AARS HOT TOPICS MEMBER NEWSLETTER

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American Acne and Rosacea Society
201 Claremont Avenue • Montclair, NJ 07042
(888) 744-DERM (3376) • info@aarsmember.org
www.acneandrosacea.org

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AARS Special Announcements

Register Now: AARS 14th Annual Member Reception, Friday, March 1, 2019 6PM – 8PM, Washington, DC

Join your AARS colleagues and President Julie Harper and President-Elect Mark Jackson for a wonderful evening! We will be at Hotel Monaco, 700 F Street Northwest in Washington DC in the Paris Ballroom. All members and Corporate Benefactors are welcome! Click here to register now!

Industry News

Almirall launches Seysara™ (sarecycline). News provided by: Almirall. Jan 17, 2019, 08:25 ET. PRNewswire. https://www.prnewswire.com/news-releases/novel-oral-antibiotic-treatment-seysara-sarecycline-now-available-300779895.html

EXTON, Pa., Jan. 17, 2019 /PRNewswire/ -- Almirall LLC announces the launch of Seysara™ (sarecycline), a novel tetracycline-derived oral antibiotic developed specifically for the treatment of acne. Seysara™ was approved in October 2018 by the U.S. Food and Drug Administration (FDA) for the treatment of moderate to severe non-nodular inflammatory acne vulgaris in patients 9 years of age and older and is now commercially available. "Seysara™ was the first new chemical entity for the treatment of acne to be approved by the FDA in a decade, and the acquisition of the product in September 2018 represented a significant investment by our company in the future of medical dermatology," said Peter Guenter, CEO of Almirall. "This launch further demonstrates our commitment to our healthcare partners and patients in the U.S." Seysara™ is one of five former Allergan products acquired by Almirall, comprising a balanced portfolio of mature and growth brands including Aczone® (dapsone), Tazorac® (tazarotene), Azelex® (azelaic acid) and Cordran® Tape (flurandrenolide). In the two identical Phase 3 clinical trials (SC1401 and SC1402), a significant number of patients receiving once-daily Seysara™ experienced improvement of their acne severity at 12 weeks versus placebo based on the Investigator's Global Assessment (IGA) (21.9% vs 10.1% SC1401; 22.6% vs 15.3% SC1402). Seysara™ also led to a reduction in the number of inflammatory acne lesions at 12 weeks (51.8% vs 35.1% SC1401; 49.9% vs 35.4% SC1402), with significant results seen as early as week 3 (29.6% vs 22.4% SC1401; 28% vs 18.6% S1402). "Unlike most other pivotal acne studies, the Seysara™ trials analysed the impact of the study drug on chest and back acne where it was also shown to be effective," stated Angela Moore, MD a coordinating investigator and Clinical Assistant Professor in Dermatology at the University of Texas Southwestern (UTSW), "In addition, this will be one of very few acne treatments that are FDA approved for patients 9 years of age." In clinical trials, treatment with Seysara™ was found to be generally safe and well-tolerated, with low rates of treatment-emergent adverse events (TEAEs) reported in the Seysara™ safety study which followed subjects up to 52 weeks. Patients receiving Seysara™ reported no cases of vertigo or tinnitus and fewer cases of dizziness than seen in the placebo group. Less than one percent of patients experienced photosensitivity or sunburn, and rates of GI issues were relatively low. The most common adverse reaction (incidence ≥ 1%) was nausea. "Acne is affecting an increasing number of patients, and we are always looking for ways to improve our treatment management. Seysara™ showed a statistically significant reduction in inflammatory acne lesion counts with an early onset, and a favorable tolerability profile. I believe that Seysara™ can play a major role in our future treatment decisions," said Linda Stein Gold, MD, coordinating investigator and Director of Dermatology Clinical Research at Henry Ford Health System in Detroit, Michigan. Acne vulgaris is a common skin condition involving blockage and/or inflammation of hair follicles and their glands, which can present as non-inflammatory lesions, inflammatory lesions, or a mixture of both, affecting the face, back and chest. According to the Global Burden of Disease study, acne vulgaris affects 85 percent of young

