Quali risultati ci possiamo ragionevolmente attendere dai topici?

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UNIVERSITÀ DEGLI STUDI DI FERRARA
- EX LABORE FRUCTUS -

European evidence-based (S3) guideline for the treatment of acne – update 2016 – short version

A. Nast,[1,*] B. Dréno,[2] V. Bettoli,[3] Z. Bukvic Mokos,[4] K. Degitz,[5] C. Dressler,[1] A.Y. Finlay,[6] M. Haedersdal,[7] J. Lambert,[8] A. Layton,[9] H.B. Lomholt,[10] J.L. López-Estebaranz,[11] F. Ochsendorf,[12] C. Oprica,[13] S. Rosumeck,[1] T. Simonart,[14] R.N. Werner,[1] H. Gollnick[15]

JEADV 2016, 30, 1261–1268

GUIDELINES

BJD
British Journal of Dermatology

Guidelines for the management of acne: recommendations from a French multidisciplinary group

L. Le Cleach,[1,2] B. Lebrun-Vignes,[3] A. Bachelot,[4,5] F. Beer,[6] P. Berger,[7] S. Brugère,[8] M. Chastaing,[9] G. Do-Pham,[1] T. Ferry,[10,11] J. Gand-Gavanou,[12] B. Guigues,[13] O. Join-Lambert,[14,15] P. Henry,[16] R. Khallouf,[17] E. Lavie,[18] A. Maruani,[19,20] O. Romain,[21] B. Sassolas,[22] V.T. Tran,[23,24] and B. Guillot[25] for the French Acne Guidelines Working Group and Centre of Evidence of Dermatology

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Guidelines of care for the management of acne vulgaris

Work Group: Andrea L. Zaenglein, MD (Co-Chair),[a] Arun L. Pathy, MD (Co-Chair),[b] Bethanee J. Schlosser, MD, PhD,[c] Ali Alikhan, MD,[d] Hilary E. Baldwin, MD,[e] Diane S. Berson, MD,[f,g] Whitney P. Bowe, MD,[e] Emmy M. Graber, MD,[h,i] Julie C. Harper, MD,[j] Sewon Kang, MD,[k] Jonette E. Keri, MD, PhD,[l,m] James J. Leyden, MD,[n] Rachel V. Reynolds, MD,[o,p] Nanette B. Silverberg, MD,[q,r] Linda F. Stein Gold, MD,[s] Megha M. Tollefson, MD,[t] Jonathan S. Weiss, MD,[u] Nancy C. Dolan, MD,[c] Andrew A. Sagan, MD,[v] Mackenzie Stern,[c] Kevin M. Boyer, MPH,[w] and Reva Bhushan, MA, PhD[w]
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Differences

- ✓ Three different grading system
- ✓ General recommendations not described as first-line and second-line therapy but as strength of recommendation, (high, medium and low)

- ✓ Topica dapsone is one of the option for second-line treatment for mild acne

- ✓ Included Complementary/ alternative therapy

- ✓ Low dose of systemic isotretinoin is one option for maintenance treatment

- ✓ …

European evidence-based (S3) guideline for the treatment of acne – update 2016 – short version

A. Nast,[1,*] B. Dréno,[2] V. Bettoli,[3] Z. Bukvic Mokos,[4] K. Degitz,[5] C. Dressler,[1] A.Y. Finlay,[6] M. Haedersdal,[7] J. Lambert,[8] A. Layton,[9] H.B. Lomholt,[10] J.L. López-Estebaranz,[11] F. Ochsendorf,[12] C. Oprica,[13] S. Rosumeck,[1] T. Simonart,[14] R.N. Werner,[1] H. Gollnick[15]

Induction therapy

Summary of therapeutic recommendations[1] for induction therapy

	Comedonal acne[3]	Mild to moderate papulopustular acne	Severe papulopustular/moderate nodular acne	Severe nodular/conglobate acne[13]
High strength of recommendation	-	Adapalene + BPO (f.c.) or BPO + Clindamycin (f.c.)[5]	Isotretinoin	Isotretinoin
Medium strength of recommendation	Topical retinoid[4]	Azelaic acid or BPO or Topical Retinoid[4] or Topical Clindamycin + Tretinoin (f.c.)[5,6] or Systemic Antibiotic[5,7,8] + Adapalene[9]	Systemic Antibiotic[5,8] + Adapalene[9] or Systemic Antibiotic[5,8] + Azelaic acid[10] or Systemic Antibiotic[5,8] + Adapalene + BPO (f.c.)	Systemic Antibiotic[5,8] + Azelaic Acid or Systemic Antibiotic[5,8] + Adapalene + BPO (f.c.)
Low strength of recommendation	Azelaic acid or BPO	Blue Light or Oral Zinc or Systemic Antibiotic[5,7,8] + Azelaic Acid[10] or Systemic Antibiotic[5,7,8] + Adapalene + BPO (f.c.)[11] or Systemic Antibiotic[5,7,8] + BPO[12] or Topical Erythromycin + Isotretinoin (f.c.)[5] or Topical Erythromycin + Tretinoin (f.c.)[5]	Systemic Antibiotic[5,8] + BPO[12]	Systemic Antibiotic[5,8] + Adapalene[9,11] or Systemic Antibiotics[5,8] + BPO[11]
Alternatives for females[2]	-	-	Hormonal Anti-androgens + Systemic Antibiotic[5,8] + Topicals (apart from antibiotics) or Hormonal Anti-androgens + Topical Treatment (apart from antibiotics)	Hormonal Anti-androgens + Systemic Antibiotic[5,8] + Topicals (apart from antibiotics) or Hormonal Anti-androgens + Topical Treatment (apart from antibiotics)

