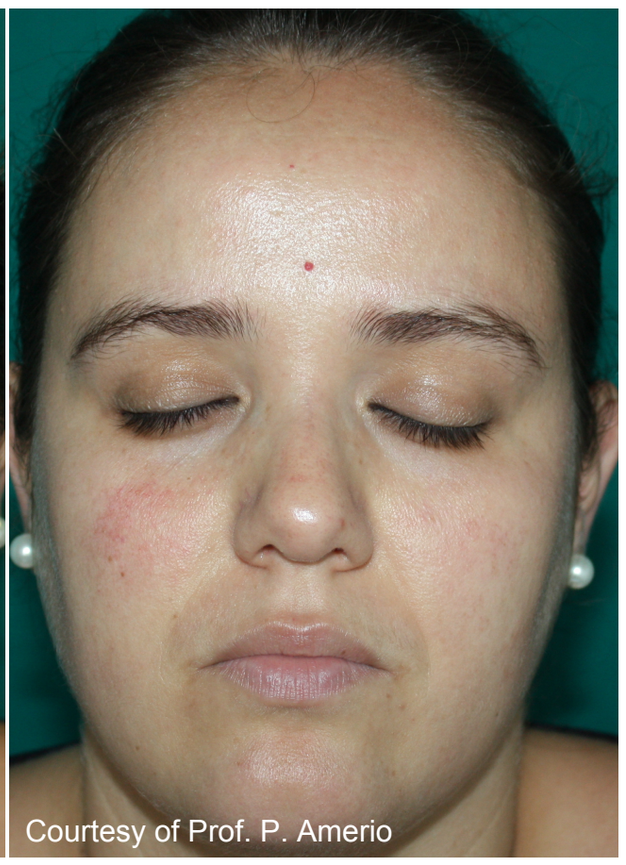
T 0



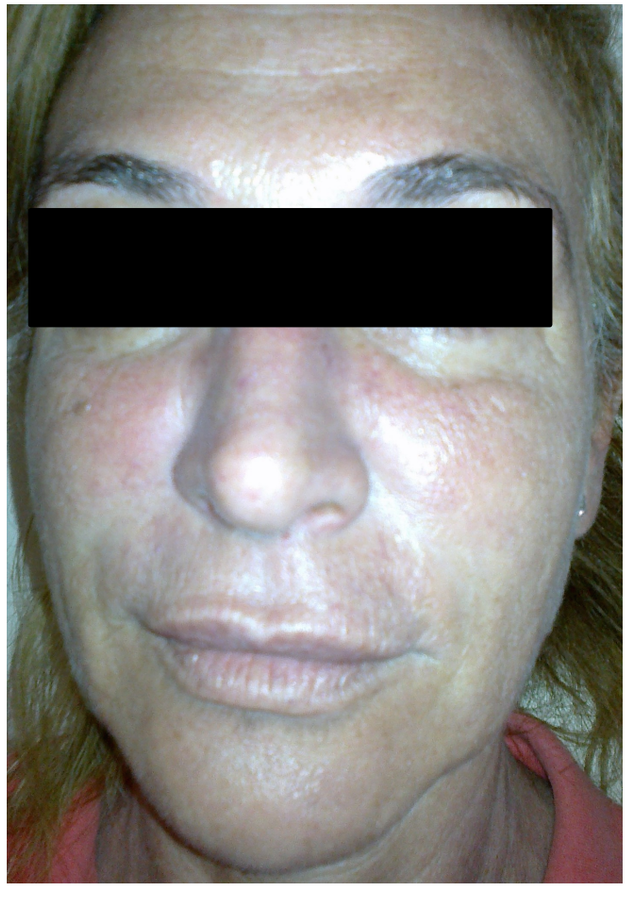
T 30 m



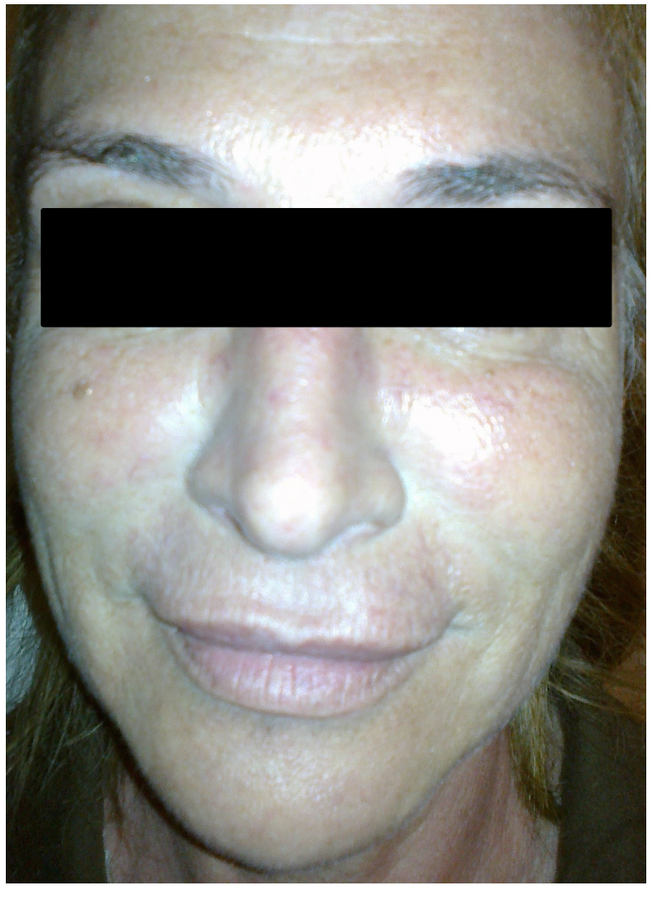
T 0



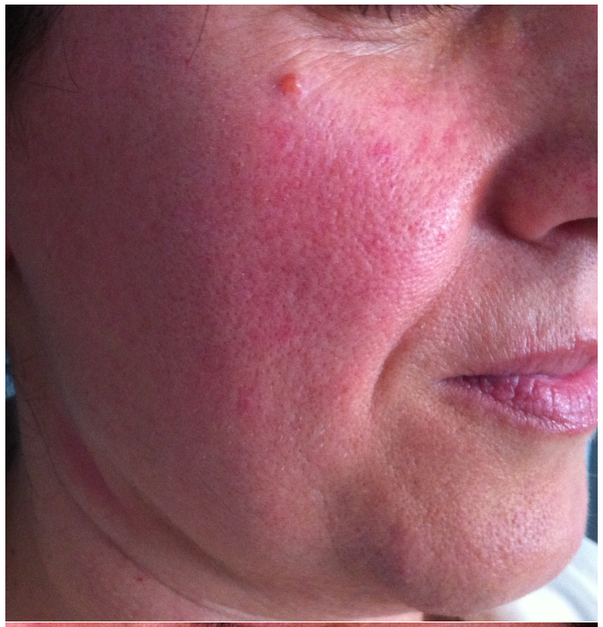
T 30 m

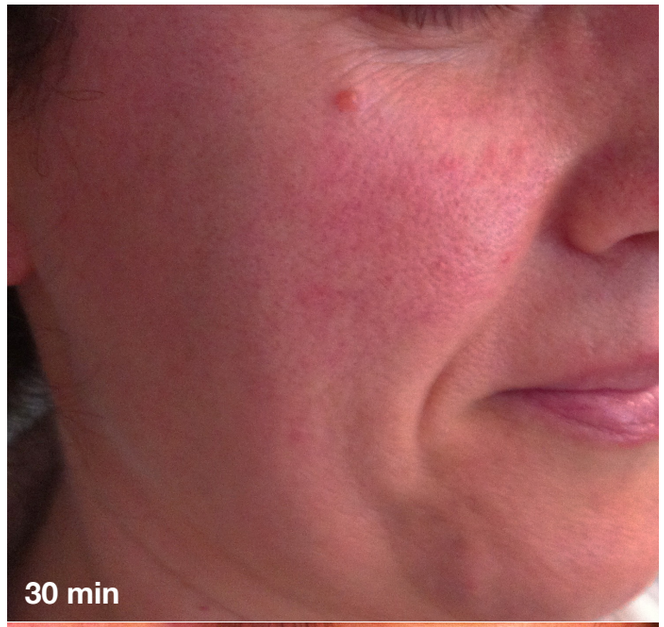


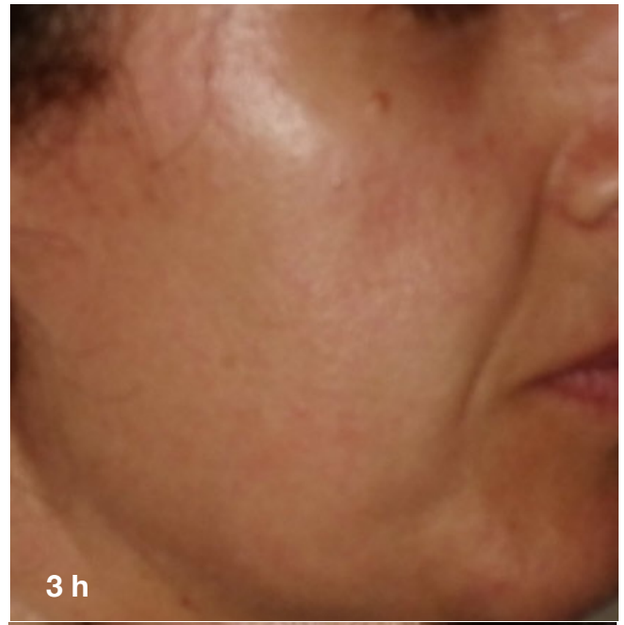
T 0

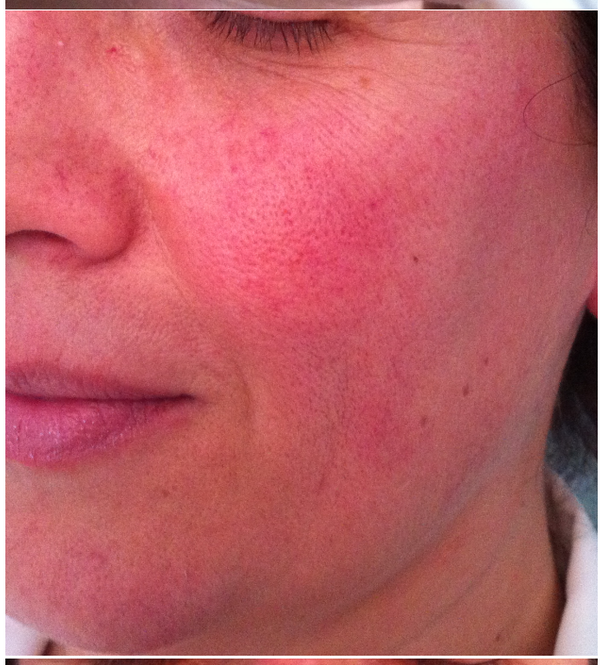


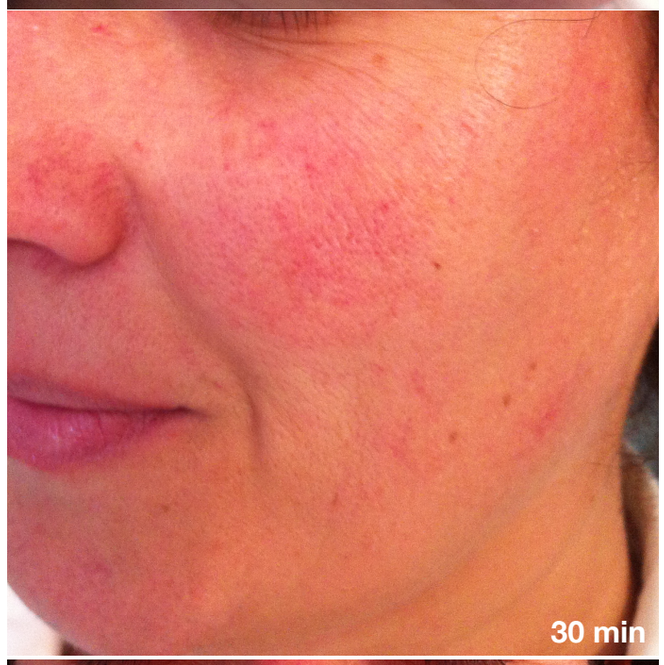
T 30 m




30 min


3 h

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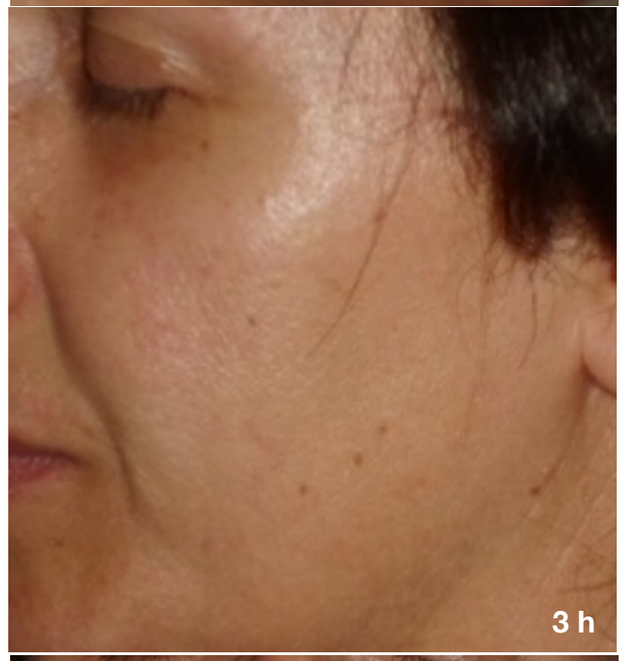
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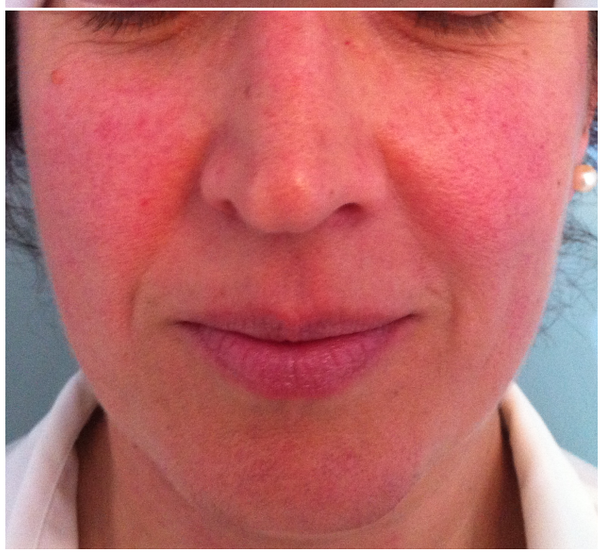
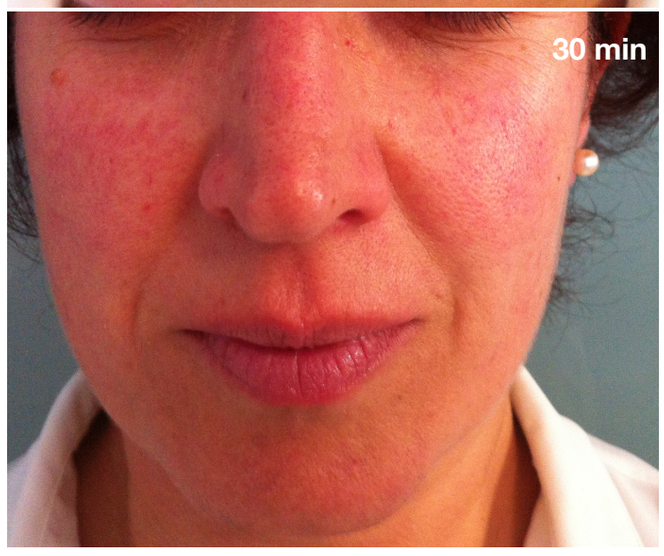
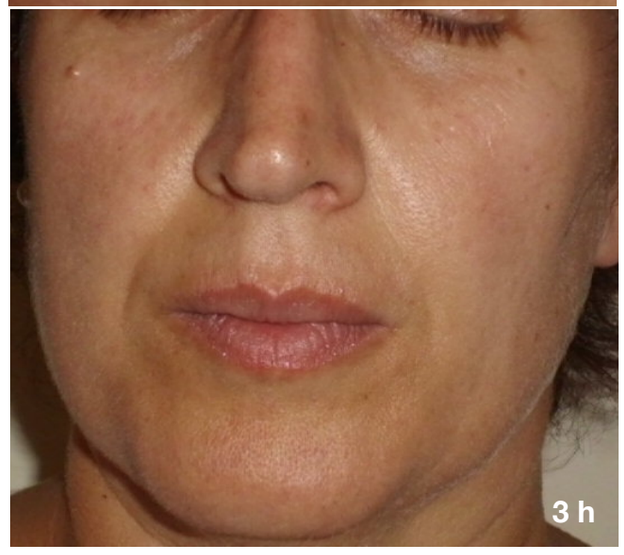
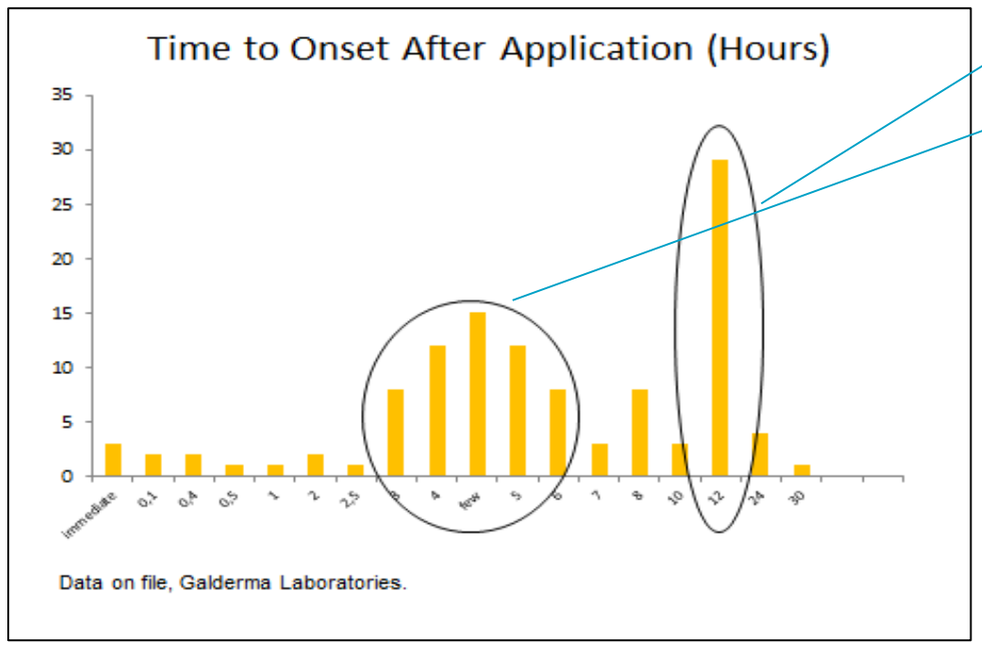



30 min


3 h

Adverse events

- Adverse events post-launch (to end of April 2014): conditions aggravated' were most likely to occur in the first 15 days after initiation of therapy
- As reported in the cases published in the literature, typically there was a rapid recovery