adults aged 12–25 years around the world. In the United States, 80 percent of people will experience acne vulgaris at some time during their lives, one in five of whom have severe acne. "Seysara™ is an exciting new product in the acne space, where unmet needs still exist for patients ranging from pre-teens through adulthood," said Ron Menezes, President and General Manager of Almirall U.S. He went on to state, "We have a passionate, committed team, and we are looking forward to partnering with the dermatology community to deliver innovative therapies like Seysara™ to those who may benefit from them, building on our shared goal of improving skin health outcomes for patients." To access the Seysara™ patient copay card visit Almirall Copay. For more information on the Almirall product portfolio please visit Almirall US.

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New Medical Research

Clinical efficacy of 0.5% topical mangosteen extract in nanoparticle loaded gel in treatment of mild-to-moderate acne vulgaris: A 12-week, split-face, double-blinded, randomized, controlled trial. Lueangarun S Sriviriyakul K, Tempark T, et al. J Cosmet Dermatol. 2019 Jan 27. doi: 10.1111/jocd.12856. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/30688020

Background: Acne vulgaris is the most common inflammatory sebaceous gland disorder in young adults. The resistant strains of Propionibacterium acnes (P. acnes) are of increasing concern in the treatment of acne. Objectives: To evaluate the efficacy of 0.5% topical mangosteen extract in nanoparticle loaded gel (containing alpha-mangostin) compared with 1% clindamycin gel for treatment of mild-to-moderate acne vulgaris. Methods: Patients aged 18-40 years were enrolled in this double-blinded, split-face, randomized, control study. The 2.5% benzoyl peroxide cream was applied to both sides of the faces once daily for 5 minutes and washed off. Each patient was randomly treated with the mangosteen fruit rind extract on one side and 1% clindamycin on another side of the face twice daily for 12 weeks. Treatment efficacies and side effects were evaluated on every follow-up. Results: Twenty-eight patients, 24 female (85.7%), mean ± SD age of 25.14 ± 5.8, with Global Acne Grading system (GAGs) score of 15.43 ± 5.96 were included. Mangosteen fruit rind extract significantly showed significant 66.86% and 67.05% reduction of comedone and inflammatory lesions ($P < 0.001$) after 12-week treatment. The improvement on both treated sides significantly showed since 2 weeks after treatment, without statistical difference between two groups. Nonetheless, the mangosteen fruit rind extract revealed significantly better improvement of clinical severity, with no severe side effects. Conclusions: The mangosteen fruit rind extract formation could be a phytopharmaceutical medication for effective treatment of mild and moderate acne vulgaris treatment comparable to 1% clindamycin gel, with no severe side effects.

The anti-inflammatory potency of biologics targeting TNF-α, IL-17A, IL-12/23 and CD20 in hidradenitis suppurativa: An ex vivo study. Vossen ARJV, Ardon CB, van der Zee HH, et al. Br J Dermatol. 2019 Jan 18. doi: 10.1111/bjd.17641. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/30657173

Background: Biologics targeting inflammatory mediators are able to clinically improve hidradenitis suppurativa (HS). However, their clinical efficacy shows great inter-patient variability in daily practice. Objective: To investigate the anti-inflammatory potency of a selection of currently available biologics for the treatment of HS in an ex vivo skin culture system using lesional HS biopsies. Methods: Lesional skin samples of ten HS patients and skin samples of five healthy controls were cultured ex vivo and exposed to prednisolone or biologics targeting TNF-α, IL-17A, IL-12/23p40,