JEADV 2016, 30, 1261–1268

Maintenance therapy

	Comedonal acne	Mild to moderate papulopustular acne	Severe papulopustular/moderate nodular acne	Severe nodular/conglobate acne
High strength of recommendation	-	-	-	-
Medium strength of recommendation	-	-	-	-
Low strength of recommendation	Azelaic Acid or Topical Retinoid [2]	Azelaic Acid or BPO or Topical Retinoid [2]	Adapalene + BPO (f.c.) [3] or Azelaic Acid or BPO [3] or Low Dose Systemic Isotretinoin (max. 0.3 mg/kg/day) or Topical Retinoid [2]	Adapalene + BPO (f.c.) [3] or Azelaic Acid or BPO [3] or Low Dose Systemic Isotretinoin (max. 0.3 mg/kg/day) or Topical Retinoid [2]
Alternatives for females [1]	-	-	Continued Hormonal Anti-androgens [4] + Topical Treatment (apart from antibiotics)	Continued Hormonal Anti-androgens [4] + Topical Treatment (apart from antibiotics)

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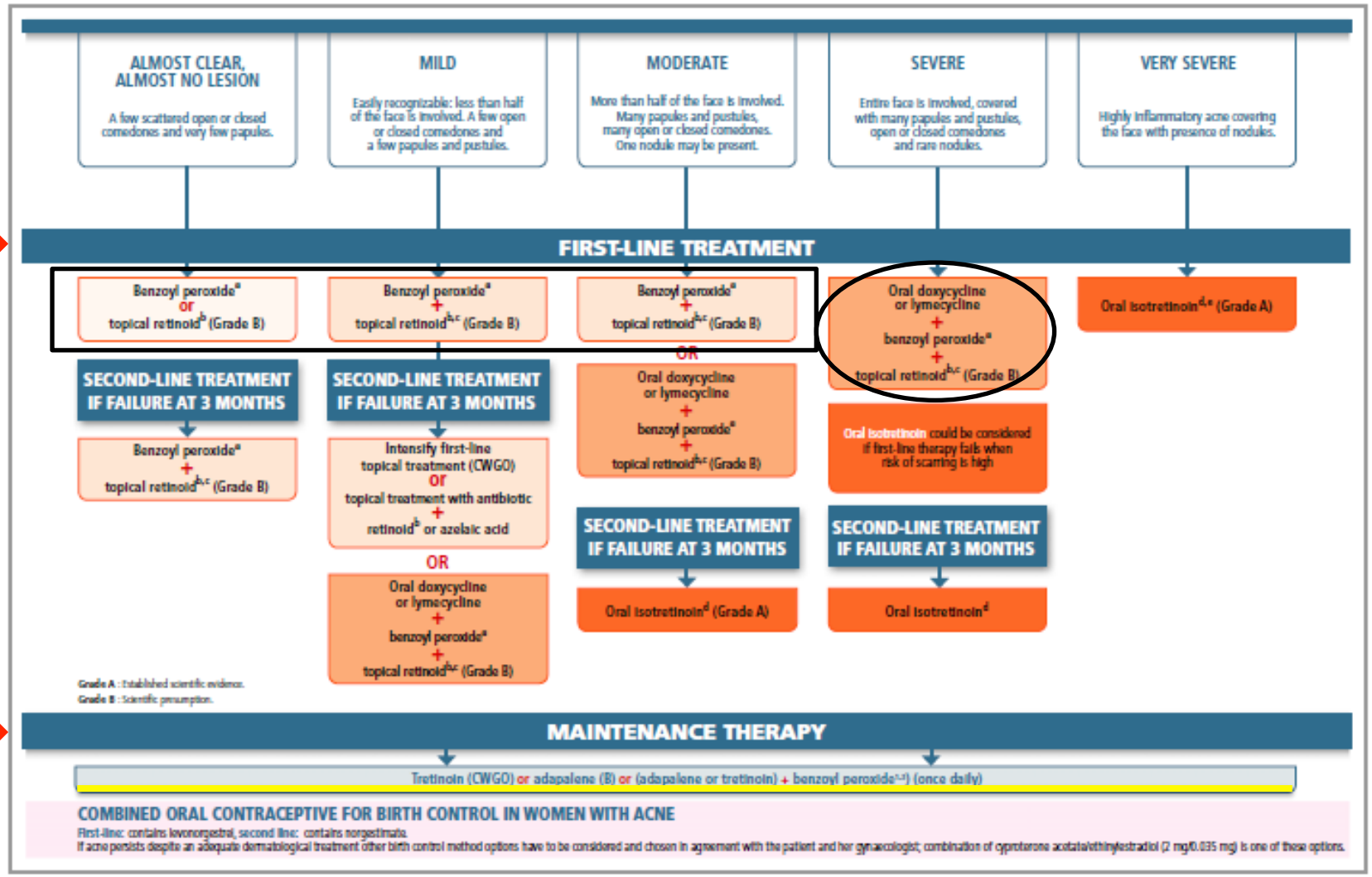

	Mild	Moderate	Severe
1st Line Treatment	Benzoyl Peroxide (BP) or Topical Retinoid -or- Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic	Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic -or- Oral Antibiotic + Topical Retinoid + BP -or- Oral Antibiotic + Topical Retinoid + BP + Topical Antibiotic	Oral Antibiotic + Topical Combination Therapy** BP + Antibiotic or Retinoid + BP or Retinoid + BP + Antibiotic -or- Oral Isotretinoin
Alternative Treatment	Add Topical Retinoid or BP (if not on already) -or- Consider Alternate Retinoid -or- Consider Topical Dapsone	Consider Alternate Combination Therapy -or- Consider Change in Oral Antibiotic -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin	Consider Change in Oral Antibiotic -or- Add Combined Oral Contraceptive or Oral Spironolactone (Females) -or- Consider Oral Isotretinoin