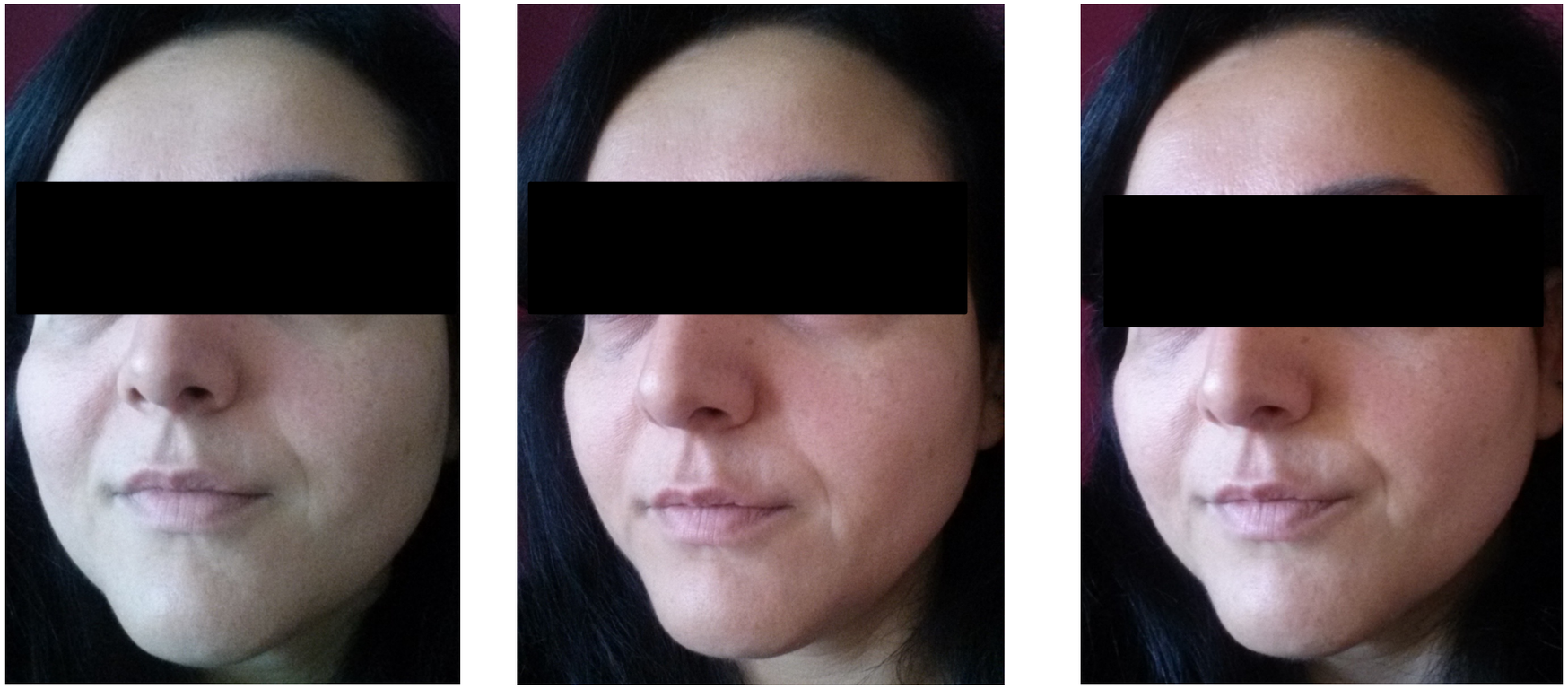


Two peaks in time to onset of erythematous event:

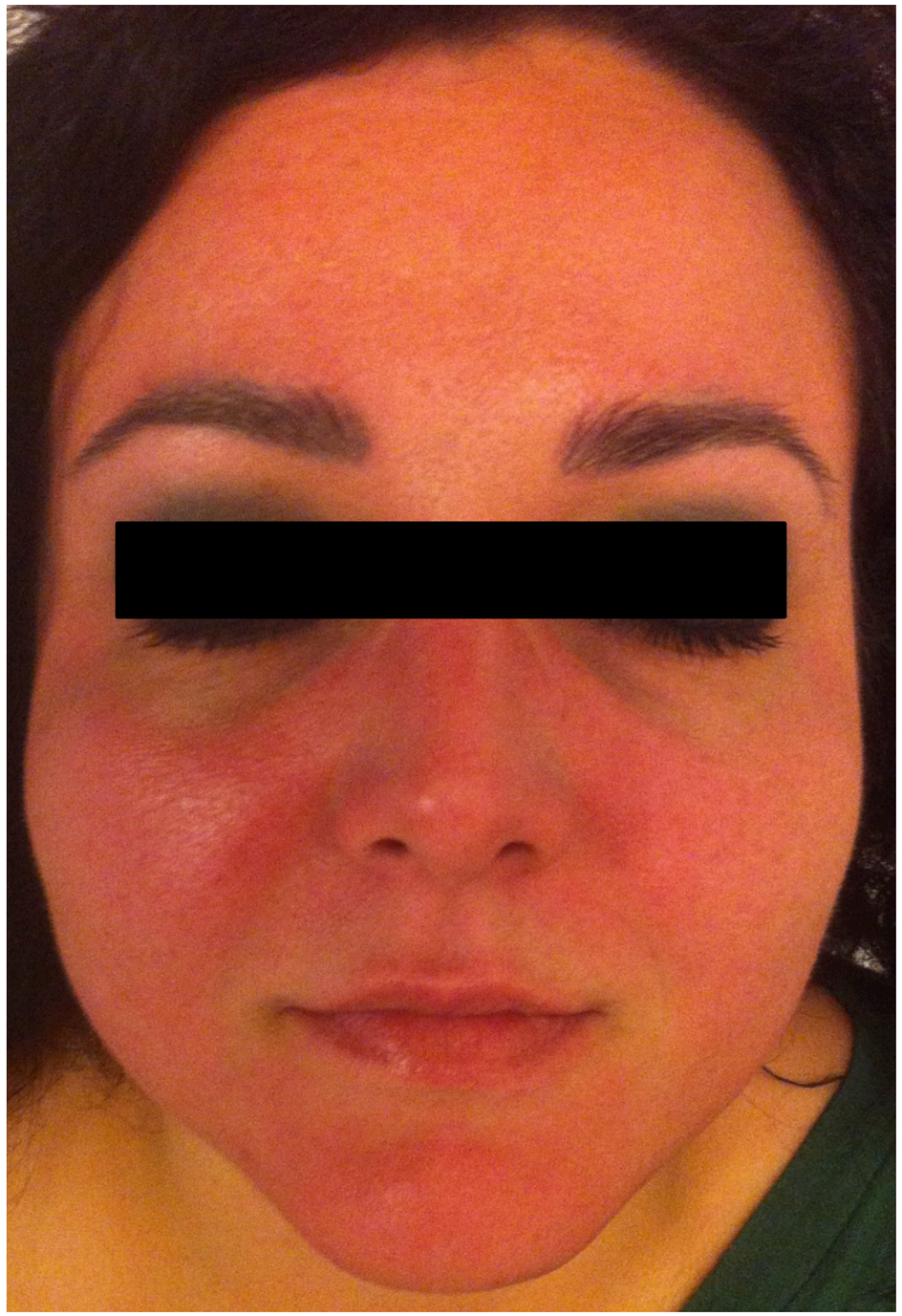
- 3–6 hours
- 10–12 hours

Tanghetti EA, et al. J Drugs Dermatol 2014;14(1);33–40.
Holmes A et al. J Clin Aesthet Dermatol 2015:8:29–35.
Ilkovitch D & Pomerantz RG. J Am Acad Dermatol 2014;70(5);e109–e110.
Routt ET & Levitt JO. J Am Acad Dermatol. 2014;70(2);e37–e38.

Adverse events



T 0 T 30’ T 1h

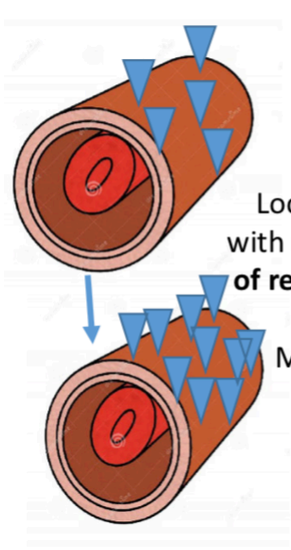


- Skin side effect from Brimonidine: Persistent erythema
- Erythema reduction after 10-12h from Brimonidine use
- No recurrence in the absence of use

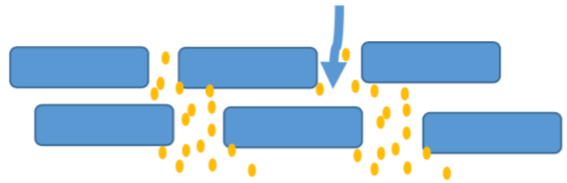
The following could contribute to erythema after application:

(1) local inflammation and perivascular inflammatory cells with **abnormally functioning ARs** may lead to vasodilatation;
(2) **abnormal saturation** and **cells** expressing different AR subtypes **with varying ligand affinity**;
(3) **barrier dysfunction** and increased skin concentrations of brimonidine with increased actions at endothelial and presynaptic receptors, resulting in increased vasodilation;
(4) genetic predisposition and **receptor polymorphism**(s) leading to different smooth muscle responses.

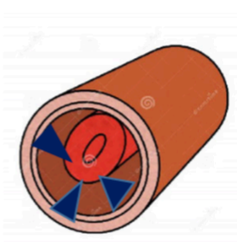
Docherty JR, Steinhoff M et al. Adv Ther. 2016 Nov;33(11):1885-1895



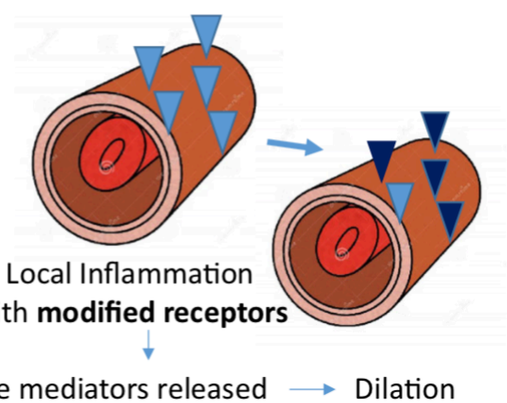
Local inflammation with **increased number of receptors** as targets → More mediators released → Dilation



Increased drug concentration due to barrier disruption (drug penetrates further)

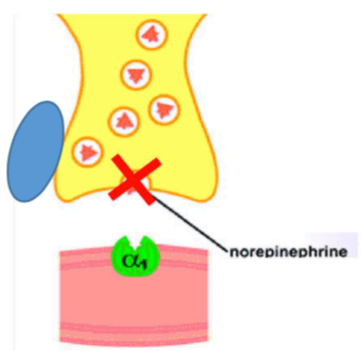


Drug penetrates to endothelium → endothelium-dependent dilation (possibly mediated by NO)



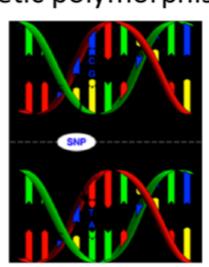
Local Inflammation with **modified receptors** → More mediators released → Dilation

Inhibition of norepinephrine release



Leads to vasodilation

Genetic polymorphism



Adv Ther (2016) 33:1885–1895

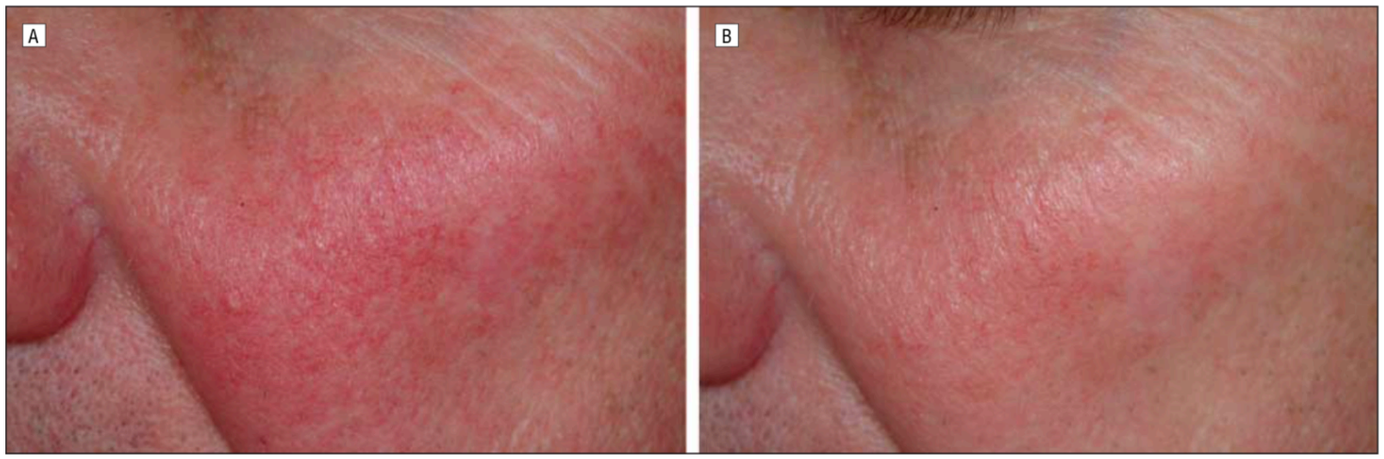
α-adrenergics

Oxymetazoline α-1 receptor agonist

Oxymetazoline hydrochloride

- Oxymetazoline hydrochloride 1%, potent alpha-1 and partial alpha-2 receptor agonist, cream: evaluated for treatment of persistent facial erythema of rosacea vs vehicle in 2 randomized, controlled , pivotal trials (N=885), and in 365 subjects who completed the long-term (52-week) open-label study, with efficacy and safety established
- there has not been sufficient time to gather information from post-marketing use in the clinical setting or through pharmacovigilance from “real-world” use
- **application-site erythema was noted in one percent of actively treated subjects** versus 0.4 percent in vehicle-treated subjects in the pivotal studies and in two percent of actively treated subjects in the long-term study
- treatment-related worsening of facial erythema occurring during active use and/or after discontinuation of therapy (defined as rebound in pivotal clinical studies) are uncommon

J Clin Aesthet Dermatol. 2017;10(7):28–32
Rhofade (oxymetazoline 1% cream) package insert. Allergan Pharmaceuticals, Irvine, California. 2017
Kircik lH, DuBois J, Draelos ZD. Efficacy and safety of topical oxymetazoline 1.0% cream for treatment of facial erythema associated with rosacea; findings from 2 pivotal trials. Poster presentation. 5th Annual Dermatologic and Aesthetic urgery International league (DAsIl) Congress, Dubai, October 19–23, 2016
Draelos ZD, Gold mH, Weiss RA, et al. long-term safety and efficacy of topical oxymetazoline 1.0% cream for treatment of persistent facial erythema associated with rosacea. Poster presentation. 5th Annual Dermatologic and Aesthetic surgery International league (DAsIl) Congress, Dubai, October 19–23, 2016



Oxymetazoline hydrochloride 0,05 solution: before and after 3h

ARCH DERMATOL/VOL 143 (NO. 11), NOV 2007

α-adrenergics differences

Maintenance of vascular tone occurs at the junctional synapse between the sympathetic nerve terminal and the blood vessel wall. The α-1 receptors are located postsynaptically in the vascular smooth muscle within the region of the synapse; α-2 receptors are located presynaptically at the nerve terminal, postsynaptically in the vascular smooth muscle outside the direct region of the synapse, and within the endothelial wall.[23–25,27,28]

- ✔ These anatomic differe
  certain clinical circums
  expressions and locati
- ✔ In most mammalian sp
  vascular smooth musc
  receptors also play a rc
  significantly to venous

The presence of presynaptic a-2 receptors appear to inhibit norepinephrine release, which may contribute to vasodilation via a negative feedback loop mechanism.[2,23,28]

- ✔ It is not clear when th
  activity may potential
  adrenoreceptor activit
- ✔ More data are needed
  setting where worsen

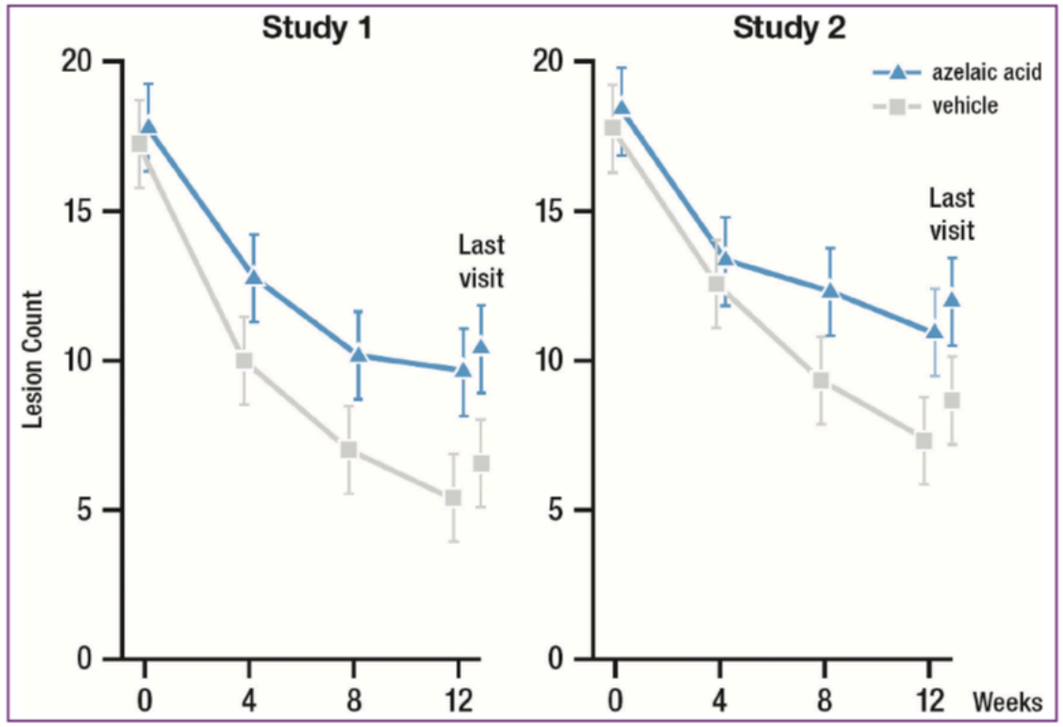
The presence of α-2 receptors on endothelial cells has been shown to mediate release of nitric oxide (NO), which induces vasodilation.[24–26] Hence, stimulation of endothelial cell α-2 receptors may invoke a vasodilatory response.

- ✔ α-1 receptor stimulation on vascular smooth muscle is able to override the NO-induced vascular relaxation response.[24–26]
- ✔ The potential triggers that may induce release of endothelium-derived NO are increased levels of shear stress, neurotransmitters, autacoids, and hormonal stimuli.[24]
- ✔ In any given patient, the extent of α-2 receptor-induced vasoconstriction or vasodilation may reflect the net effect of α-2-invoked vascular smooth muscle stimulation (which causes vasoconstriction) versus α-2-mediated endothelial NO release (which causes vasodilation).[24–26]When the latter response dominates, vasodilation occurs.