or CD20, respectively adalimumab, infliximab, secukinumab, ustekinumab and rituximab. Real-Time quantitative PCR and cytokine bead arrays were used to measure the inhibitory effect of the biologics on cytokines and antimicrobial peptides (AMPs). Results: The relative mRNA expression of all tested cytokines and AMPs was significantly downregulated by all anti-inflammatory agents (p<0·0001). The protein production of the pro-inflammatory cytokines TNF-α, IFN-ɣ, IL-1ß, IL-6, and IL-17A was significantly inhibited by adalimumab, infliximab, ustekinumab, prednisolone (all p<0·0001) and rituximab (p=0·0071), but not by secukinumab (p=0·0663). On both mRNA and protein level, adalimumab, infliximab and prednisolone reduced the levels of a broader mix of individual cytokines than secukinumab, ustekinumab and rituximab. Moreover, a significant inhibitory effect on the mRNA expression levels of inflammatory markers in healthy control skin was observed only for prednisolone (p=0·0015) and the TNF-α inhibitors (p<0·0001). Conclusions: This ex vivo study suggests that TNF-α inhibitors and prednisolone are the most powerful inhibitors of pro-inflammatory cytokines and AMPs in HS lesional skin, which is in accordance with our clinical experience in patients with HS.

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The microbiome in preadolescent acne: Assessment and prospective analysis of the influence of benzoyl peroxide. Ahluwalia J, Borok J, Ahluwalia RS, et al. Pediatr Dermatol. 2019 Jan 18. doi: 10.1111/pde.13741. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/30656737

Background/objectives: The pathogenesis of preadolescent acne has not been well studied, and it is uncertain if Cutibacterium acnes is a predominant organism in the microbiome in this age group. The aim of this study was to analyze the microbiome of preadolescent females and to assess whether benzoyl peroxide impacts the microbiome. Methods: The study enrolled girls, aged 7-12 years, with evidence of at least six acne lesions who had not been previously treated. Participants' skin surface of forehead, cheeks, nose, chin, left retroauricular crease, and extruded contents of a comedonal lesion were sampled at baseline. Participants used benzoyl peroxide 4% wash for 6-8 weeks and returned for skin surface sampling and extraction collection. Microbiome analysis was performed using 16S ribosomal RNA gene amplicon sequencing on all swab and lesional extraction samples. Results: Fifty-one participants were enrolled with a median IGA score of 2 (mild). Changes in microbiome diversity were associated with increasing age and number of acne lesions (P = 0.001). C. acnes had higher abundances on forehead and nose, as opposed to cheeks and chin (P = 0.009). Bacterial diversity (alpha diversity) of the skin microbiome was comparable between preadolescent at baseline and after treatment with benzoyl peroxide. Conclusion: This is the first large assessment characterizing female acne microbiome in early and late preadolescence. Results show that preadolescent acne can vary in its microbial profile, reflecting surrounding changes associated with the onset of puberty. Although benzoyl peroxide use was associated with decreased acne counts, its effect on microbial diversity was not demonstrated in our study.

Sarecycline: First global approval. Deeks ED. Drugs. 2019 Jan 18. doi: 10.1007/s40265-019-1053-4. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/30659422

Sarecycline (Seysara™) is an oral, once-daily, tetracycline-class drug for which a tablet formulation is approved in the USA for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris in patients aged ≥ 9 years. The drug was developed by Paratek and Allergen and later acquired by Almirall S.A. (a Barcelona-based pharmaceutical company focused on medical dermatology). Sarceycline tablets were approved in early October 2018 and are planned to be available for patients in January 2019. Sarecycline capsules have also been studied in the

USA, but no recent reports of development have been identified for this formulation. There are currently no clinical trials underway assessing sarecycline in rosacea. This article summarizes the milestones in the development of sarecycline leading to this first approval for the treatment of inflammatory lesions of non-nodular moderate to severe acne vulgaris.

Novel tretinoin 0.05% lotion for the once-daily treatment of moderate-to-severe acne vulgaris in a preadolescent population. Eichenfield LF, Sugarman JL, Guenin E, et al. Pediatr Dermatol. 2019 Jan 18. doi: 10.1111/pde.13744. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/30656753