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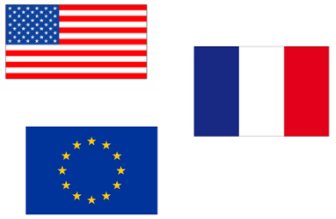
Acne: terapia topica



recommendation

- ✓ Sempre terapia topica tranne se isotretinoina
- ✓ Terapia topica anche nel mantenimento

Negative recommendation

- ✓ ***No antibiotici topici in acne comedonica***
- ✓ ***Mai antibiotici topici in monoterapia***
- ✓ *In **acne papulo-pustolosa severa**/nodulare moderata/nodulare severa/ acne conglobata **NON solo terapia topica** (anche se combinata in triplice terapia)*
- ✓ ***No monoterapia topica** in **acne severa anche se associata a terapia antibiotica sistemica***
- ✓ ***Antibiotici topici** in monoterapia o terapia combinata **mai nel mantenimento***

Topical treatment for acne

Acido azelaico 20%

- ✓ Proprietà: antinfiammatorio, antiossidante, antimicrobico, comedolitico, cheratolitico, depigmentante
- ✓ Effetti avversi: prurito, bruciore, disestesie
- ✓ No farmacoresistenza
- ✓ No DAC

Perossido di benzoile (BPD) 2,5-5%

- ✓ Antimicrobico lipofilo
- ✓ BPD→ Acido benzoico + perossido di idrogeno → ROS
- ✓ No farmacoresistenza, previene l'antibioticoresistenza
- ✓ BPO 4% gel comparabile a adapalene 0,1% gel (↓lesioni infiammatorie e non infiammatorie)
- ✓ Effetti avversi: DIC, bianca tessuti e capelli, …DAC

Kosmadaki et al. Clinics in Dermatology. 2017;35:173-179

Topical treatment for acne

Antibiotici:

- ✓ Eritromicina 2-4%, clindamicina1%
- ✓ Propietà: antibatteriche, antinfiammatorie
- ✓ Ottima tollerabilità
- ✓ Sviluppo di farmacoresistenza

Dapsone 5%:

- ✓ USA, nell'acne della donna adulta
- ✓ Antimicrobico, antinfiammatorio
- ✓ Sicuro ed efficace nella terapia a lungo termine / nel mantenimento
- ✓ Farmacoresistenza non nota
- ✓ Effetti avversi: xerosi, irritazione modesta
- ✓ Classe di rischio C

Kosmadaki et al. Clinics in Dermatology. 2017;35:173-179

*«**Retinoids** are the **core of topical terapy** for acne»*

Zaenglein et al. J Am Acad Dermatol 2016;74:945–73.e33

tretinoina 0,025-0,05%, isotretinoina 0,05%,
adapalene 0,1-0,3%, tazarotene 0,1%

- ↓ proliferazione dei cheratinociti e né favoriscono la differenziazione, azione **anticomedogenica** e **comedolitica**.
- **Bloccano importanti *pathways* infiammatori**
  (↓ espessione dei Toll-like receptor, ↓ rilascio di citochine, inibizione chemiotassi leucocitaria)
- ↓ **l'iperpigmentazione post infiammatoria** (accelerato il turnover cellulare ed inibizione del trasferimento dei melanosomi ai cheratinociti)
- Azione indiretta contro P. acnes