J Clin Aesthet Dermatol. 2017;10(7):28–32

Azelaic acid

AzA



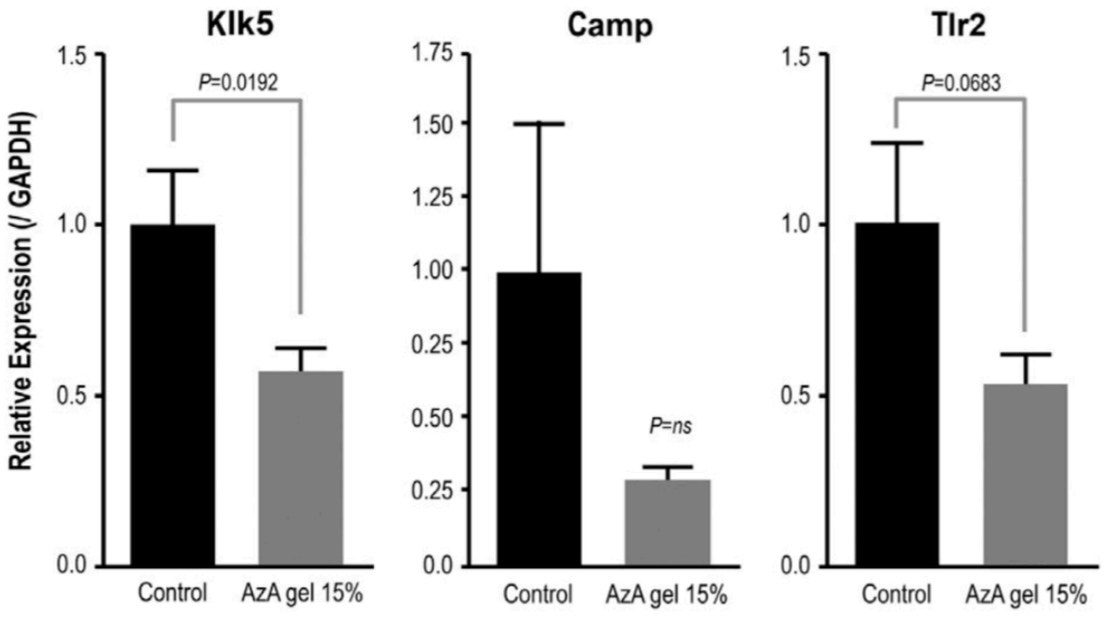
JDDG | 1610-0379/2016/14 (Suppl. 6) 17–27: Reduction in mean inflammatory lesion count at each visit and end of treatment with azelaic acid 15 % gel or vehicle (Last observation carried forward; LOCF). Modified according to Thiboutot et al. J Am Acad Dermatol 2003; 48: 836–45

- use of 15% AzA gel twice daily for 15 weeks demonstrated significant superiority over using 0.75% metronidazole gel in improving principal signs of rosacea

  Arch Dermatol. 2003;139:1444-1450
- anti- inflammatory and antioxidant properties
- downregulation of cathelicidin (LL-37) activation via inhibition of serine protease (kallikrein-5) gene expression and TLR2 expression
- antimicrobial, antioxidant, and anti- keratinization effects

JCAD journal of clinical and aesthetic dermatology • March 2017 • Volume 10 • Number 3

Skin Therapy Lett. 2017 Nov;22(6):5-7



15% Azelaic acid (AzA) gel suppressed CAMP, kallikrein 5 (*Klk5*), and Toll-like receptor 2 (*Tlr2*) messenger RNA (mRNA) expression in mouse skin. mRNA expression measured by quantitative real-time polymerase chain reaction of mouse skin treated with 15% AzA gel. *Klk5* (P = .0192), *Camp* (P = not significant [ns]), and *Tlr2* (P = .0683) genes as compared with vehicle-treated skin. Relative gene expression is shown after normalization by expression of glyceraldehyde 3-phosphate dehydrogenase (GAPDH).

J Am Acad Dermatol. 2013 October ; 69(4): 570–577

Metronidazole

Metronidazole

- Metronidazole (0.5–1.0%; cream or gel) as monotherapy or in combination —> effective for the treatment of moderate to severe rosacea

- Metronidazole is safe and effective in PR.

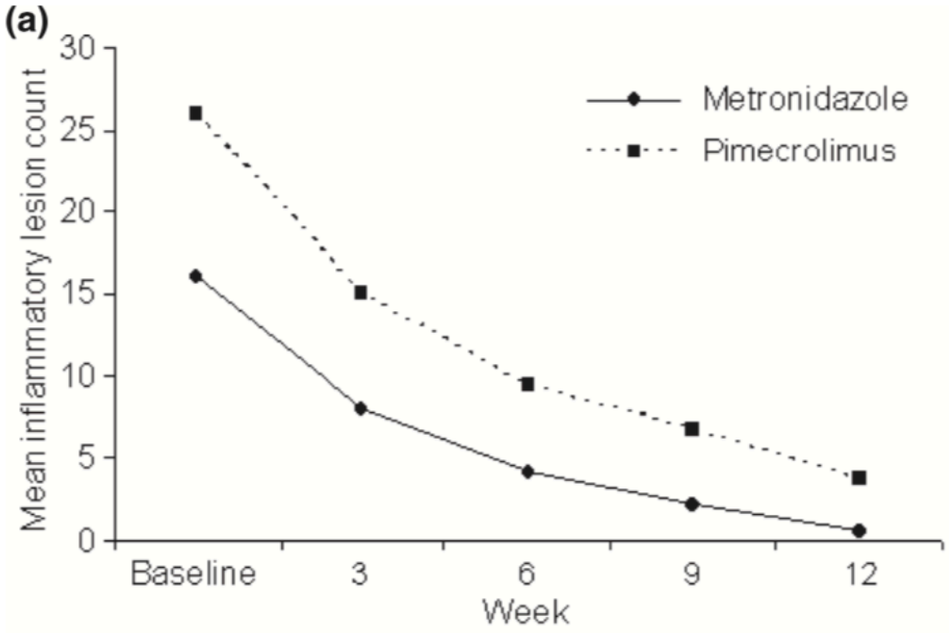
- The erythema-reducing effect of topical metronidazole is limited.

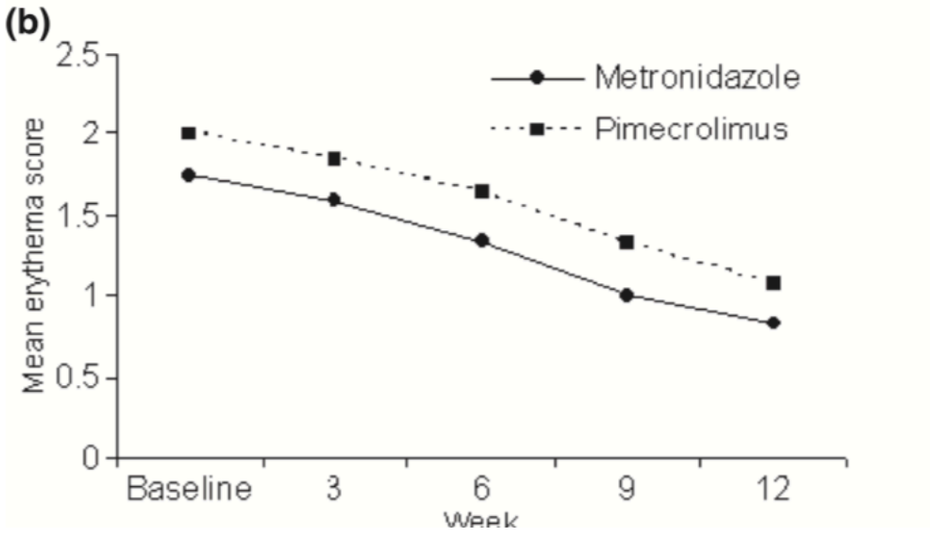
- MoA of metronidazole is not completely understood: an anti-inflammatory effect that interferes with neutrophil release of reactive oxygen species

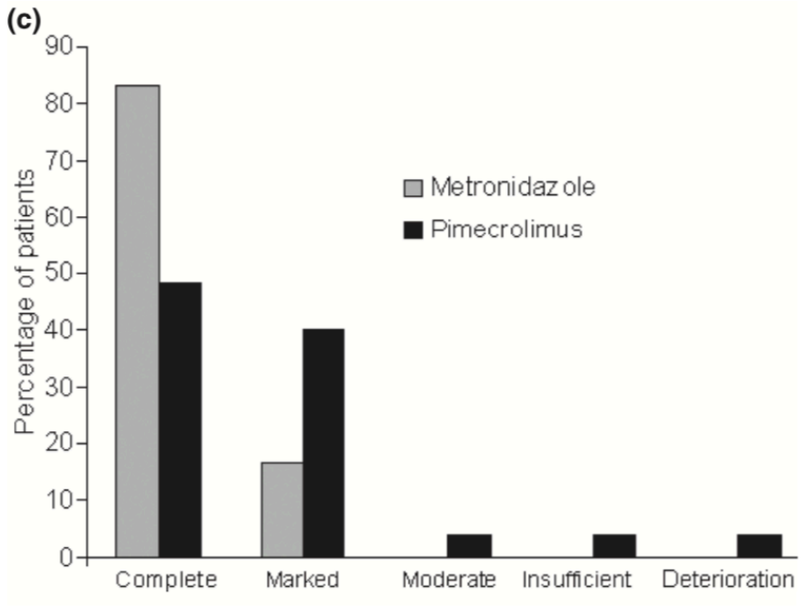
Table 1 Patient demographics and baseline characteristics.

Patient characteristics (n = 49)	Metronidazole (n = 24)	Pimecrolimus (n = 25)
Age, years	50.7 ± 9.1	48.4 ± 9.4
Gender (M/F), n (%)	16 (66.7)/8 (33.5)	13 (52)/12 (48)
Mean disease duration, months*	16.8 ± 18.3	33.7 ± 33.4
Mean inflammatory lesion count, n	16.0 ± 4.6	26.0 ± 11.7
Mean erythema score	1.7 ± 0.4	2.0 ± 0.6
Mean telangiectasia score	1.7 ± 0.6	1.5 ± 0.5

Results are expressed as mean ± SD (%) unless otherwise indicated. *$P < 0.05$.







Clinical and Experimental Dermatology, 35, 251–256

Ivermectine

Ivermectin: dual mechanism of action

- A dual MoA to treat inflammation + trigger features
- MoA of IVM for inflammatory lesions has not been confirmed
- Hypothetical MoA of IVM based on a literature review (*in vitro & in vivo* studies)

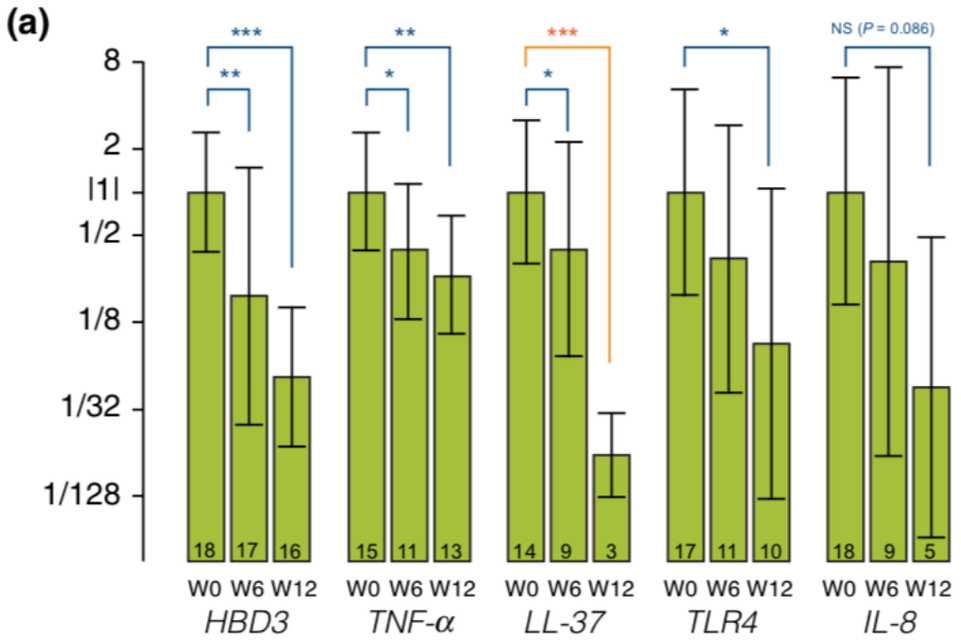
Anti-inflammatory

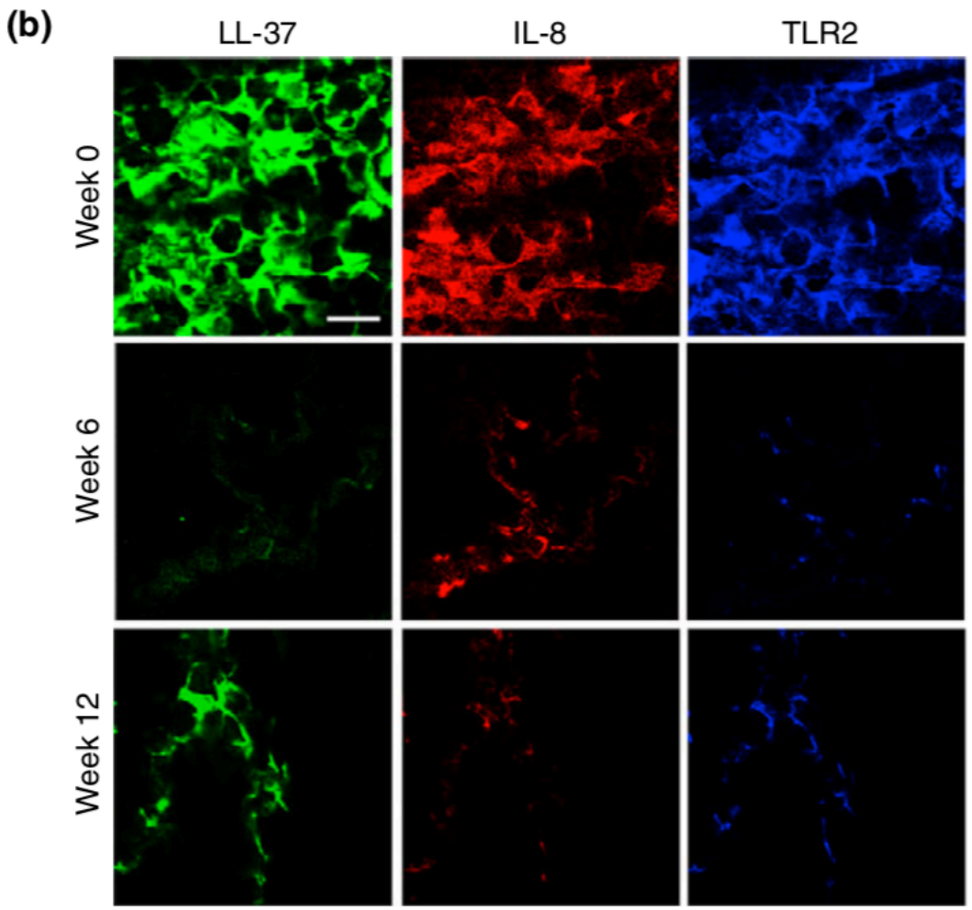
- Decreases cellular and humoral immune responses
- Reduces **neutrophil** phagocytosis, chemotaxis and oxidant production by phagocytes (similar to macrolide antibiotics)
- Parent compound avermectin has been shown to significantly regulate TNF-α, IL-1β and IL-10 in lipopolysaccharide-induced inflammation in *in vitro* studies

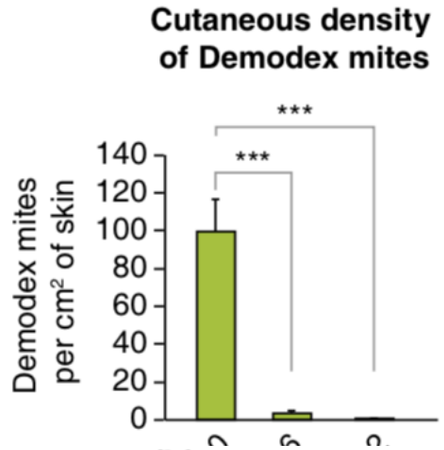
Antimicrobial

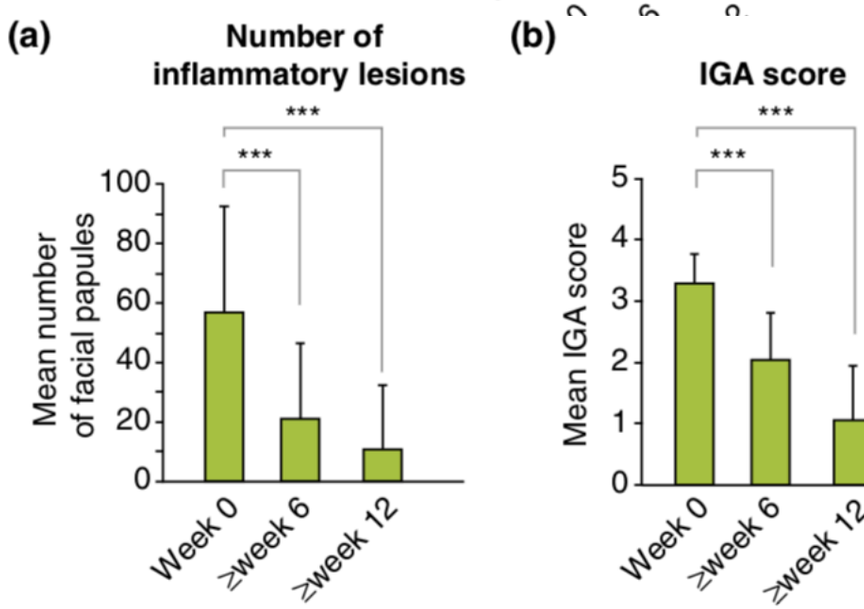
- Antiparasitic
- Antivermicide
- *Demodex* mites:
  - No direct data (not possible to culture *Demodex*)
  - Little supporting literature
  - Published clinical case series
- Demodicidosis, blepharitis and skin diseases
  - Veterinary practice in dogs

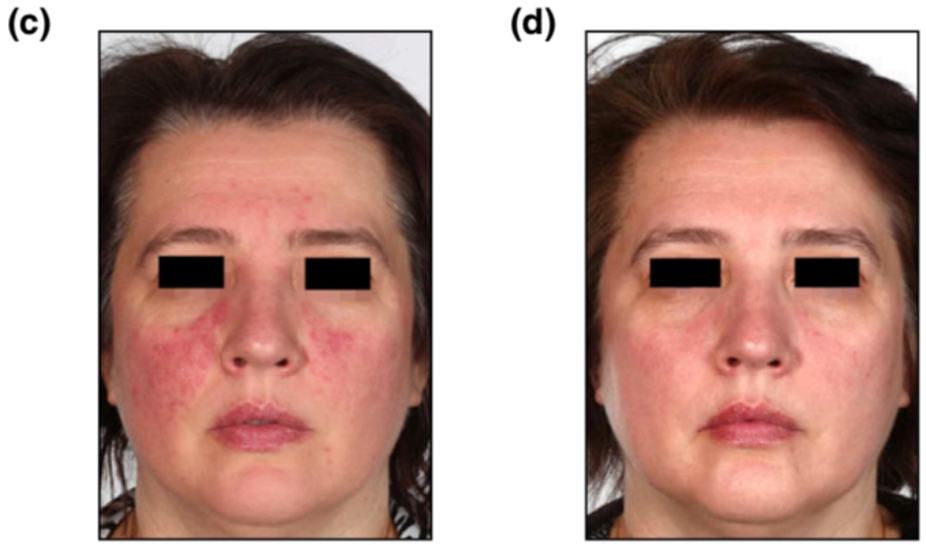
Stankiewicz M, *et al. Vet Immunol Immunopathol* 1995;44:347–58.
Labro M. *J Antimicrob Chemother*1998;41:37–46.
Ci X, *et al. Fundam Clin Pharmacol* 2009;23:449–55.