Background: Acne vulgaris (acne) is a common skin condition in children and adolescents. Efficacy of tretinoin is well documented in studies that included pediatric patients (12-18 years of age). With acne routinely presenting in younger patients, data are needed in this important group. Lotion formulations are commonly used across dermatology and are well liked by patients. Objective: To evaluate the safety and efficacy of a novel once-daily tretinoin 0.05% lotion in preadolescent subjects (≤ 13 years) with moderate-to-severe acne. Methods: Post hoc analysis of two multicenter, randomized, double-blind, vehicle-controlled phase 3 studies in moderate-to-severe acne. Preadolescent subjects (N = 154) randomized (1:1) to receive tretinoin 0.05% lotion or vehicle, once daily for 12 weeks. Efficacy assessments included changes in baseline inflammatory/noninflammatory lesions and treatment success (at least 2-grade reduction in Evaluator's Global Severity Score [EGSS] and clear/almost clear). Safety, adverse events (AEs), and cutaneous tolerability evaluated throughout. Results: At Week 12, mean percent reduction in inflammatory and noninflammatory lesion counts were 49.5% and 44.0% compared with 31.4% and 18.8% with vehicle (both P = 0.001). Treatment success was achieved by 23.7% of subjects by Week 12, compared with 7.2% (P = 0.009). The majority of AEs were mild and transient: most frequently were application site pain (5.6%) and application site dryness (2.8%). Local cutaneous safety and tolerability assessments were generally mild-to-moderate and improved by Week 12. Conclusions: Tretinoin 0.05% lotion was significantly more effective than vehicle in achieving treatment success and reducing inflammatory and noninflammatory lesions in preadolescent acne. It was well tolerated, with all treatment-related AEs deemed mild or moderate.

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Nicastrin haploinsufficiency alters expression of type I interferon-stimulated genes: The relationship to familial hidradenitis suppurativa. Cao L, Morales-Heil DJ, Roberson EDO. Clin Exp Dermatol. 2019 Jan 17. doi: 10.1111/ced.13906. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/30656721

Background: Hidradenitis suppurativa (HS), also called acne inversa, is a chronic skin disease. The symptoms can be severe and include intensely painful nodules and abscesses in apocrine-gland rich inverse skin, such as the buttocks, under the arms and in the groin. Autosomal dominant forms of HS exist but are rare. Some of these kindred have heterozygous loss-of-function rare variants in the γ-secretase complex component nicastrin (NCSTN). Aim: To investigate the effect of NCSTN haploinsufficiency on human keratinocytes and assess potential mechanisms for lesion development. Methods: NCSTN was knocked down using a small hairpin RNA construct in both a keratinocyte cell line (HEK001) and an embryonic kidney cell line (HEK293), and differential gene expression was assessed using RNA microarray. Using the HEK293 line, a heterozygous deletion of NCSTN was created with CRISPR/Cas9 genome editing, and nuclear factor kappa B activity was assessed using a luciferase reporter. Results: Compared with controls, the keratinocyte NCSTN knockdown cell line showed a significantly increased expression of genes related to the type I interferon response pathway. Both HEK001 and HEK293 knockdowns demonstrated evidence of altered

growth. There was a small but significant increase in nuclear factor kappa B signalling in response to tumour necrosis factor treatment in HEK293 cells genome-edited for reduced NCSTN. Conclusions: Our data suggest a role for increased keratinocyte inflammatory responsiveness in familial HS. Confirming this phenotype and characterizing additional effects in different cell types will require study beyond cell lines, such as in primary cells and tissues.

SAPHO syndrome with pathological fractures of vertebral bodies: A case report. Li Y, Liu G, Zhao Y, et al. BMC Musculoskelet Disord. 2019 Jan 17;20(1):27. doi: 10.1186/s12891-019-2410-x. https://www.ncbi.nlm.nih.gov/pubmed/30654792

Background: It's difficult to diagnose and treat synovitis-acne-pustulosis-hyperostosis-osteomyelitis (SAPHO) syndrome due to its rare and unknown pathogenesis. There is no effective treatment for SAPHO syndrome and the consequences of empirical treatment are unpredictable. This study reports a case of a young female diagnosed as SAPHO syndrome with pathological fractures of vertebral bodies. Case presentation: A 29-year-old female complained of the right sternoclavicular joint and back pain accompanied limited activities and cutaneous lesions. Laboratory assays revealed abnormal inflammatory factors. Multiple imaging studies illustrated bone lesions and pathological fractures of vertebral bodies. A diagnosis of SAPHO syndrome was made. The patient was treated with Compound Troxerutin and Poreine Cerebroside Injection, non-steroidal anti-inflammatory drugs (NSAIDs), bisphosphonates, corticosteroids and the thoracolumbar brace. The patient was followed up for 6 months and showed improved results. Conclusions: The case supports that multiple image inspections and laboratory tests contribute to diagnose SAPHO syndrome, and combination therapies of Compound Troxerutin and Poreine Cerebroside Injection, NSAIDs, bisphosphonates, corticosteroids and the thoracolumbar brace in the treatment of SAPHO syndrome with pathological fractures of vertebral bodies are crucial to regain health.