Leyden et al. Dermatol Ther. 2017;7:293-304

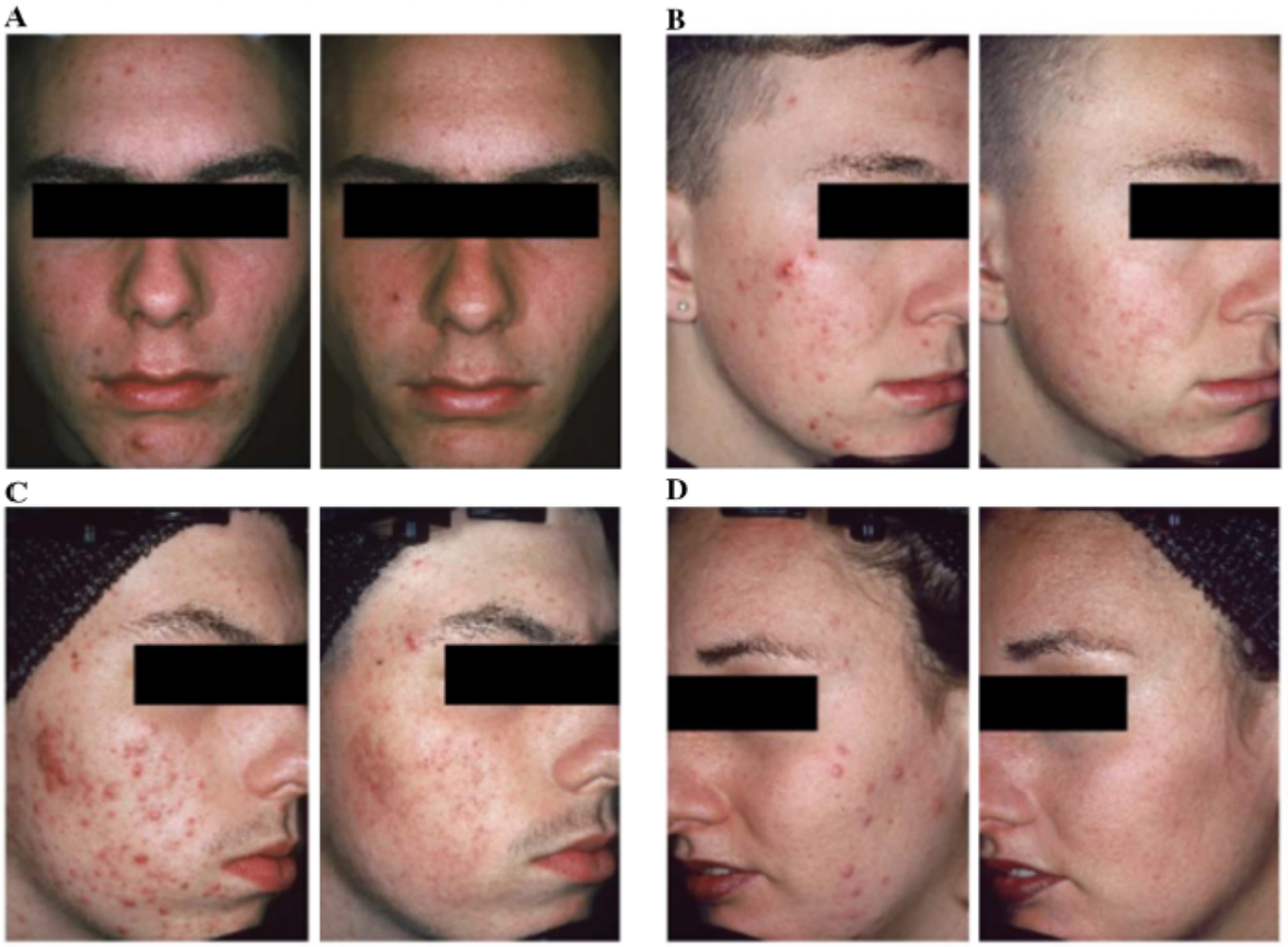


Fig. 3 Clinical efficacy of topical retinoid monotherapy on inflammatory lesions after 12 or 15 weeks therapy. From Leyden et al. [37]

Leyden et al. Dermatol Ther. 2017;7:293-304
Leyden et al. Clin Ther. 2005;27:216-24

Retinoids

- ✓ **Efficacia dipendente da: molecola, concentrazione, veicolo, idratazione**
  - Tretinoina 0,1% vs 0,025%: riduzione microcomedoni -80% vs -35%
  - Efficacia comparabile: Tretinoina 0,025 gel, tretinoina 0,1% microsfere gel, tretinoina 0,05% crema, adapalene 0,1% gel o crema, isotretinoina 0,05% gel.
  - Tazarotene 0,1% più efficace, più irritante
- ✓ **Effetti collaterali**: eritema, xerosi, desquamazione, irritazione, prurito, bruciore
- ✓ **Categoria di rischio C, isotretinoina e tazarotene categoria X**
- ✓ **< 12 aa uso off-label con eccezioni…Tretinoina** gel 0,05% dai 9 anni di età; Adapalene 0,1% + BPO 2,5% dai 10 anni