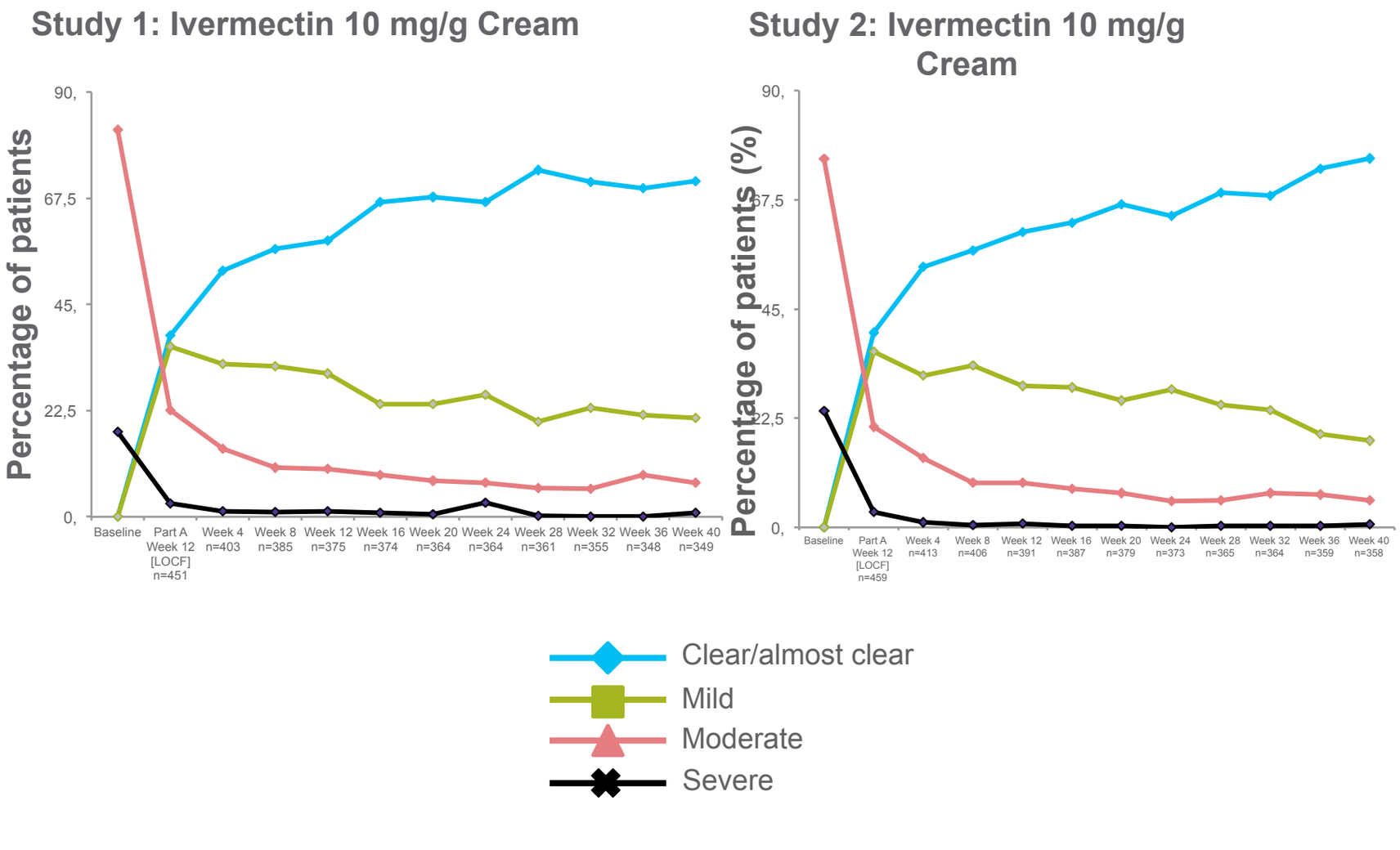




M Shaller. JEADV 2017, 31, 1907–1911

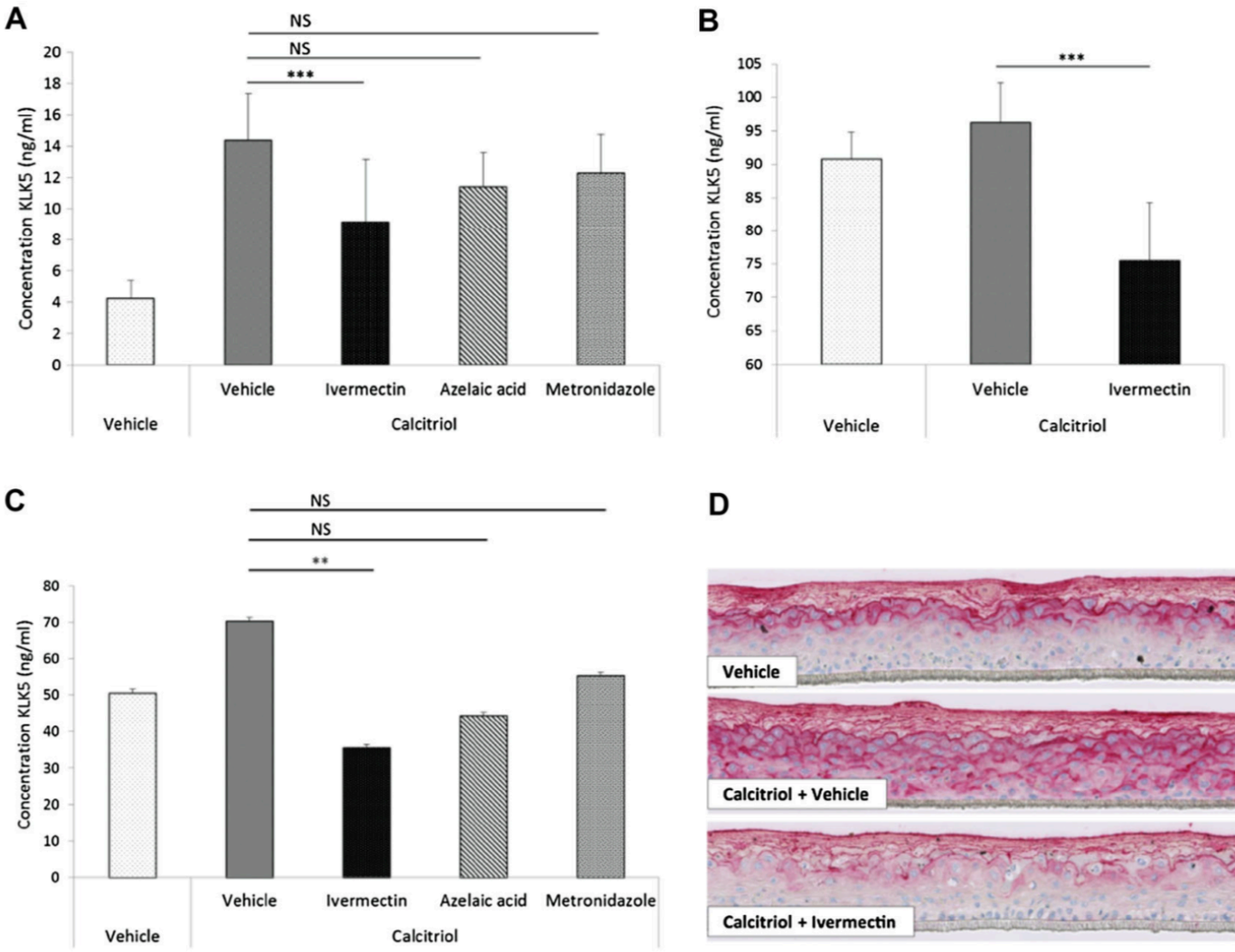
*Continuous improvement with Ivermectin Cream IGA scores*1*

*Clear/almost clear combined



Stein Gold L, *et al. J Drugs Dermatol* 2014;13(11):1380–6.

IVM superiority



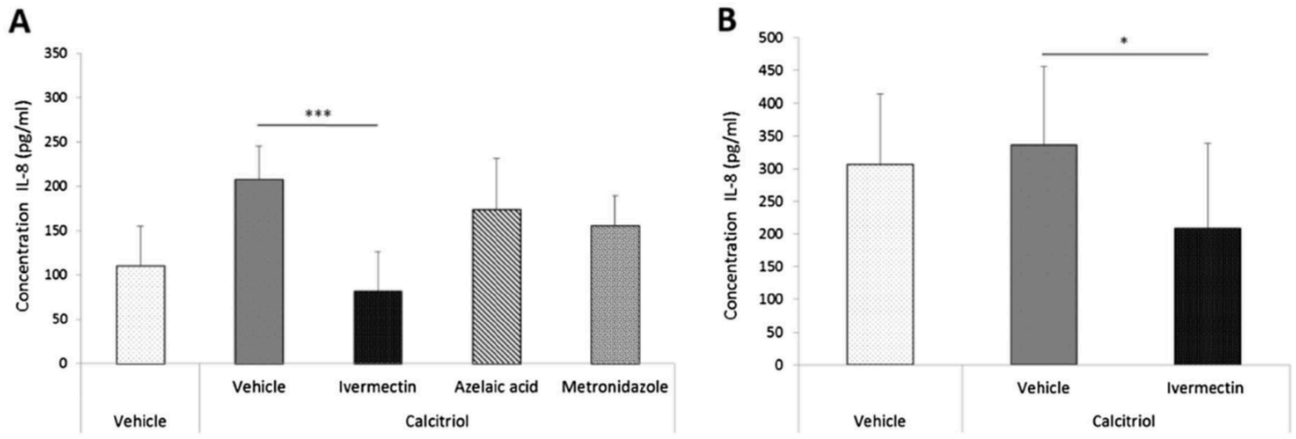
IVM inhibits KLK5 secretion from human epidermal cells.

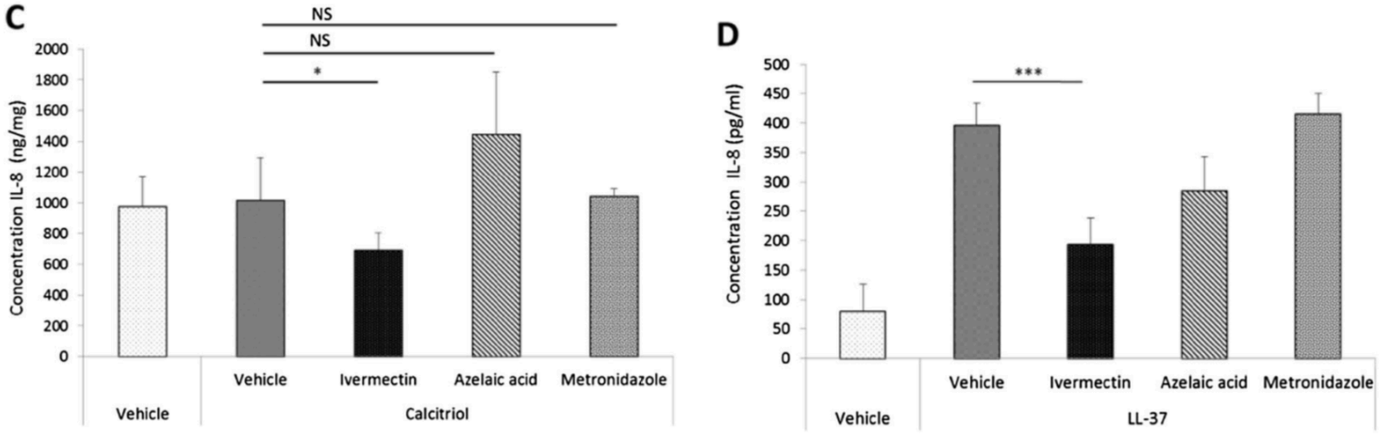
a NHEK cells were pre-treated with IVM, AzA, metronidazole at 1 lM or vehicle control overnight before 48 h stimulation with 100 nM calcitriol. KLK5 release was measured by ELISA. Data show mean ± SD from 3 independent experiments.

b RHE was pre-treated with IVM, AzA, metronidazole at 1% w/v or vehicle control (100% ethanol) overnight before 24 h topical stimulation with 10 lM calcitriol. KLK5 release was measured by ELISA. Data show mean ± SD from two independent experiments.

c Ex vivo skin biopsies were pre-treated with IVM, AzA, metronidazole at 1% w/v or vehicle control overnight before 48 h topical stimulation with 10 lM calcitriol. KLK5 release was measured by ELISA. Data show mean ± SD from two independent experiments. NS not significant. **P \ .01, ***P \ .001, Student's t test. d Immunohistologic staining of paraf- fin-embedded reconstructed epidermis using anti-KLK5 antibody. Top panel RHE was pre-treated with vehicle control overnight and then was stimulated with vehicle control. Middle panel RHE was pre-treated with vehicle control overnight before being stimulated topically with 10 lM calcitriol. Lower panel RHE was pre-treated with ivermectin at 1% w/v overnight before being stimulated topically with 10 lM calcitriol. The epidermis was then paraffin-embedded and stained with anti-KLK5 antibody (in red). Scale bars 100 lm

Dermatol Ther (Heidelb) (2017) 7:213–225





IVM prevents the augmentation of the cathelicidin immune pathway, which has a positive impact on the downstream inflammatory pathway (e.g., decreased IL-8, IL-6 and CCL2 secretion).

These results suggest that IVM can prevent the inflammatory effects of rosacea triggered by abnormal LL-37 processing, through the inhibition of KLK5 and CAMP gene expression in the epidermis

IVM treatment inhibits IL-8 secretion from human epidermal cells.

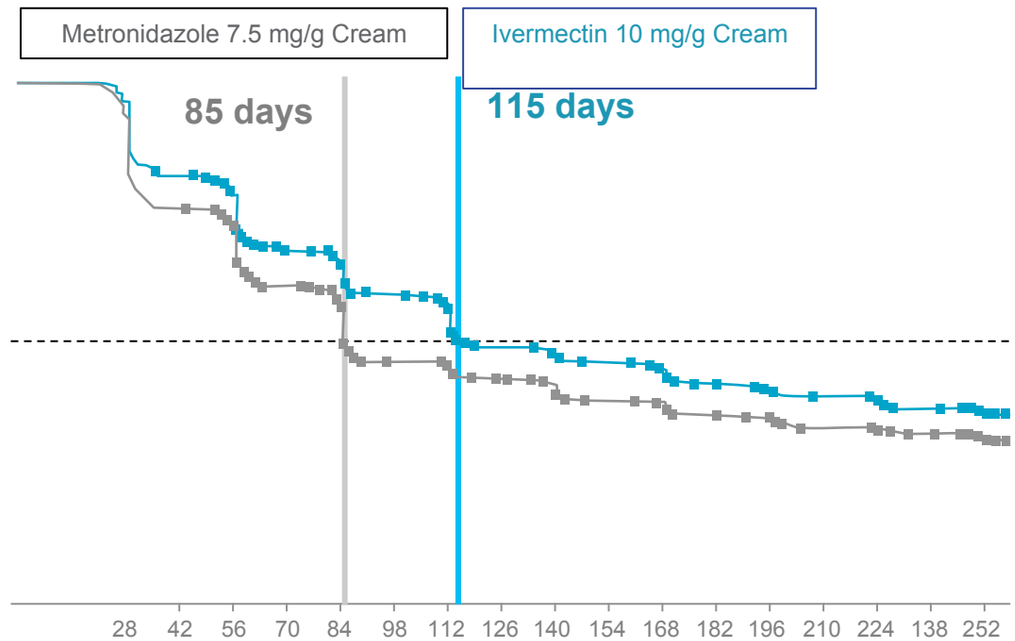
a NHEK cells were pre-treated with vehicle control (100% ethanol) or 1 lM IVM, AzA or metronidazole overnight before 48h stimulation with 100nM calcitriol. IL-8 release was measured by HTRF. Data show mean ± SD from 6 independent replicates.

b RHE was pre-treated with IVM, AzA, metronidazole at 1% w/v or vehicle control overnight before 24 h topical stimulation with 10lM calcitriol. IL-8 release was measured by HTRF. Data show mean ± SD from two independent experiments.

c Ex vivo skin biopsies were pre-treated with IVM, AzA, metronidazole at 1% w/v or vehicle control overnight before 48 h topical stimulation with 10lM calcitriol. IL-8 release was measured by HTRF. Data show mean ± SD from two independent experiments. d NHEK cells were pre-treated with iver- mectin, azelaic acid, metronidazole or vehicle control overnight before 24 h stimulation with LL-37 25 lg/ml. IL-8 release was measured by HTRF. Data show mean ± SD from two independent experiments. NS not significant. **P \ .01, ***P \ .001, Student's t test

Relapse rate and time to relapse

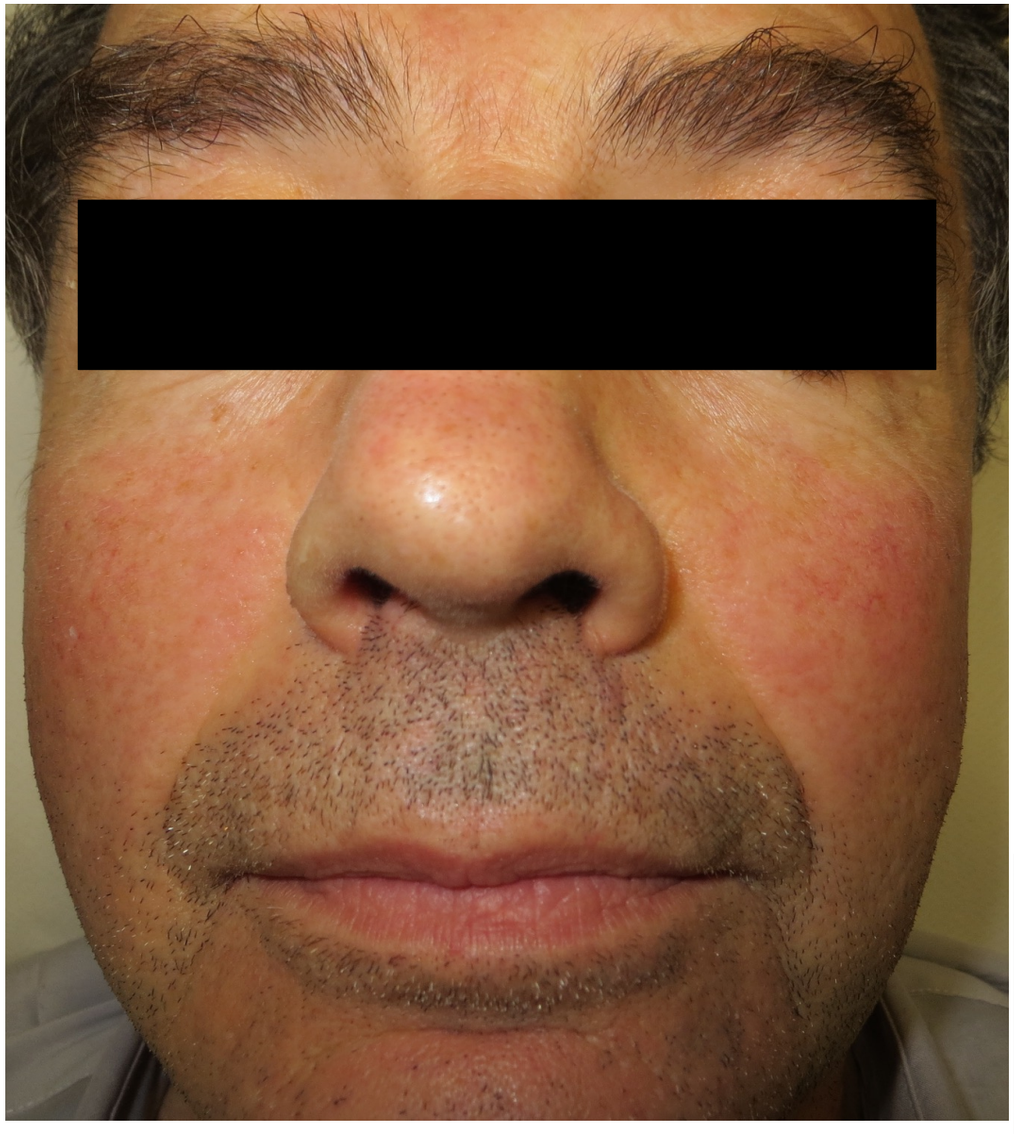
- Relapse rates* were 62.7% and 68.4% for the IVM group and Metronidazole
- 50% of pt remained free of disease after median of 115 days with IVM once daily vs. 85 days for patients treated with Metronidazole Cream twice daily (P<0.05)



*Relapse is based on IGA only and is defined as an IGA score equal or above to 2. Time to relapse = 1st occurrence of IGA≥2

Taieb A, *et al. J Eur Acad Dermatol Venereol* 2015.