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A phase 1 randomized, placebo-controlled trial with a topical inhibitor of stearoyl-coenzyme a desaturase 1 under occluded and nonoccluded conditions. Brigandi RA, Zhu J, Murnane AA, et al. Clin Pharmacol Drug Dev. 2019 Jan 16. doi: 10.1002/cpdd.644. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/30650256

Stearoyl-coenzyme A desaturase 1 (SCD-1) in sebaceous glands is a key enzyme in the synthesis of monounsaturated fatty acids essential for acne development. GSK1940029 gel, a novel SCD-1 inhibitor, is being developed as a potential treatment for acne. To assess the irritation potential, pharmacokinetics (PK), and safety of topical GSK1940029 to the skin of healthy adults, two interdependent studies were conducted in parallel. Study 1 (n = 54) investigated the irritation potential of GSK1940029 (0.3% and 1%, occluded application) to allow for its application to larger surface areas in study 2 (n = 39), which investigated the safety, tolerability, and PK of GSK1940029 after single and repeat doses as occluded and nonoccluded applications. GSK1940029 was not a primary or cumulative irritant after 2 and 21 days of dosing in study 1. In study 2, single and repeat applications of GSK1940029 (0.1% to 1%) doses were well tolerated with little or no influence on AUC and Cmax under occluded or unoccluded conditions. Systemic exposure increased proportionally with surface area and was higher in occluded conditions. Design of these interdependent studies allowed for the assessment of the irritation potential for topical GSK1940029 in parallel with the investigation of PK and safety profiles.

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Long-wave medical infrared thermography: A clinical biomarker of inflammation in hidradenitis suppurativa/acne inversa. Zouboulis CC, Nogueira da Costa A, Jemec GBE, Trebing D. Dermatology. 2019 Jan 16:1-6. doi: 10.1159/000495982. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/30650424

Background: A more reliable classification of skin inflammation and severity of active disease results from ultrasound sonography and the new hidradenitis suppurativa/acne inversa (HS) classification system IHS4. However, an objective assessment of skin inflammation in a continuous mode is still the ultimate goal. Long-wave medical infrared thermography (MIT) may offer a blood flow and temperature differential assessment in inflammatory conditions. Objective: To evaluate the application of MIT in HS. Methods: Standardized photography of the areas involved or previous candidates for HS involvement was performed and MIT pictures were taken simultaneously and superimposed on the photographs of 18 patients (11 female, 7 male, median age 38.75 years [95% confidence interval 28.5-51 years], Hurley score I 5.6%, Hurley score II 38.9%, and Hurley score III 55.5%). A modification of the Otsu method facilitated the automatic lesion segmentation from the background, depicting the inflammation area. Moreover, MIT was administered in real-time mode during radical HS surgery. Results: A 1°C temperature difference from a corresponding symmetric body region was indicative of inflammation. MIT figures detected a gradual increase of skin temperature from 33.0°C in healthy skin on average to 35.0-36.6°C at the center of inflamma tory lesions in the axilla and to 35.4-36.9°C at the center of inflammation in the groin area. Real-time MIT assessment enabled the definition of the margins and depth of the surgical intervention during the procedure. Conclusion: MIT is a promising tool for the detection of inflammation severity in HS lesions and can be used as a clinical biomarker in evaluation studies of medical and surgical HS treatment.