Kosmadaki et al. Clinics in Dermatology. 2017;35:173-179

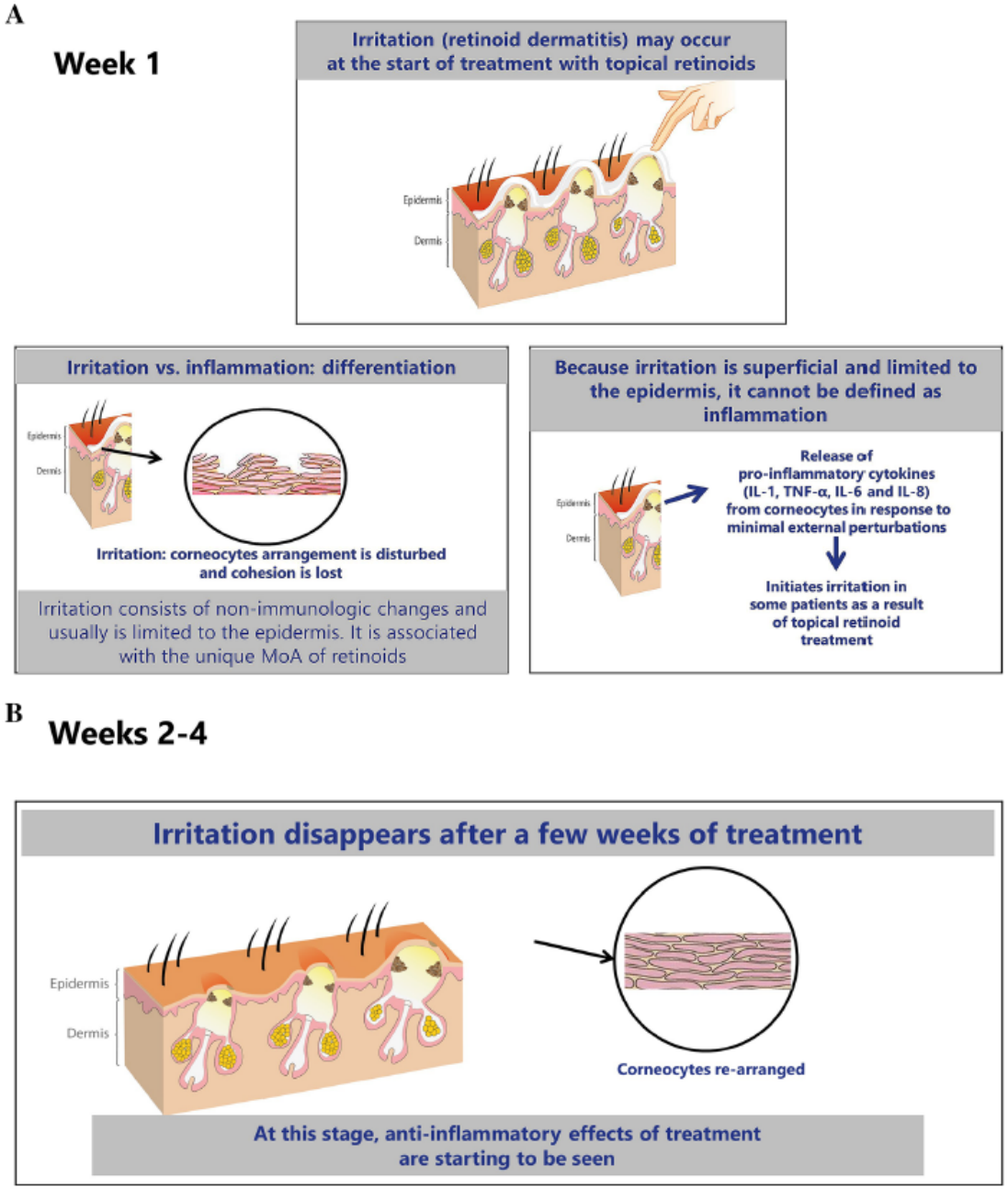


Fig. 4 Changes over time in the skin with retinoid therapy, differentiating transient irritation versus inflammation. *MoA* mechanism of action, *IL* interleukin, *TNF* tumor necrosis factor

Table 1 Strategies to minimize tolerability issues [7, 53, 69]

Take a detailed patient history
Past tolerability problems?
Educate patient
Mild irritation can be part of the treatment process, but usually subsides within 1–2 weeks and can be managed with appropriate steps
How to apply the retinoid in a thin layer (fingertip or pea-sized dose)
Gentle cleansing regimen and avoiding over-cleansing
Select most tolerable retinoid formulation for climate and season
Titrate retinoid dose at initiation
Apply retinoid every other day for first 2–4 weeks (based on clinical trial evidence that this is when irritation is most likely to occur)
Apply a gentle, non-comedogenic moisturizer
Use a short contact method for the first 2–4 weeks (apply retinoid to full face for 30–60 min then wash off)

Leyden et al. Dermatol Ther. 2017;7:293-304

Polymer Conjugated Retinoids for Controlled Transdermal Delivery

Steven A. Castleberry[1,2,3,4], **Mohiuddin A. Quadir**[1,2], **Malak Abu Sharkh**[1], **Kevin E. Shopsowitz**[1,2], and **Paula T. Hammond**[1,2,3,*]

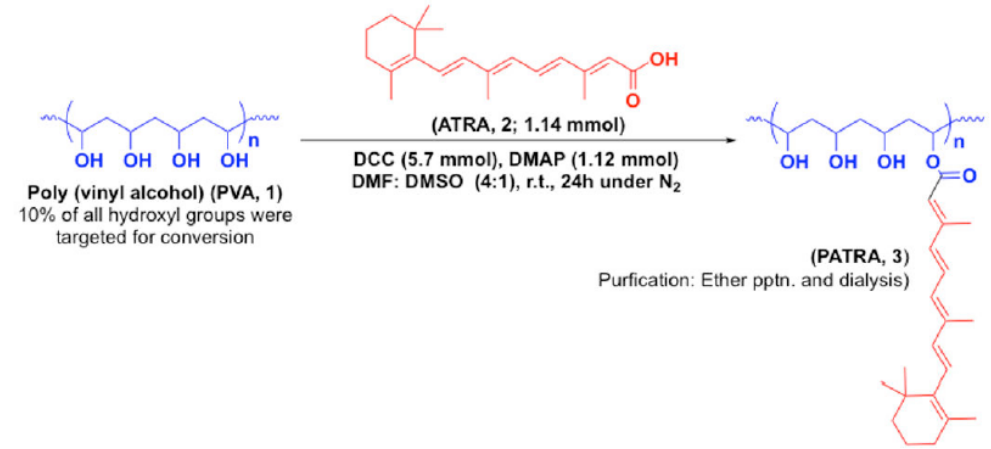


Figure 1. Chemical synthesis of PATRA
Conjugation of ATRA (2) to PVA (1)

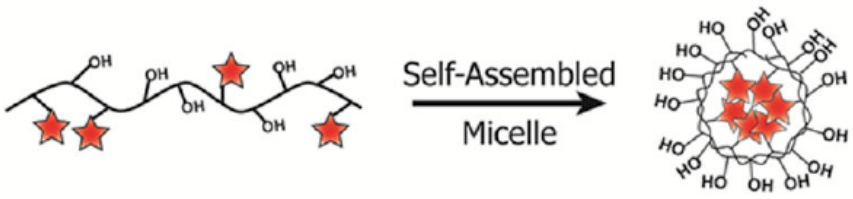
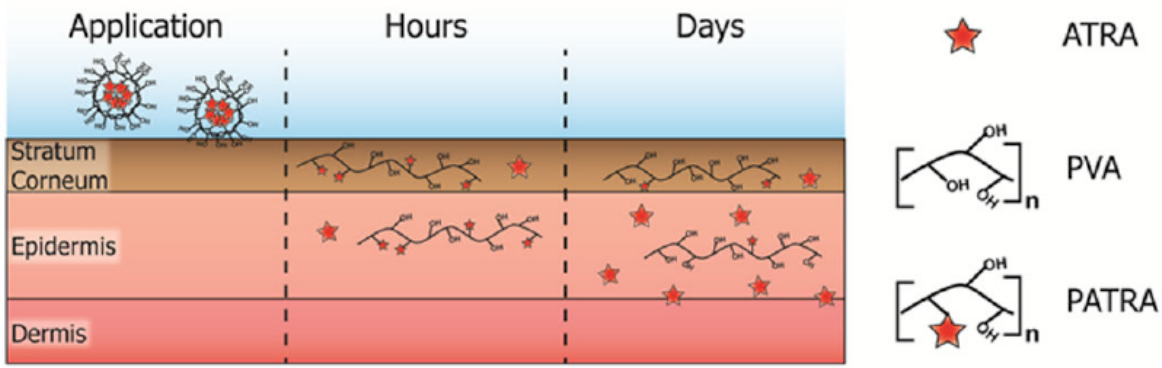