Off label

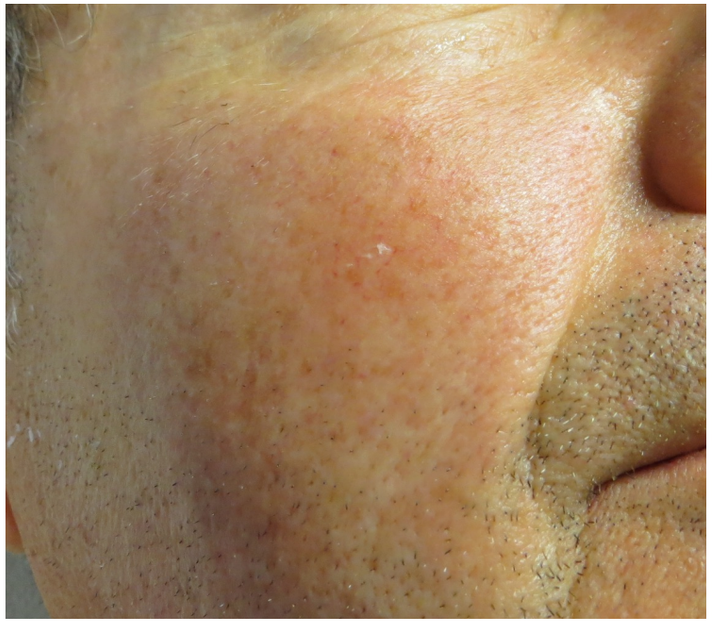


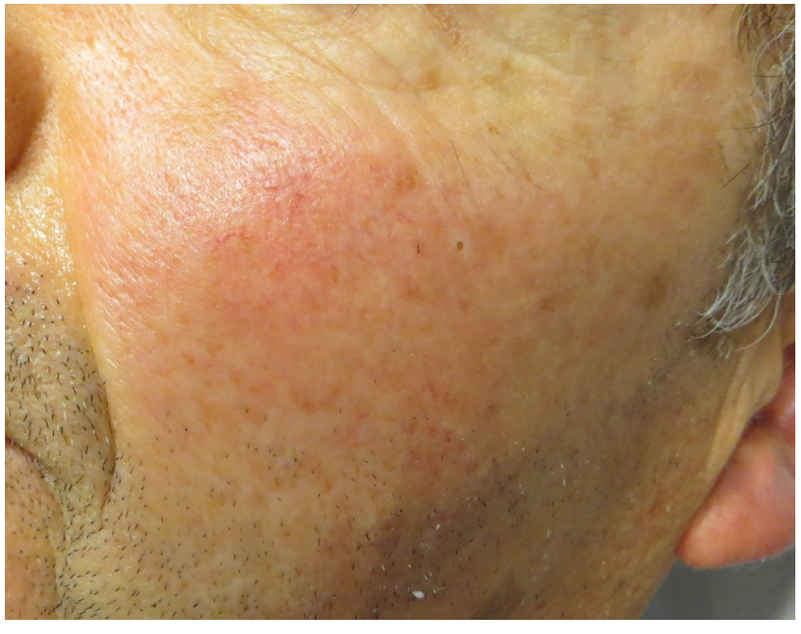
- L.P. 58 y.o. male pz
- Previous treatments:
  - ***Metronidazole***: no improvement
  - ***Pimecrolimus***: worsening
  - ***Brimonidine:*** useless

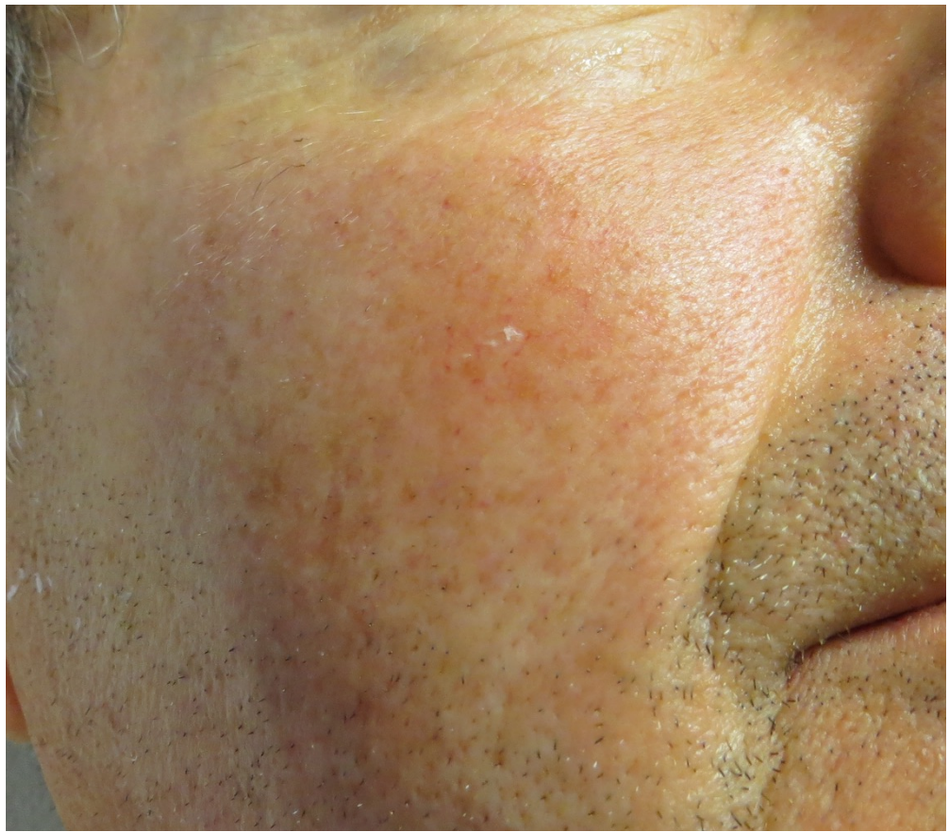
No.	Sex/age (years)	Previous disease	History	Onset time	Agent used	Treatment	Reference
1	Female/54	AD	Rosacea	9 months	Tacrolimus 0.1%	Doxycycline	Bernard *et al.*[6]
2	Female/56	Rosacea	Rosacea	14 days	Tacrolimus 0.1%	Doxycycline	Antille *et al.*[7]
3	Male/49	Rosacea	Rosacea	3 weeks	Tacrolimus 0.03%	Ciprofloxacin	Antille *et al.*[7]
4	Male/27	SD + rosacea	Rosacea	10 days	Tacrolimus 0.1%	Isotretinoin + topical metronidazole	Antille *et al.*[7]
5	Female/36	SD + rosacea	Acne	2 weeks	Tacrolimus 0.1%	No other treatment	Antille *et al.*[7]
6	Female/35	ACD	Acne excoriée	3 weeks	Tacrolimus 0.1%	Doxycycline	Antille *et al.*[7]
7	Female/49	AD	–	5 months	Tacrolimus 0.03%	Doxycycline	Antille *et al.*[7]
8	Female/43	AD	–	3 days	Pimecrolimus 1%	Doxycycline	Lübbe *et al.*[8]
9	Male/36	SD	–	4 days	Pimecrolimus 1%	Minocycline	Gorman and White[9]
10	Male/43	SD	–	7 days	Pimecrolimus 1%	Minocycline	Present case

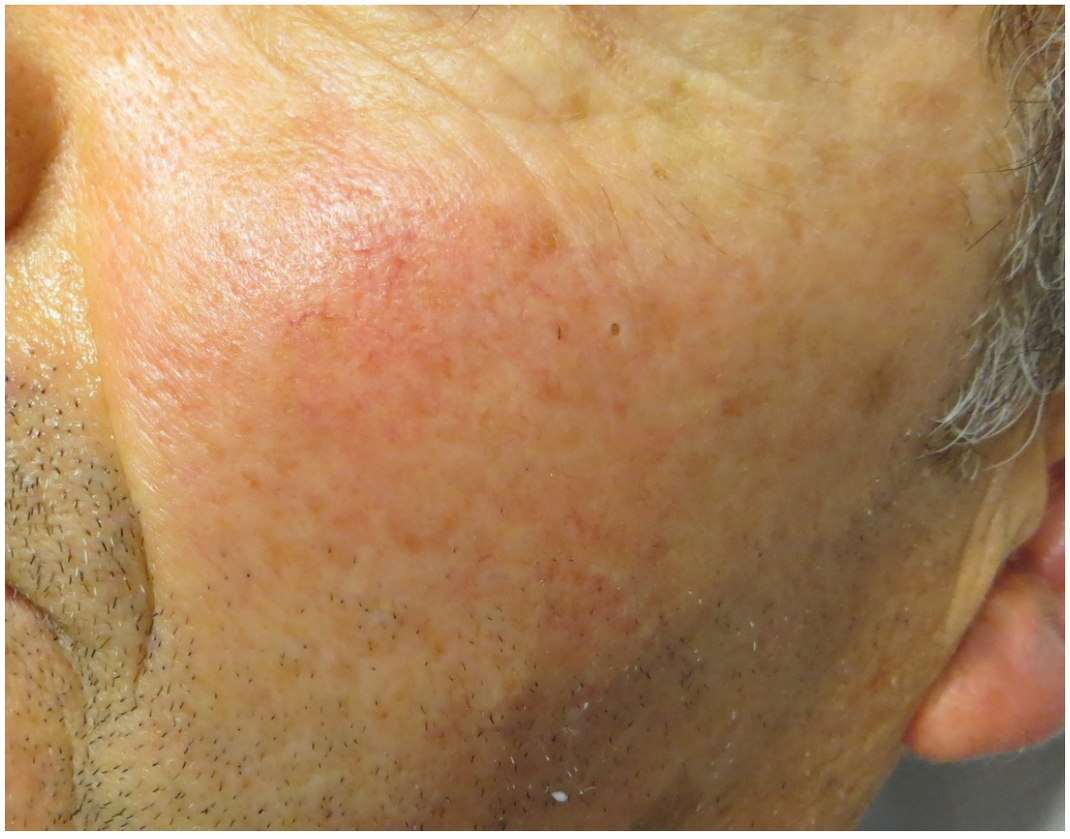
ACD, allergic contact dermatitis; AD, atopic dermatitis; SD, seborrheic dermatitis.

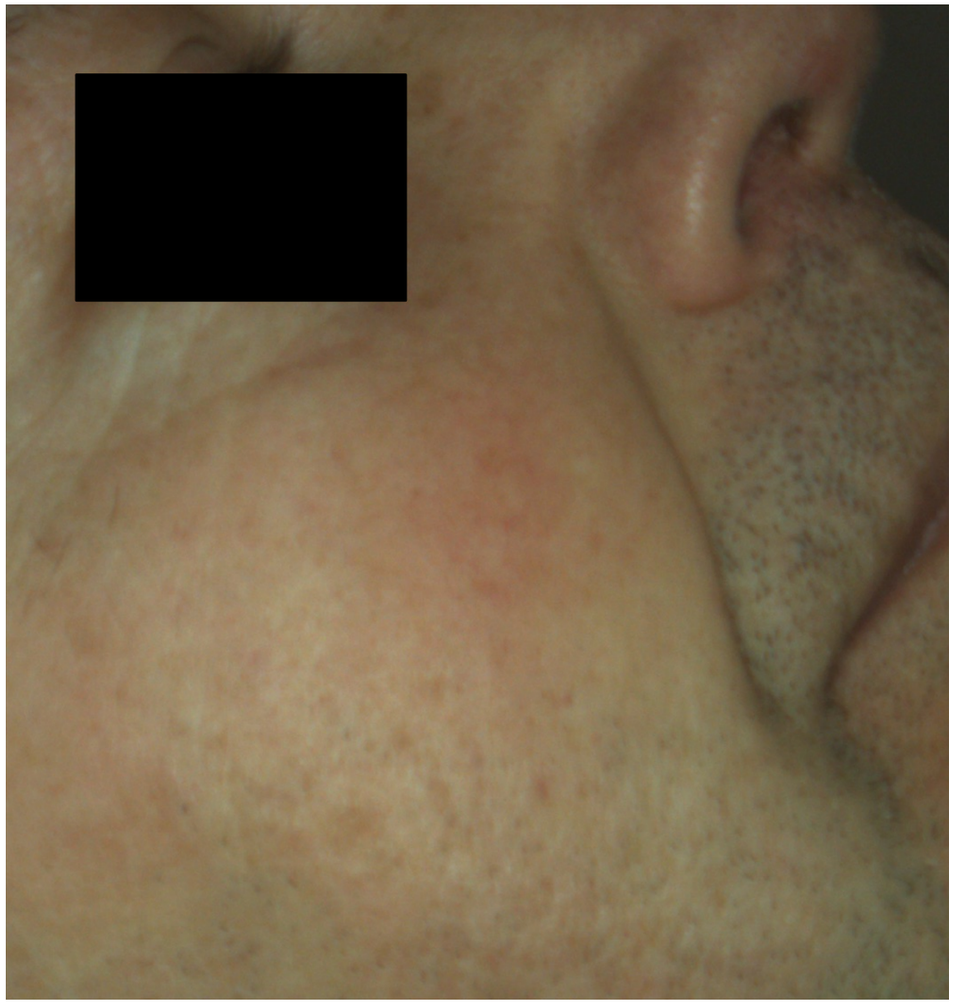
Off lable use
of Ivermectine
QD for 2 mts

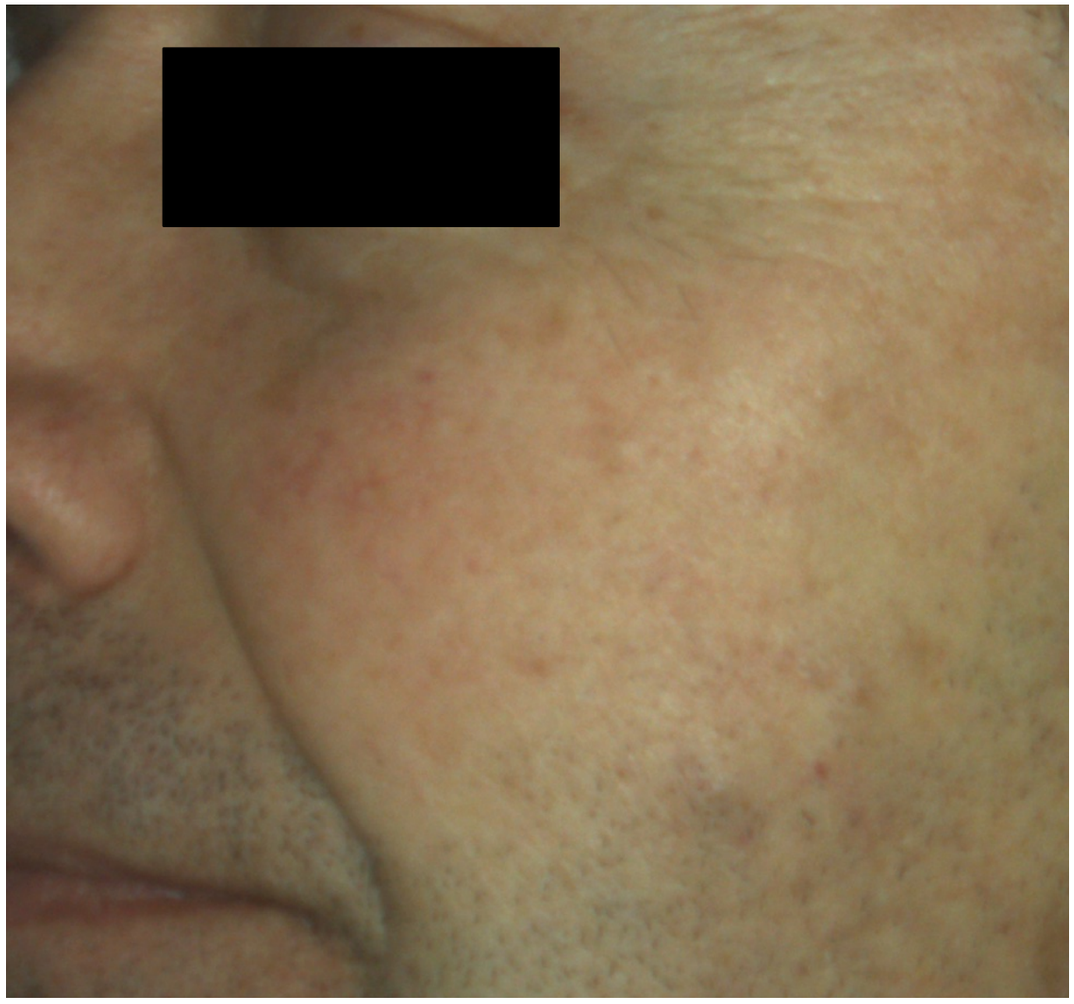












- 1 mts after 3 IPL session one mts apart

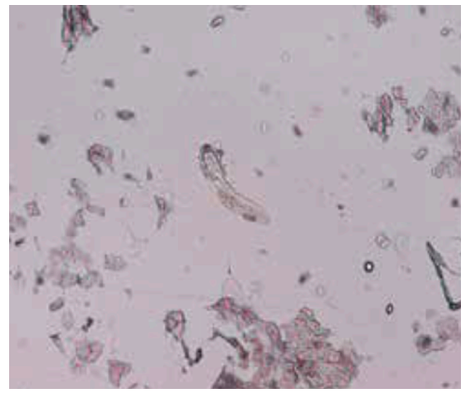
- D. folliculorum counts are notably higher but D. brevis inhabits a larger area of the human body.
- The proportion of D. brevis to D. folliculorum differs among men (1 : 4, respectively) and women (1 : 10).
- **D. folliculorum** is more often associated with **erythema** and epithelial **desquamation**
- **D. brevis** is linked with **papulo-pustular eruption**, symmetrical **rashes** and conditions arising on the background of a pre-existing disease
- Pts with papulo-pustular rosacea produce sebum with an altered fatty acid profile, suggesting that the nature of the sebum, rather than its quantity, may favour the development of Demodex mites
- An increase in mite density on facial skin is observed in perioral dermatitis
- Higher numbers of Demodex mites have been noted in pts undergoing immunosuppressive therapy (children receiving chemotherapy for leukaemia, pts with HIV-infection or AIDS and chronic dialysis pts)

Differential diagnosis

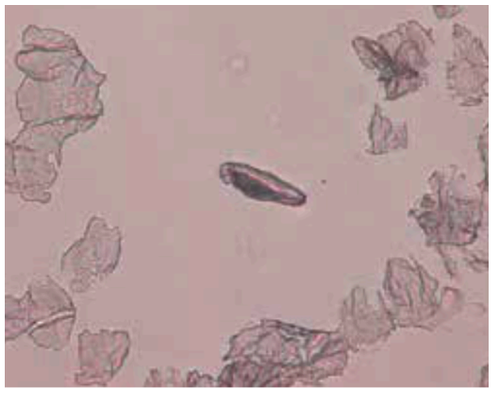
- *Pityriasis folliculorum* is characterized by small, follicular, scaling papules, the feeling of skin dryness and pruritus. Lesions in pityriasis folliculorum are usually unilateral, located mainly on the cheeks, but may also reach the eyelids.