Figure 2. Cartoon schematic of the adsorption of micellar PATRA into the dermis
Release of ATRA from the PATRA conjugate occurs in the hydrated dermis.



J Control Release. 2017 September 28; 262: 1–9.

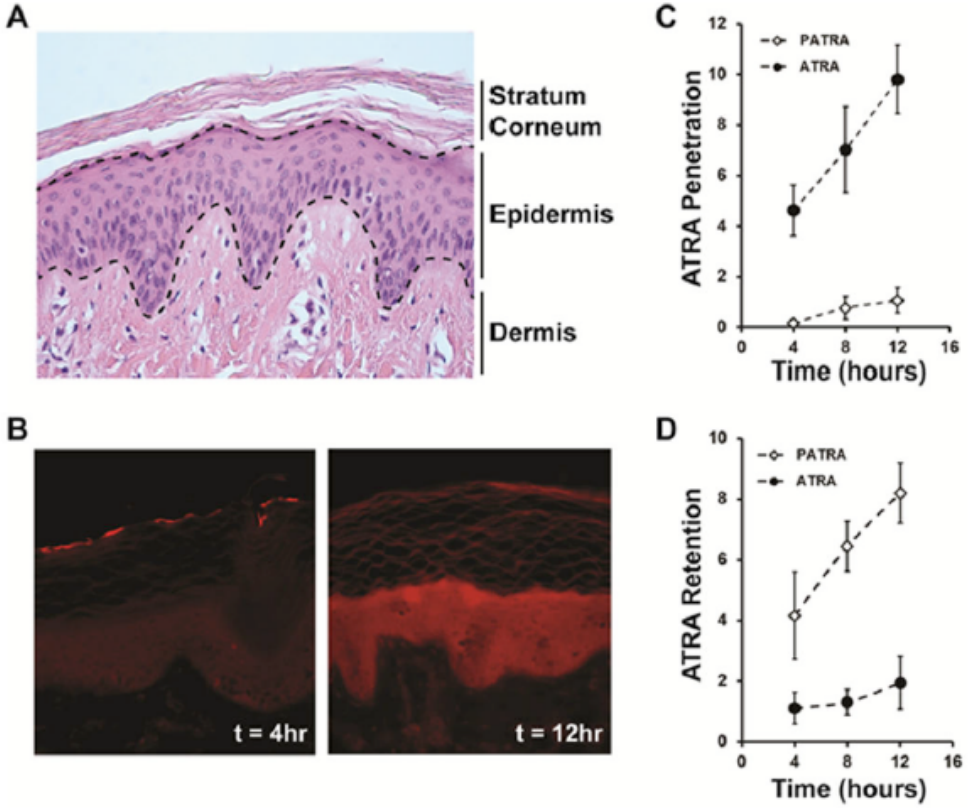


Figure 6. Uptake and transport of ATRA in explant pig skin
(a) Histological appearance of pig dermis. (b) Uptake of fluorescently labeled PATRA after 4 and 12 hours of exposure. Uptake is seen to significantly increase over this time and accumulate within the epidermis. (c) Fraction penetration of ATRA through pig dermis followed over 12 hours. (d) Quantification of fraction of ATRA accumulated within the pig dermis over 12 hours of exposure. Data shown is mean ± S.D., n=4.

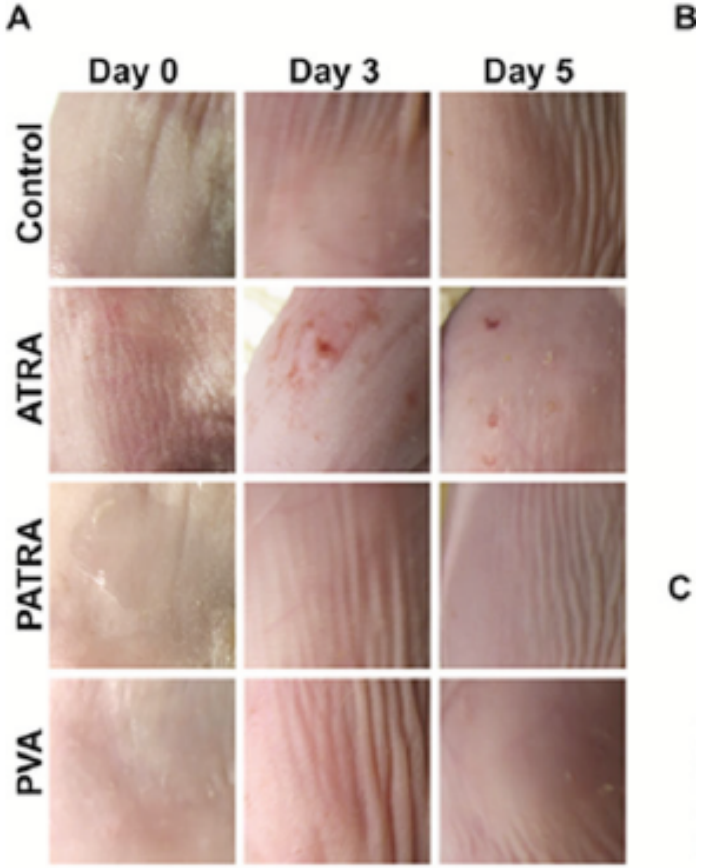


Figure 7. Reaction to ATRA application to the dermis
(a) Digital imaging of mouse dermis 0, 3, and 5 days post-application. (b) Histological sections of treated mouse dermis. Changes in epidermal and stratum corneum thickness are clearly observed due to bolus administration of ATRA. These changes are not observed in other treatment groups. (c-d) Quantification of histological findings for the treatment groups after five days. Data shown are mean ± S.D., n = 4.

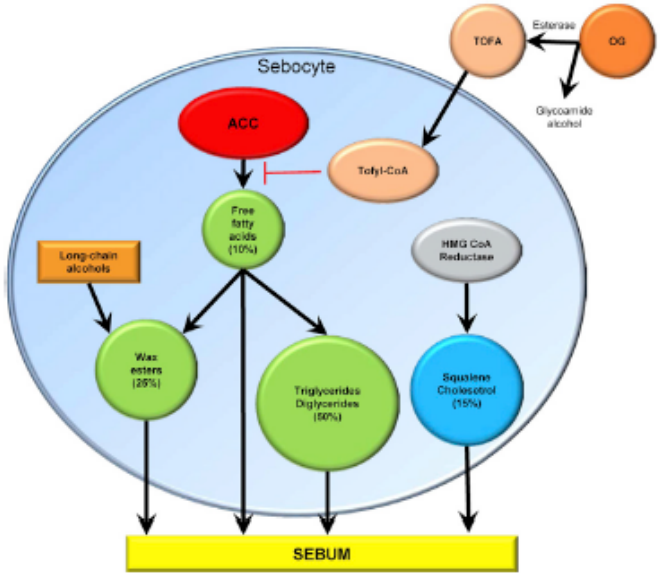
- ✓ Ridotta in vivo flogosi/irritazione in sede di applicazione
- ✓ Aumentata in vivo la concentrazione nell'epidermide di PATRA

J Control Release. 2017 September 28; 262: 1–9.

Inhibition of Sebum Production with the Acetyl Coenzyme A Carboxylase Inhibitor

Olumacostat Glasaretil.

- Inhibitor of acetyl coenzyme A carboxylase (ACC) enzyme that controls fatty acid biosynthesis
- 80% of human sebum components contain fatty acids



- ✓ OG inhibited in vitro human sebocyte lipid production
- ✓ OG Decreases in vivo sebaceous gland size in hamster ears
- ✓ OG mediated sebum suppression may reduce Propionibacterium acnes growth and biofilm formation, comedogenesis, and inflammation.

Hunt DW et al. J Invest Dermatol. 2017 Jul;137(7):1415-1423.

Olumacostat glasaretil, a novel topical sebum inhibitor, in the treatment of acne vulgaris: A phase IIa, multicenter, randomized, vehicle-controlled study

Robert Bissonnette, MD,[a] Yves Poulin, MD,[b] Janice Drew, MPH,[c] Hans Hofland, PhD,[c] and Jerry Tan, MD[d]
Montreal and Québec City, Quebec, and Windsor, Ontario, Canada, and Menlo Park, California

OBJECTIVES: Safety and efficacy of OG 7.5% gel were evaluated in patients with moderate to severe facial acne vulgaris.

METHODS: Patients were randomized (1:1) **to twice-daily application of OG or vehicle for 12 weeks.**

RESULTS:

A total of 108 patients received OG (n = 53) or vehicle (n = 55);

At week 12, OG treatment showed greater **reductions from baseline in inflammatory lesions (-63.9% vs -45.9%; P = .0006) and noninflammatory lesions (-48.1% vs -28.8%; P = .0025),**

CONCLUSION: OG was well tolerated and showed evidence of efficacy, suggesting further development is warranted

J Am Acad Dermatol. 2017;76:33-39.

REVIEW

Anti-acne drugs in phase 1 and 2 clinical trials

Christos C. Zouboulis[a], Clio Dessinioti[b]*, Fragkiski Tsatsou[a]* and Harald P. M. Gollnick[c]

23 innovative topical compoudns

Table 2. Mechanism of actions of innovative investigational drugs for acne treatment (alphabetic order).

Drug	Mechanisms of action
Topical	
ADPS (sodium 3-(ethyl(3-methoxyphenyl)amino) propane-1-sulfonate)	Anti-inflammatory agent
ASC-J9	Synthetic androgen receptor degradation enhancer
ANT-1207	Botulinum neurotoxin type A
B244	Ammonia-oxidizing bacteria-based compound
Calcipotriene	Inhibition of sebaceous lipogenesis
CD5789	Retinoic acid receptor-γ agonist
Cortexolone 17α-propionate	Synthetic, steroidal antiandrogen
GSK1940029	Stearoyl-CoA desaturase-1 inhibitor
Ingenol disoxate	PKC activator
JNJ 10229570-AAA	Melanocortin-5 receptor antagonist
Lupeol	Alcoholic, pentacyclic triterpenoid (modulator of NF-κB and PI(3)K/Akt pathways, induces Fas-mediated apoptosis via inhibition of Ras signaling)
MTC896	α-Melanocyte-stimulating hormone mimetic compound
N-Acetyl-GED-0507–34-LEVO	Peroxisome proliferator-activated receptor-γ modifier
NAI	Semi-synthetic thiopeptide highly selective against *P. acnes*
Neramexane	N-methyl-D-aspartate (NMDA) receptor antagonist
Next Science Acne Gel	Biofilm matrix degradation
Olumacostat glasaretil	Inhibitor of malonyl-CoA synthesis and fatty acid production
Omiganan pentahydrochloride	Cationic peptide derived from indolicin
SB204	Polymer-based nitric oxide-releasing compound
Timolol	β-blocker
TSN 2898	Stearoyl-CoA desaturase-1 inhibitor
Tyrothricin	Mixture of linear and cyclic polypeptides (gramicidine and tyrocidine groups)
XEN801	Stearoyl-CoA desaturase-1 inhibitor