- *Rosacea-like demodicosis*, caused by the presence of abundant D. folliculorum mites and characterized by erythema, dryness and fine follicular scaling; old people and immunocompromised patients

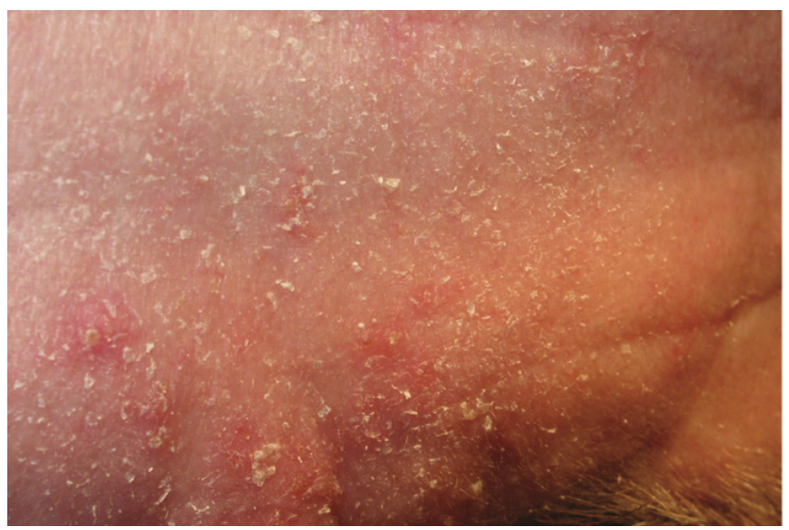
- Skin lesions associated with an abnormal increase in *Demodex* mites (secondary demodicosis) occur mostly in *pts undergoing treatment with topical steroids or calcineurin inhibitors*



Demodex folliculorum smear,10x

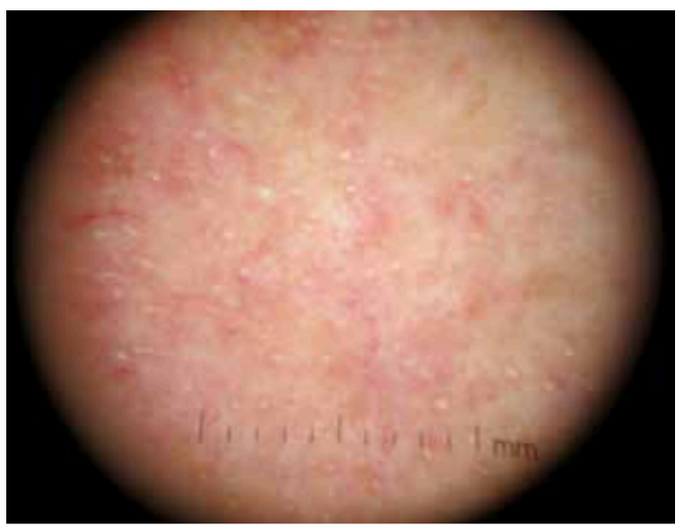


Demodex brevis smear,20x



Forehead with follicular and non-follicular scales and pustules

Acta Derm Venereol 2017; 97: 242–248.



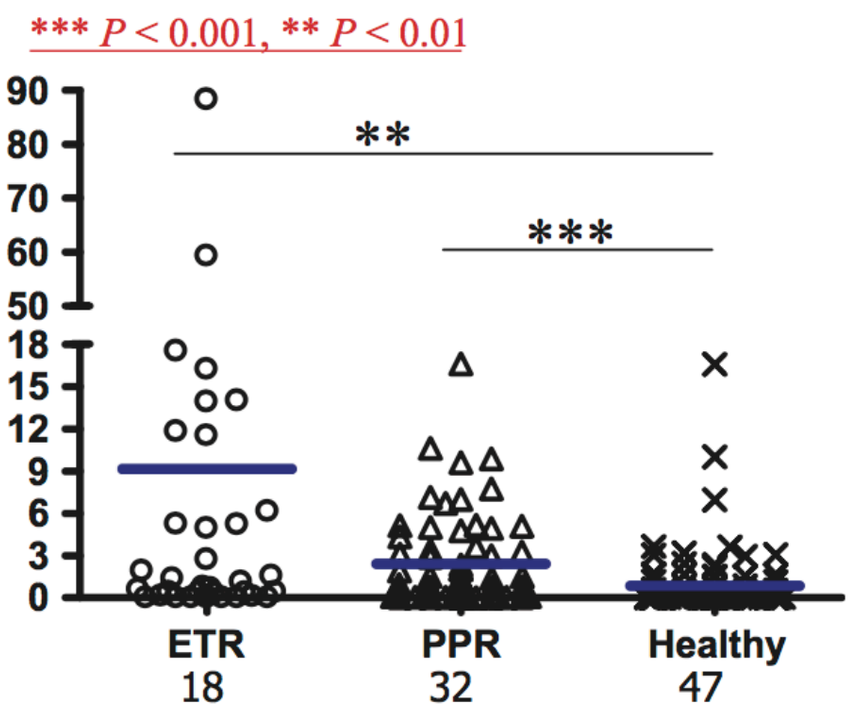
Dermoscopic follicular plugs and *Demodex* tails

An Bras Dermatol. 2016;91(5):676-8.

Journal of Medical Microbiology (2012), 61, 1504–1510

Demodex & Rosacea

- The pathogenic role of human Demodex mites in certain inflammatory skin disorders is debating.
- High prevalence of mites: in rosacea, seborrhoeic dermatitis, perioral dermatitis, blepharitis and chalazion.
- Human primary demodicosis has been recognized as a primary disease sui generis.
- A secondary form of human demodicosis is mainly associated with systemic or local immunosuppression.



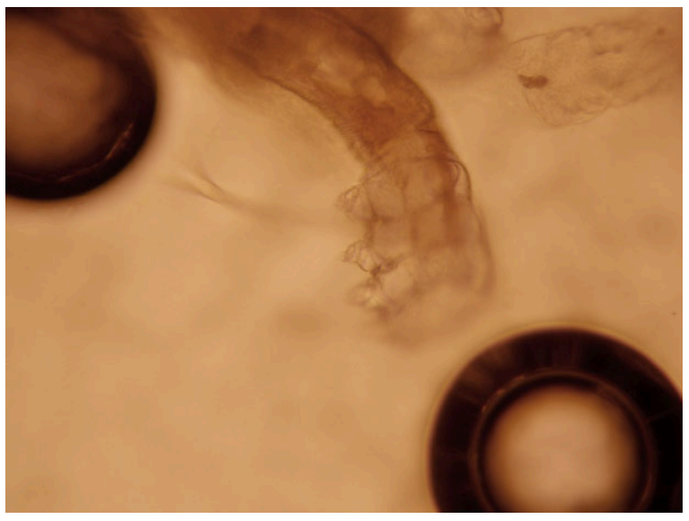
Graphical representation of the distribution of Demodex folliculorum density found in the different groups. The density is given as the number of DNA copies coding for 18S rRNA of D. folliculorum per ng of human genomic DNA (gDNA). The blue line represents the median. ***P < 0.001, **P < 0.01.

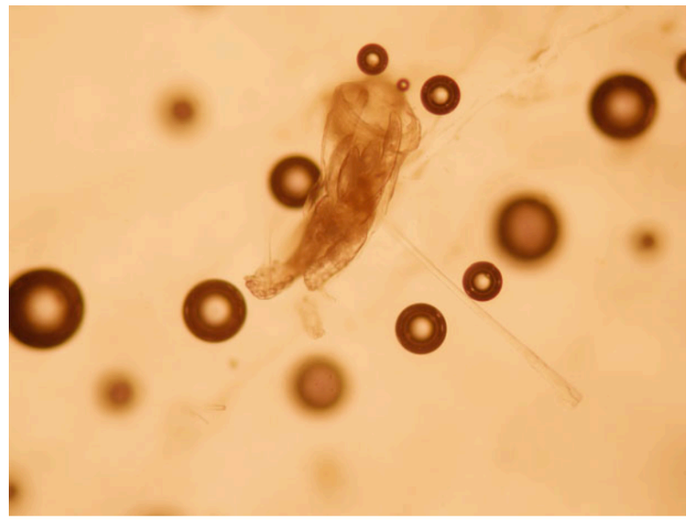
Experimental Dermatology, 2012, 21, 906–910

Iran J Parasitol: Vol. 12, No. 1, Jan-Mar 2017, pp. 12-21

Pts with rosacea had significantly higher prevalence and degrees of Demodex mite infestation than did control patients. Demodex mites may play a role in both ET-rosacea and PPR

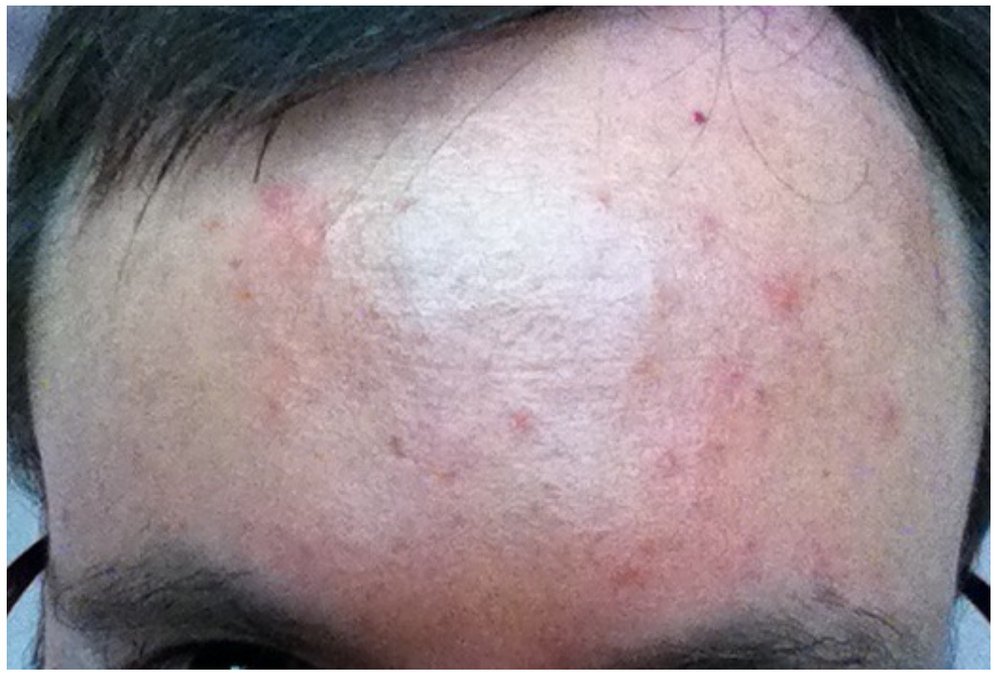
J Am Acad Dermatol. 2017 Sep;77(3):441-447.e6. doi: 10.1016/j.jaad.2017.03.040



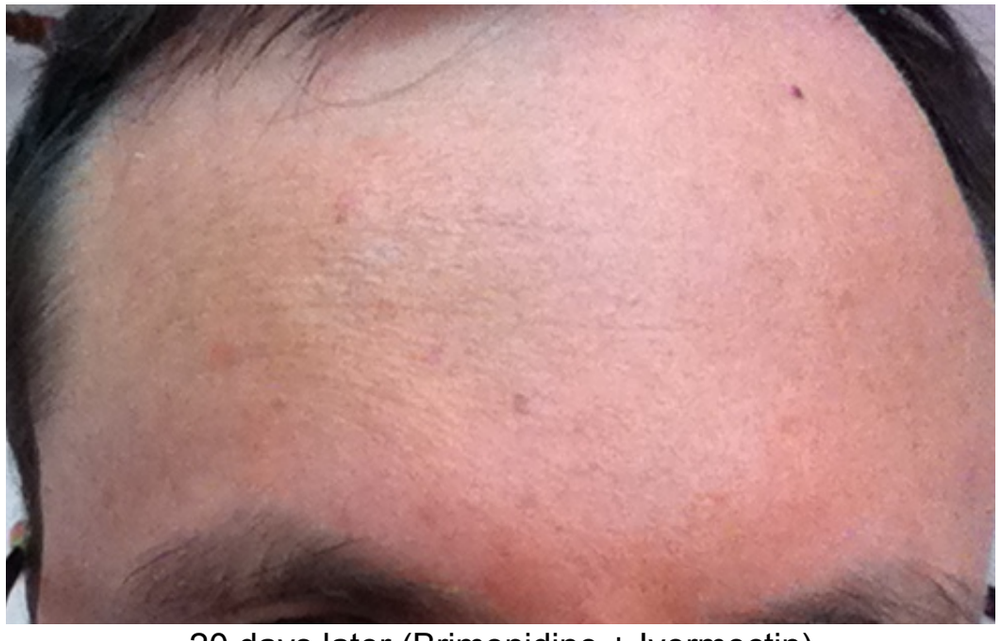


International Journal of Dermatology 2015, 54, e14–e17

Failure by failure: Br + IVM



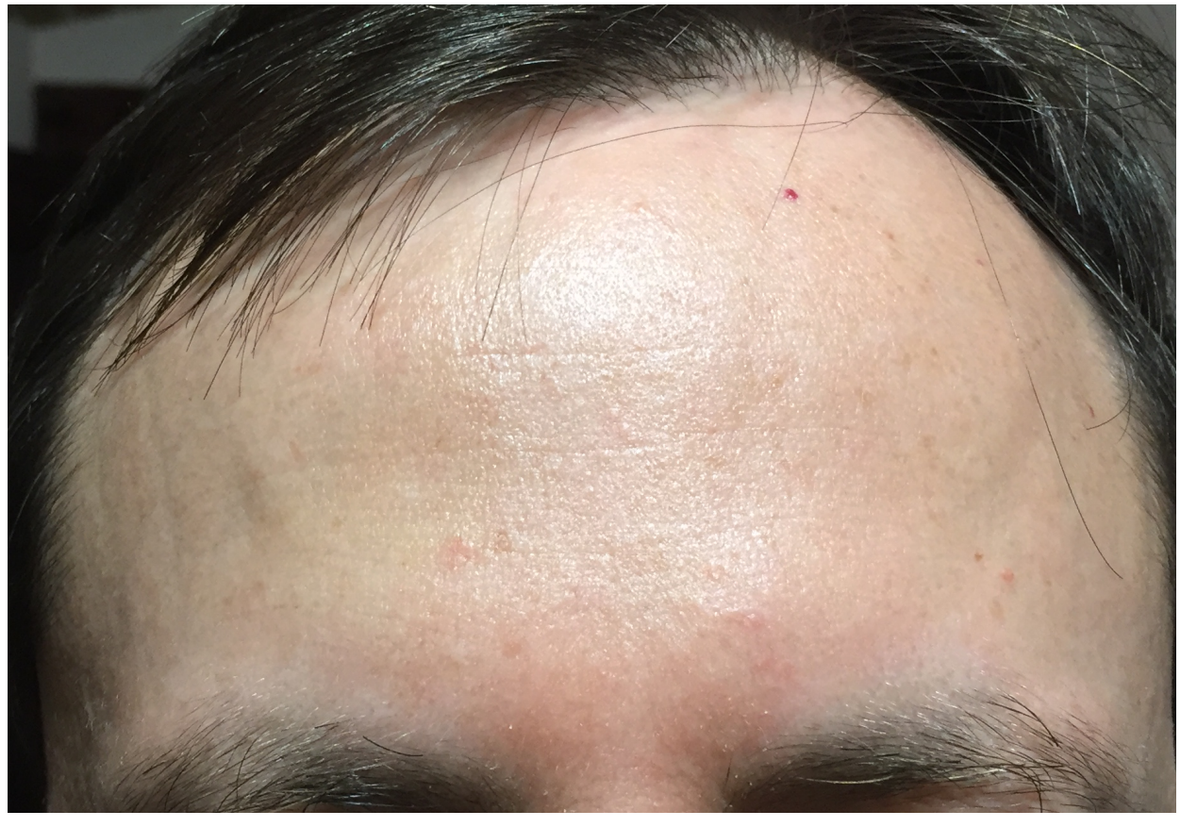
After 3 months of Doxycycline 40mg



20 days later (Brimonidine + Ivermectin)

38y.o Male pz: Rosacea and Seborrheic dermatitis: past treatment: Metronidazole, sulfur, topical steroids

- Doxycyclin 40mg QD for 3 months
- Due to lower efficacy:
  - Metronidazole cream QD for 4 months
  - Brimonidine on demand QD + Ivermectin QD for 4 mts



One year after treatment withdrawal

J Drugs Dermatol. 2017 Sep 1;16(9):909-916.

Treatment of Rosacea With Concomitant Use of Topical Ivermectin 1% Cream and Brimonidine 0.33% Gel: A Randomized, Vehicle-controlled Study.

Gold LS, Papp K, Lynde C, Lain E, Gooderham M, Johnson S, Kerrouche N.