Expert opinion on investigational drugs 2017; 26(7):813-23

Anti-acne drugs in phase 1 and 2 clinical trials

Christos C. Zouboulis[a], Clio Dessinioti[b]*, Fragkiski Tsatsou[a]* and Harald P. M. Gollnick[c]

Table 1. Topical investigational drugs in phase 1 or 2 trials for acne.

Study identifier	Title	Phase	Compound	Sponsor	Completion date
Innovative compounds					
NCT02774590	Timolol for the treatment of acne and rosacea	1	Timolol	Johns Hopkins University	Ongoing
2014–001491-62	Clinical efficacy and safety of NAI-acne gel 3% applied twice-a-day to patients with facial acne vulgaris	2	Semi-synthetic thiopeptide highly selective against *P. acnes*	Naicons	Ongoing
NCT02796066	Safety and efficacy of TSN2898 in the treatment of acne vulgaris	2	TSN2898	Thesan	2017
NCT02720627	An evaluation of the adrenal suppression potential and PK of CB-03–01 cream in pediatric patients with acne vulgaris	2	Cortexolone 17α-propionate	Cassiopea	2017
NCT02656043	A safety, tolerability, efficacy and exposure study of XEN801 topical gel	2	XPF-005 (active compound XEN801)	Xenon	2017
NCT02832063	Clinical trial in subjects with mild to moderate acne vulgaris	2/3	B244	AOBiome	2017
2016–000540-33	A double-blind, randomised, placebo-controlled clinical study to evaluate the efficacy and safety of N-Acetyl-GED-0507–34-LEVO gel, 1 and 2%, applied once daily for 12 weeks in patients with mild to moderate facial acne vulgaris	2	N-Acetyl-GED-0507–34-LEVO	PPM	2017
NCT02571998	A study to evaluate the safety and efficacy of omiganan (CLS001) Topical gel versus vehicle in female subjects with moderate to severe acne vulgaris	2	Omiganan pentahydrochloride	Cutanea	2016
NCT02935036	Efficacy study in patients with acne vulgaris	2	Sodium 3-(ethyl(3-methoxyphenyl) amino)propane-1-sulfonate product	Taro	2016
NCT02431052	A dose-ranging study of DRM01 in subjects with acne vulgaris	2b	Olumacostat glasaretil	Dermira	2016
NCT02575950	Explorative trial evaluating the efficacy and tolerability of LEO43204 in moderate to severe acne	2	Ingenol disoxate	LEO	2016
NCT02395549	A study to determine the efficacy of topically applied MTC896 gel in subjects with acne vulgaris	2	MTC896	Mimetica	2016
2013–001716-30	Exploratory, controlled, randomized, observer-blind intra individual clinical trial to evaluate the efficacy and the tolerability of topically applied 0.1% tyrothricin (Tyrosur® Gel) in patients with mild to severe facial papulopustular acne	2	Tyrothricin	Charité-Clinical Research Center for Hair and Skin Science	2016
NCT02404285	A study to evaluate the clinical effect of daily Next Science™ Acne Gel (NAG) on mild to moderate facial acne	1–2	Next Science Acne Gel	Next Science	2015
NCT02242760	P2 multi-center study of SB204 gel in the treatment of acne vulgaris	2b	SB204	Novan	2015
NCT01938482	Study to evaluate the safety, tolerability and pharmacokinetic of single and 14 day repeat topical application of GSK1940029	1	GSK1940029	GSK	2015
NCT02205892	Clinical study for topical Lupeol in acne	NR	Lupeol	Seoul National University Hospital	2014
NCT01694433	Clinical trial to determine the efficacy of vitamin D for acne therapy	2/3	Calcipotriene	University of California Los Angeles	2014
NCT01616654	Dose range study of CD5789 in acne vulgaris	2	CD5789	Galderma	2013
2011–004998-83	A double-blind, randomized, dose selection vehicle-controlled multicenter clinical study for evaluation of the safety, tolerability, efficacy, and pharmacokinetics of topical Neramexane in subjects with moderate to severe acne	2	Neramexane	Merz	2013
NCT01326780	A study of a new drug treatment for acne	2	JNJ 10229570-AAA	Valeant	2012
NCT01289574	Topical ASC-J9 cream for acne	2	ASC-J9	AndroScience	2012
NCT01293552	Clinical trial to evaluate ANT-1207 in subjects with acne	2	ANT-1207	Anterios	2012

Grazie per l'attenzione

Bellaria Igea M. (RN) 15.08.2017

Management of Severe Acne Vulgaris With Topical Therapy.

- **Adapalene 0.3%-benzoyl peroxide (BP) 2.5%** was found **to be effective in patients with severe acne**
- **Clindamycin-BP 1.2%/3.75% gel** and **clindamycin-BP 1.2%/2.5% gel** were both found to be **effective** in **severe acne** with an apparent **BP-dose response.**

"*Realistic topical treatment options now exist for the management of severe acne where patient and physician preference can impact positive outcomes*"

Stein Gold L, Baldwin HE, Lin T.
J Drugs Dermatol. 2017;16(11):1134-1138.