Abstract

BACKGROUND: There is currently a lack of data on the simultaneous treatment of different features of rosacea. Individually, ivermectin 1% (IVM) cream and brimonidine 0.33% (BR) gel have demonstrated efficacy on inflammatory lesions and persistent erythema, respectively.

OBJECTIVE: To evaluate the efficacy, safety, patient satisfaction, and optimal timing of administration of IVM associated with BR (IVM+BR) versus their vehicles in rosacea (investigator global assessment [IGA] ≥3).

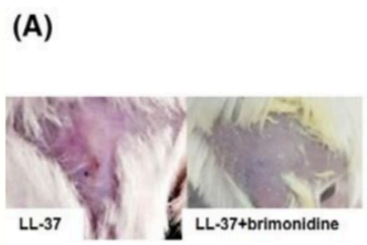
METHODS: Multicenter, randomized, double-blind study including subjects with rosacea characterized by moderate to severe persistent erythema and inflammatory lesions. The active treatment group included the IVM+BR/12 weeks subgroup (once-daily BR and once-daily IVM for 12 weeks), and the IVM+BR/8 weeks subgroup (once-daily BR vehicle for 4 weeks followed by once-daily BR for the remaining 8 weeks and once-daily IVM for 12 weeks). The vehicle group received once-daily BR vehicle and once-daily IVM vehicle for 12 weeks.

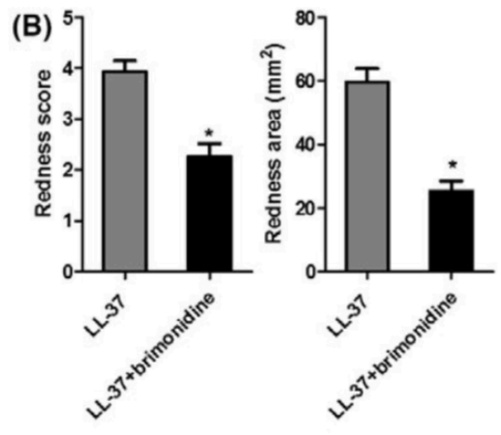
RESULTS: The association showed superior efficacy (IGA success [clear/almost clear]) for erythema and inflammatory lesions in the total active group (combined active subgroups) compared to vehicle (55.8% vs. 36.8%, P=0.007) at week 12. The success rate increased from 32.7% to 61.2% at hour 0 and hour 3, respectively, in the IVM+BR/12 weeks subgroup, and from 28.3% to 50% in the IVM+BR/8 weeks subgroup. Reductions in erythema and inflammatory lesion counts confirmed the additive effect of BR to IVM treatment. Subjects reported greater improvement in the active subgroups than in the vehicle group, and similar rates for facial appearance satisfaction after the first 4 weeks of treatment in both active subgroups. All groups showed similar tolerability profiles.

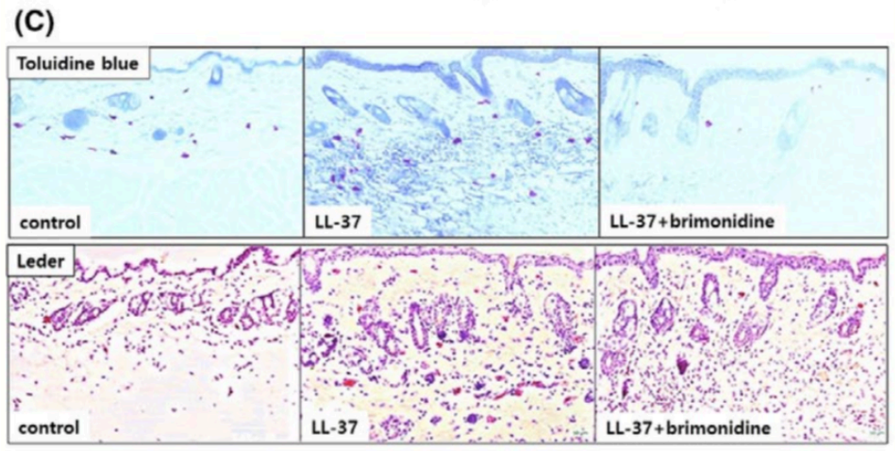
CONCLUSION: Concomitant administration of IVM cream with BR gel demonstrated good efficacy and safety, endorsing the comprehensive approach to this complex disease. Early introduction of BR, along with a complete daily skin care regimen may accelerate treatment success without impairing tolerability. J Drugs Dermatol. 2017;16(9):909-916. .

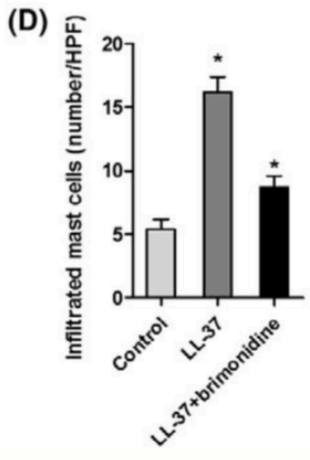
Why brimonidine in combination?

LL-37-induced rosacea-like skin lesions in Balbc mice.







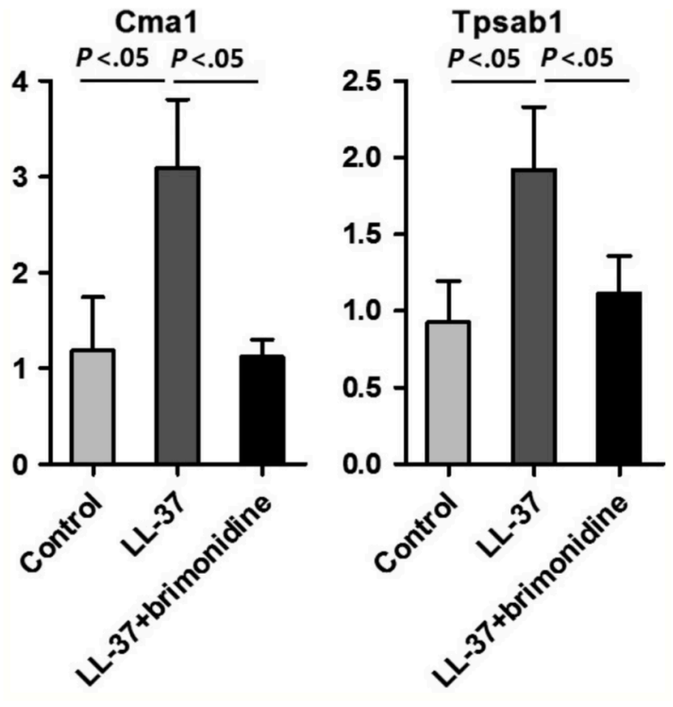


A) Representative clinical images of rosacea-like skin lesion (left) and skin lesion after topical administration of brimonidine (right). Balb/c mice were treated twice a day with 40 μl of LL-37 and brimonidine gel on the shaved dorsal skin of mice. **LL-37-induced erythema was reduced by topical administration of brimonidine gel**.

B) The severity of the clinical features of rosacea was assessed on the basis of redness scoring and redness area. The redness score and area were statistically significantly decreased in the LL-37 + brimonidine group compared with the LL-37 group.

C) The skin samples were collected at day 2 after brimonidine gel treatment for H&E and special staining for detection of MCs, and the number of MCs was counted per high- power field. Histological changes after 3 days use of brimonidine gel. MCs were stained purple in Toluidine blue stain and brightly red in Leder stain. Original magnification, ×200; scale bar=50 μm.

D) A



was increased in the LL-37 group compared with control group, while th

reduced MC compared with LL-37 group. *$P<.05$

Real-timequantitative polymerasechainreaction for chymase and tryptase mRNA expression levels.

mRNA levels of MastCells (MC) enzymes were significantly decreased after application of brimonidine gel compared to LL-37-injected mouse skin

Exp Dermatol. 2017 Nov;26(11):1143-1145. doi: 10.1111/exd.13381

Int J Infect Dis. 2013 May;17(5):e343-7. doi: 10.1016/j.ijid.2012.11.022. Epub 2013 Jan 5.

Evaluation of the efficacy of oral ivermectin in comparison with ivermectin-metronidazole combined therapy in the treatment of ocular and skin lesions of Demodex folliculorum.

Salem DA[1], El-Shazly A, Nabih N, El-Bayoumy Y, Saleh S.

Author information

Abstract

OBJECTIVE: To evaluate the efficacy of ivermectin and combined ivermectin-metronidazole therapy in the treatment of ocular and skin lesions of Demodex folliculorum.

METHODS: One hundred twenty patients with skin lesions and anterior blepharitis, whose infestation was treatment-resistant and who had a Demodex count >5 mites/cm² for skin lesions or ≥ 3 mites at the root of each eyelash, were recruited. The treatment regimens were ivermectin and ivermectin-metronidazole combined therapy. We enrolled 15 patients from each of four groups for each treatment regimen. Demodex was detected by standardized skin surface biopsy for skin lesions. Three eyelashes from each affected lower eyelid were epilated and examined. The study subjects were followed-up once a week for four visits.

RESULTS: There was a difference in the mite count between the subgroups taking ivermectin and combined therapy during all follow-up visits. At the last visit, in the combined therapy subgroup, 1.7% of patients showed no clinical improvement, 26.7% showed a marked clinical improvement, and 71.6% showed complete remission. In those on the ivermectin regimen, 27 patients had a mite count >5 mites/cm², 21.7% showed no clinical improvement, 33.3% showed a marked improvement, and 45% showed complete remission.

CONCLUSIONS: Combined therapy was superior in decreasing the D. folliculorum count in all groups and in reducing the mite count to the normal level in rosacea and in anterior blepharitis. On the other hand, the two regimens were comparable in reducing the mite count to the normal level in acne and peri-oral dermatitis lesions.

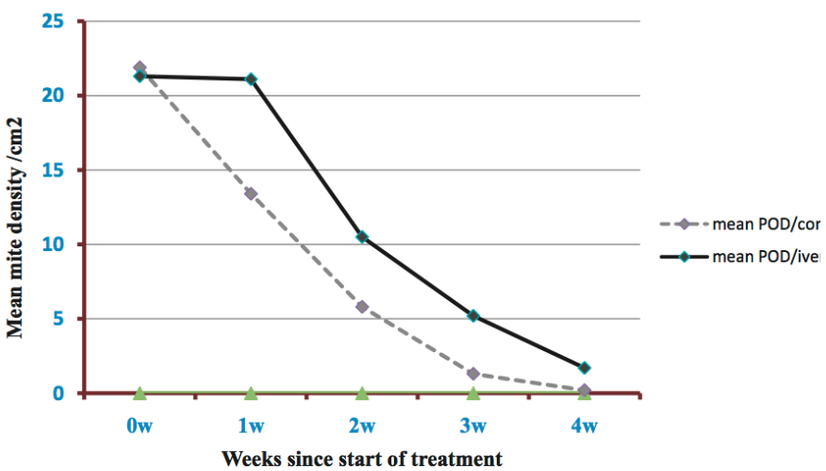


Figure 4. Mite density of peri-oral dermatitis group before treatment and throug follow up visits using different regimen therapy.

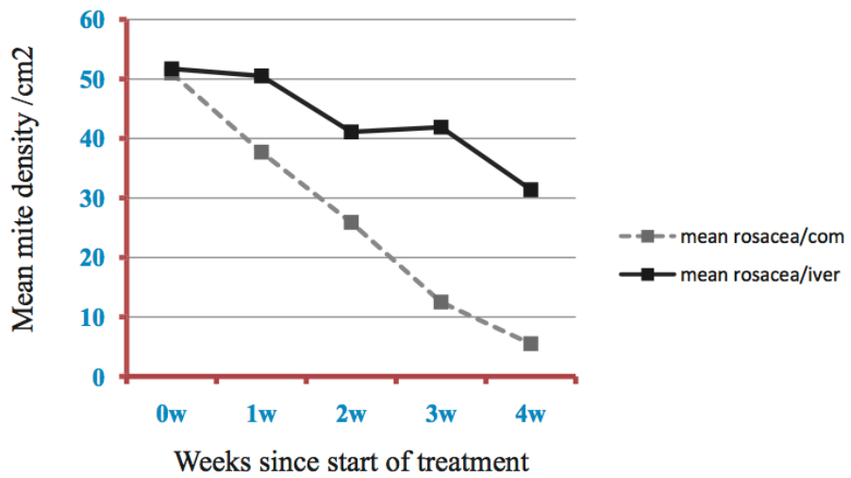
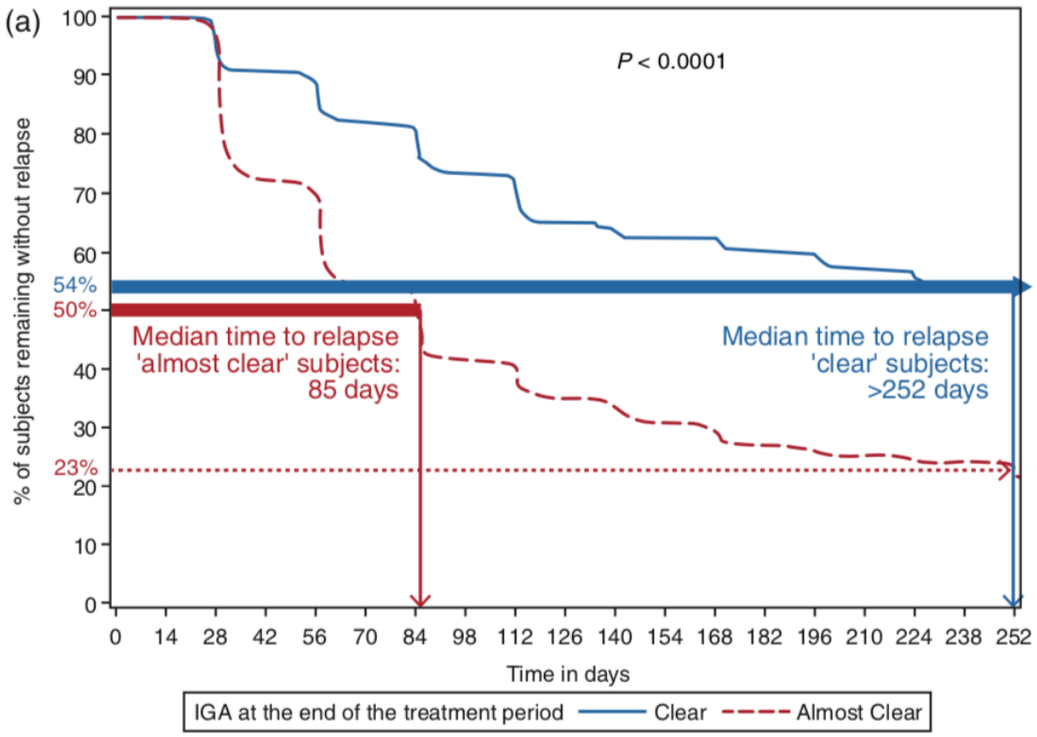


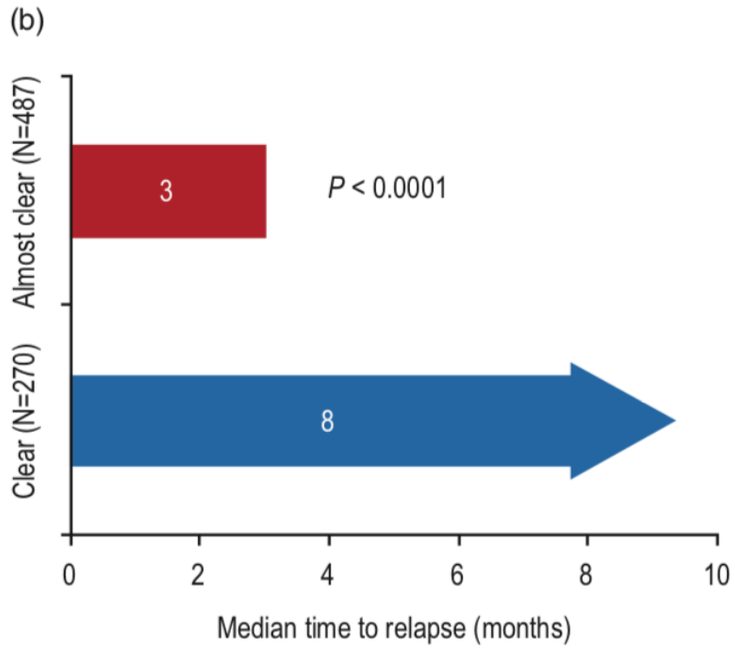
Figure 1. Mite density of rosacea group before treatment and through follow up visits using different regimen therapy.

Metronidazole and **ivermectin** are antiparasitic drugs; orally show relatively high efficiency: 71.6% of pts showed complete remission in case of rosacea and blepharitis.

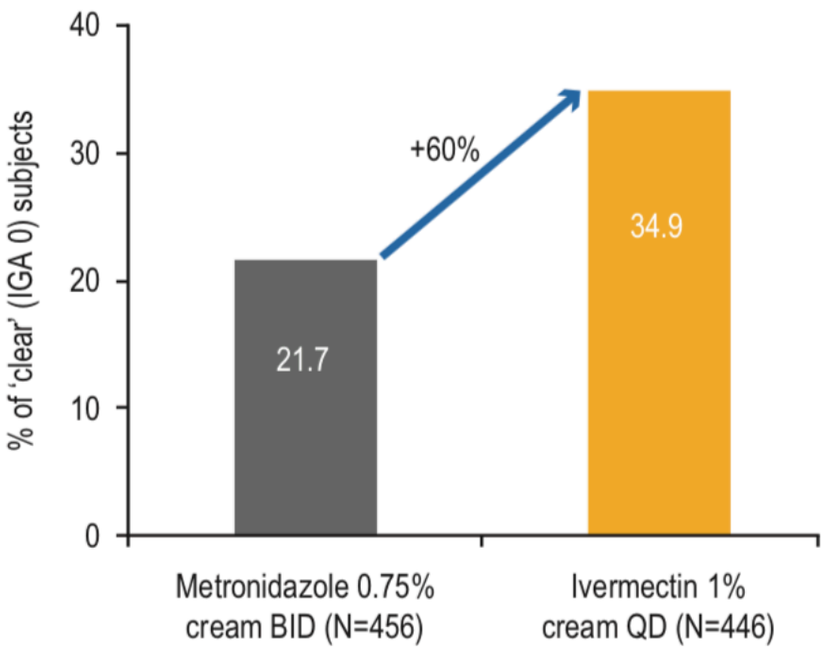
Combined therapy can be more efficient than monotherapy.

Clear vs Almost clear





Time to relapse after stopping treatment at the end of the 16-week treatment period for ‘clear’ subjects (IGA 0) vs. ‘almost clear’ subjects (IGA 1) ($p < .0001$), as shown by (a) Kaplan–Meier curve and (b) bar chart. The median time to relapse was 85 days (3 months) for ‘almost clear’ subjects and was not reached at 252 days (8 months) for ‘clear’ subjects.



Percentage of ‘clear’ subjects (IGA 0) after 16weeks treatment with once-daily ivermectin 1% cream vs. twice-daily metronizadole 0.75% cream.

Subjects achieving an endpoint of ‘clear’ on IGA with no inflammatory papules and pustules and no erythema after treatment of rosacea, however long it takes, have improved quality of life and extended time to relapse compared to ‘almost clear’ subjects.

Guy Webster, Martin Schaller, Jerry Tan, J. Mark Jackson, Nabil Kerrouche & Gregor Schäfer (2017) **Defining treatment success in rosacea as ‘clear’ may provide multiple patient benefits**: results of a pooled analysis, Journal of Dermatological Treatment, 28:5, 469-474, DOI: 10.1080/09546634.2017.1343435

Combination therapies

J Drugs Dermatol. 2012 Jul;11(7):838-44.

Optimal management of papulopustular rosacea: rationale for combination therapy.

Bhatia ND[1], Del Rosso JQ.

Author information

Abstract

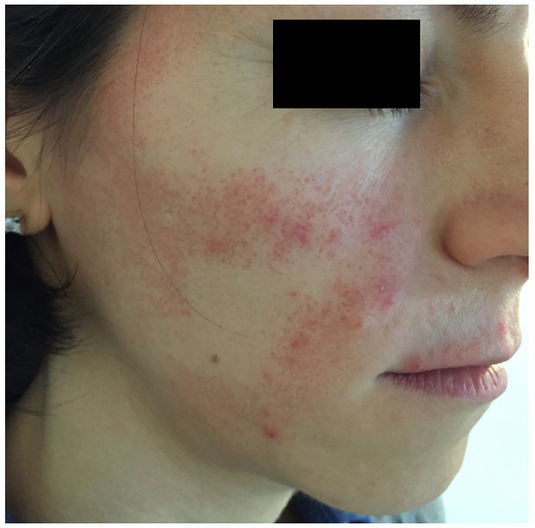
The pathophysiology of papulopustular rosacea (PPR) is primarily characterized by inflammation associated with several factors such as abnormal innate immune response, neurovascular dysregulation, stratum corneum barrier dysfunction, and depletion of antioxidant reserve, with no definitive evidence supporting an underlying microbial etiology. Several molecular inflammatory pathways have now been identified that enable the development of therapeutic agents that target the signs and symptoms of disease by modifying specific pathophysiological mechanisms. Available evidence demonstrates that topical and oral agents commonly used to treat PPR appear to modify some of these pathophysiological mechanisms and may prove to be complimentary when used in combination potentially leading to better therapeutic outcomes. During the past two decades, six clinical studies have been published on the benefits of combining oral and topical therapies for PPR. Four studies suggest that doxycycline, including anti-inflammatory dose doxycycline (doxycycline 40 mg modified-release capsule once daily) can be combined with topical metronidazole or azelaic acid in patients with PPR to achieve more rapid control of a flare. At present, subantimicrobial dosing of a tetracycline agent that also maintains anti-inflammatory activity has only been established with doxycycline. Although antibiotic doses of tetracycline agents (such as doxycycline, minocycline, and tetracycline) are known to be effective for PPR, the use of subantimicrobial dosing of doxycycline avoids the risk of antibiotic resistance.

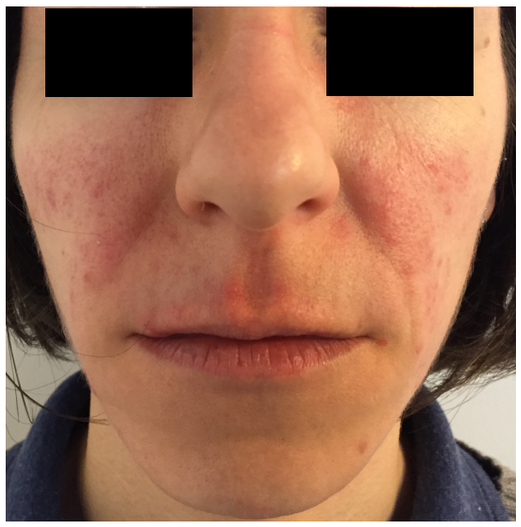
- The ROSCO panel agreed that multiple cutaneous features of rosacea can be treated with more than one agent simultaneously

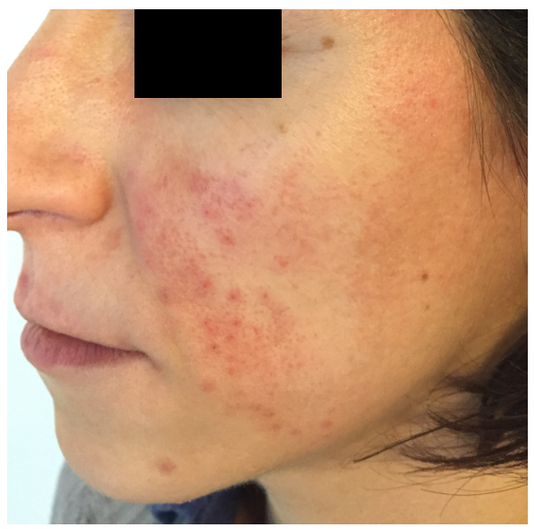
M. Schaller, J. Tan . British Journal of Dermatology (2017) 176, pp465–471

Combined therapies:

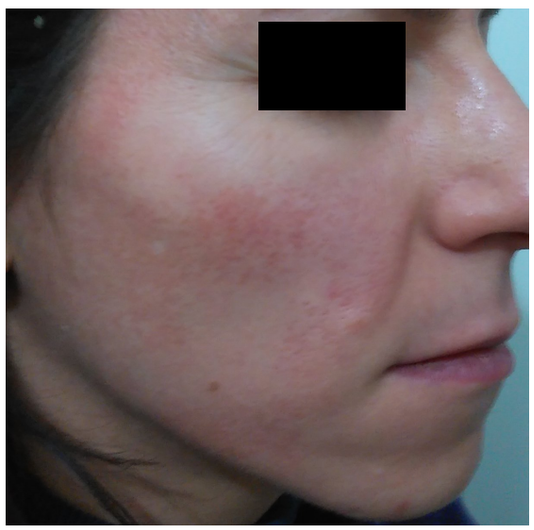
Doxy 40mg 1 month + Ivermectine 3 months

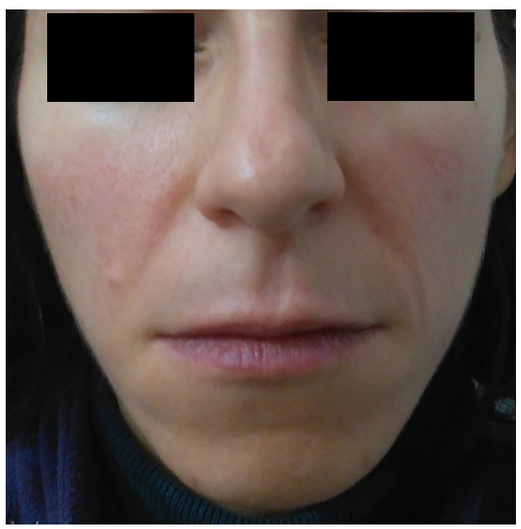


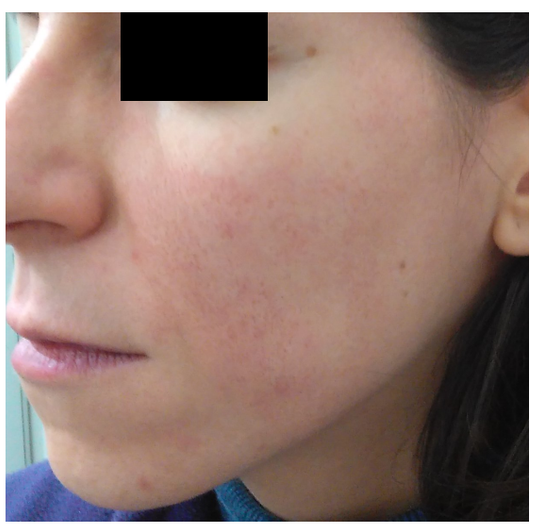




- IVM and doxy 40mg have different targets in the inflammatory pathways of rosacea
- The hypothesis is that combining treatments which act on different targets within inflammatory pathways could provide improved results for patients with inflammatory lesions of rosacea

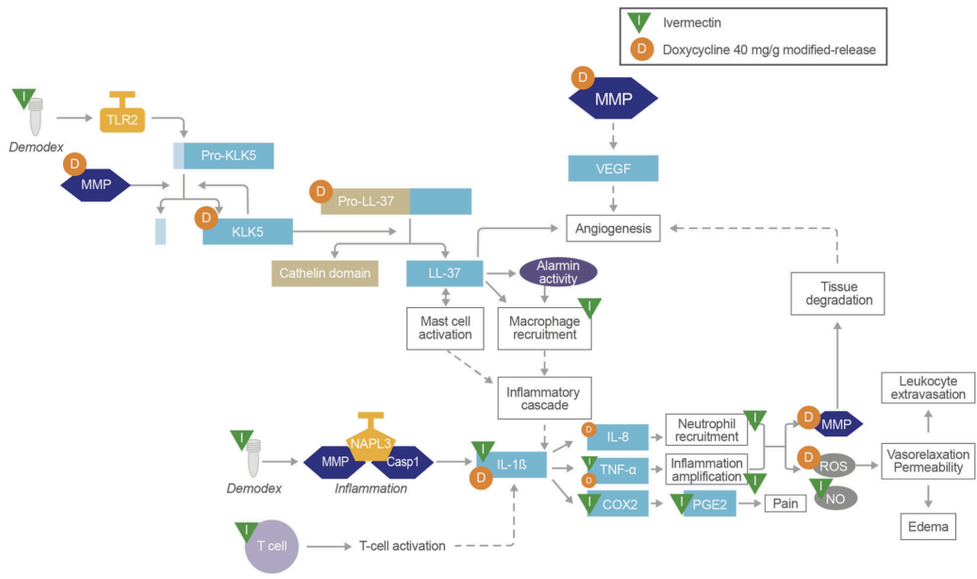






Target	Agent	
	Ivermectin	Doxycycline
Protein/step of inflammatory pathway		
Demodex	✓	
MMPs		✓
KLKs		✓
Cathelidicin cleavage/LL-37 production		✓
Cytokines		
IL-1β	✓	✓
IL-8		✓
TNF-α	✓	✓
COX2	✓	
PGE2	✓	
NO	✓	✓
ROS		✓
Angiogenesis		✓
MAPK pathway	✓	
Macrophage chemotaxis	✓	✓
Neutrophil chemotaxis	✓	✓
T cell activation	✓	
Mast cell function		✓

The combination of topical ivermectin 10 mg/g cream with oral doxycycline 40 mg modified-release could provide an intensive initial regimen, especially for those patients with more involved disease or when a fast onset of action is required.



Steinhoff M et al. Adv Ther. 2016 Sep;33(9):1481-501

Combined Therapies

Brimonidine QD + Doxy 40mg QD (1 month)+ 2 IPL session 1 month apart

1 month after last IPL session

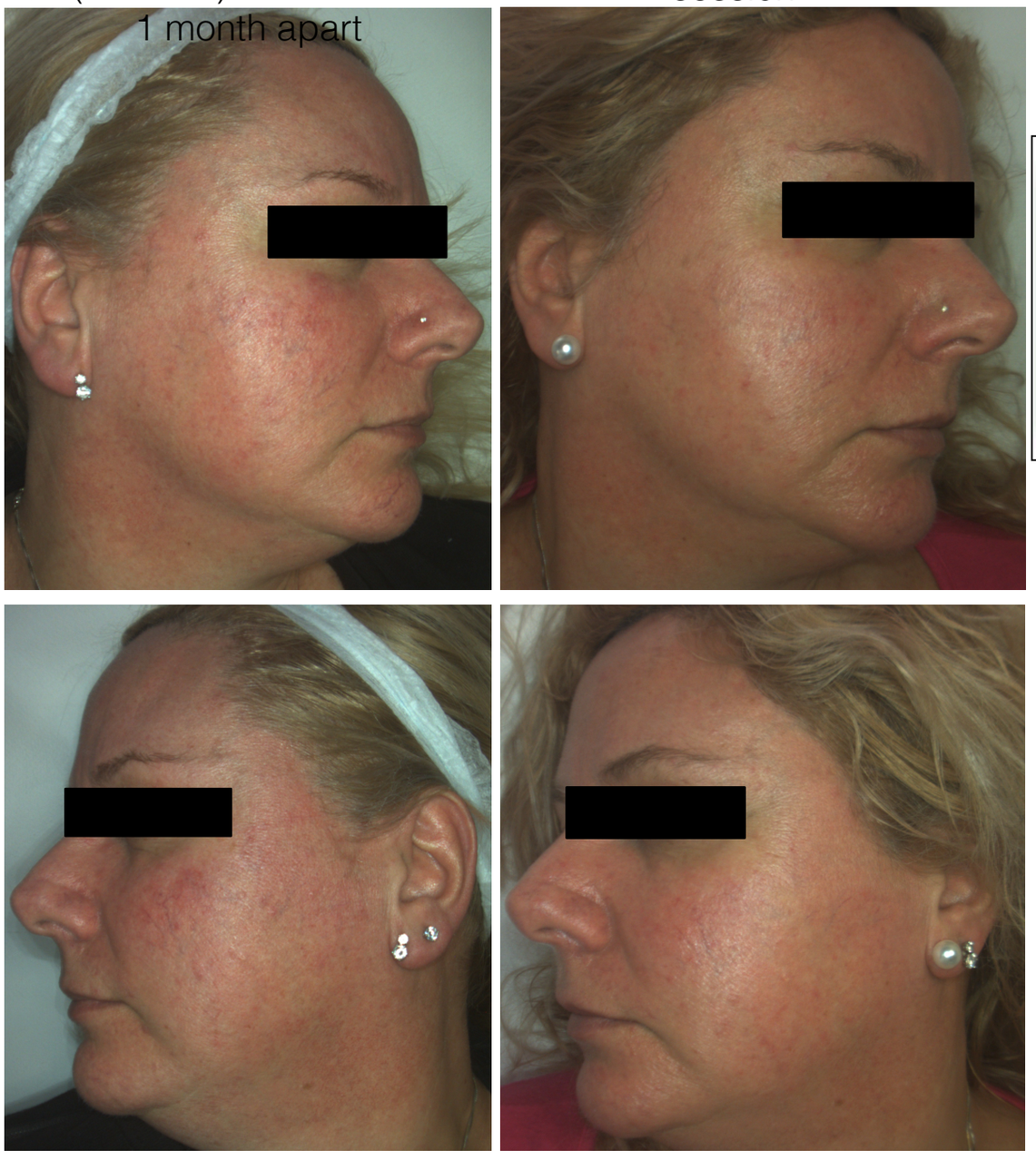
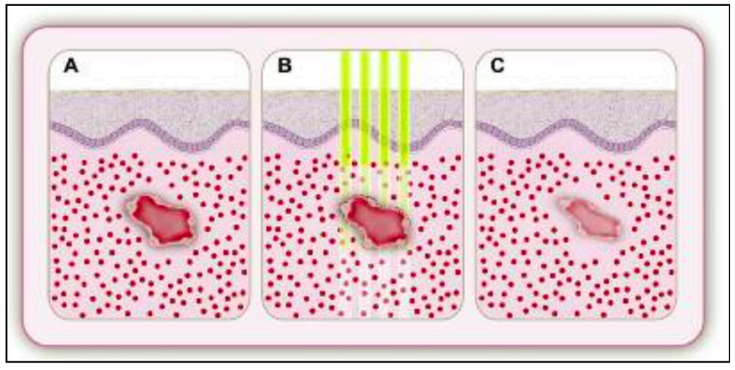
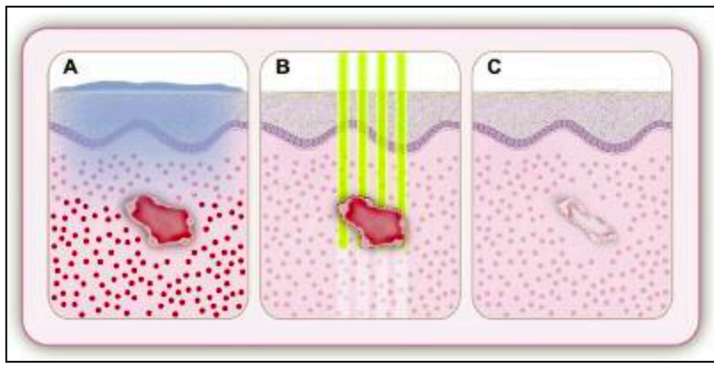
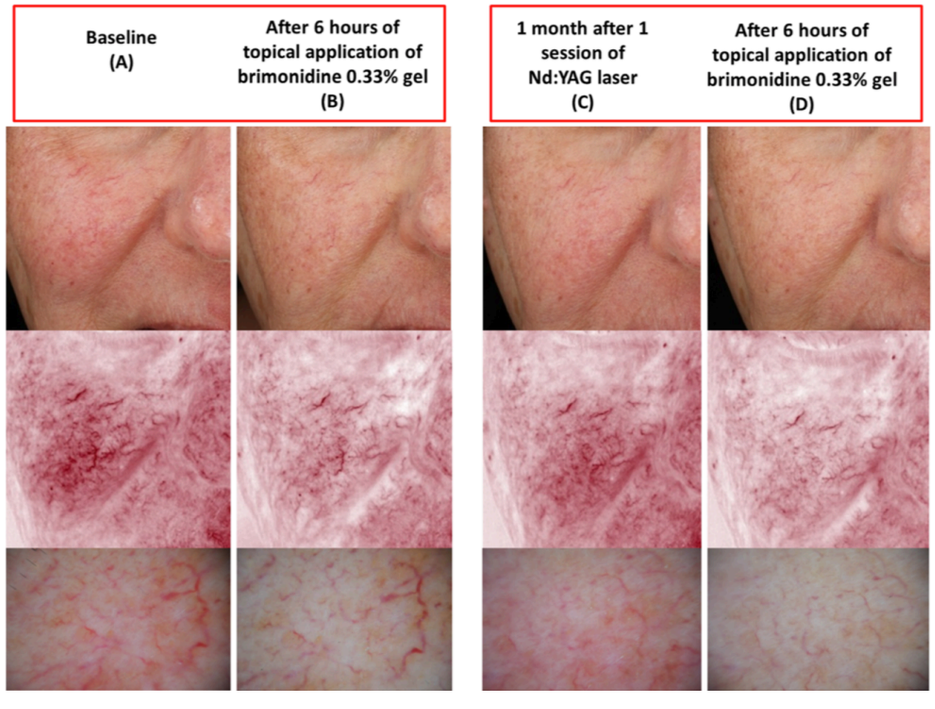


TABLE 1. Different scenarios and suggested management of patients with erythematotelangiectatic rosacea	
SCENARIO	**SUGGESTED MANAGEMENT**
Marked telangiectasia + Minimal background erythema	Laser/light-based therapy
Minimal telangiectasia + Marked background erythema	Brimonidine 0.33% gel
Marked telangiectasia + Marked background erythema	Combination brimonidine 0.33% + laser/light-based therapy





Micali g et al. Improving Treatment of Erythematotelangiectatic Rosacea with Laser and/or Topical Therapy Through Enhanced Discrimination of its Clinical Features. J Clin Aesthet Dermatol. 2016 Jul;9(7):30-9.



Micali et al. Lasers Med Sci. 2017 Sep 9. doi: 10.1007/s10103-017-2318-3

Take home message

- Sub-type vs Pheno-type switch
- Clear is better than improvement
- Combination therapies are usually more effective
- Consider “off-lable” use of drugs