Short lipopeptides specifically inhibit the growth of propionibacterium acnes with antibacterial and anti-inflammatory dual action. Yang G, Wang J, Lu S, et al. Br J Pharmacol. 2019 Jan 14. doi: 10.1111/bph.14571. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/30644534

Background and purpose: Propionibacterium acnes (P. acnes) is a Gram-positive bacterium associated with the skin disorder acne. In this study, considering the importance of fatty acids in the life habitat of P. acnes, we tested our lipopeptide library with the attempt to create potent P. acnes-specific antimicrobial agents. Experimental approach: The antimicrobial activity was determined by the minimal inhibitory concentration (MIC). Lipids from P. acnes were used to explore the mode of action. RAW264.7 cells respectively stimulated with LPS and P. acnes were used to measure the anti-inflammatory activity. Mice ears injected with P. acnes were used to assess the antimicrobial and anti-inflammatory effects of tested peptides in vivo. Key results: The most potent candidate, C16-KWKW, was observed to be more active against P. acnes with a MIC of 2 μg/mL than against other non-targeted bacterial strains, such as S. mutans, S. aureus and E. coli. The mode of action of C16-KWKW was observed to be through interference with integrity of bacterial membrane, thereby impairing membrane permeability and causing leakage of inner contents of bacterial cells. In addition, C16-KWKW inhibited the expression of pro-inflammatory cytokines, such as IL-1β, TNF-α, and iNOS stimulated by both LPS and P. acnes, thus showing potential anti-inflammatory activity, which was further assessed by in vivo animal studies. Conclusions & implications: C16-KWKW is a lipopeptide displaying both anti-P. acnes and anti-inflammatory dual function in vitro and in vivo and exhibits potential application in treatment of acne vulgaris induced by P. acnes.

Hop extract acts as an antioxidant with antimicrobial effects against propionibacterium acnes and staphylococcus aureus. Weber N, Biehler K, Schwabe K, et al. Molecules. 2019 Jan 9;24(2). pii: E223. doi: 10.3390/molecules24020223. https://www.ncbi.nlm.nih.gov/pubmed/30634461

Acne is associated with hyperkeratosis, elevated levels of skin sebum and growth of Propionibacterium acnes (P. acnes) and Staphylococcus aureus (S. aureus). Furthermore, P. acnes promotes inflammation by inducing IL-6 production and oxidative stress. The aim of this study was to assess the antioxidant, anti-inflammatory and antibacterial potential of a hop-CO_2-extract with 50% humulone and lupulone. The susceptibility of P. acnes and S. aureus to the hop extract was tested by using the broth microdilution technique. The minimal inhibitory concentrations (MIC) for P. acnes and S. aureus were 3.1 and 9.4 µg/mL, respectively. In addition, the hop extract showed an antioxidative effect with a half maximal inhibitory concentration (IC50) of 29.43 µg/mL as well as additional anti-inflammatory effects by reducing the IL-6 expression (IC50: 0.8 µg/mL). In addition, a gel formulation with 0.3% hop extract (w/w) had antibacterial activity against P. acnes and S. aureus (inhibition zone value: 5.5 mm and 3 mm, respectively) which was significantly superior to the placebo gel. The positive control (a gel with the antibiotic clindamycin) showed an inhibition zone of 9 mm. Due to its antioxidant, anti-inflammatory and antibacterial effects hop extract might be a treatment option for acne-prone skin.

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Interruption of oral clindamycin plus rifampicin therapy in patients with hidradenitis suppurativa: An observational study to assess prevalence and causes. Schneller-Pavelescu L, Caso EV, Martorell A, et al. J Am Acad Dermatol. 2019 Jan 7. pii: S0190-9622(19)30005-2. doi: 10.1016/j.jaad.2018.12.043. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/30630028

Combination therapy with oral clindamycin 300mg twice daily plus rifampicin 300mg twice daily or 600mg once daily for ten weeks is one of the keystone treatments for moderate to severe hidradenitis suppurativa (HS). Since 2006, six small studies involving a collective total of 178 patients, have investigated the efficacy of this antibiotic combo. Most had a retrospective design, and only one reported safety outcomes. Prevalence of treatment interruption ranged from 9.1% to 28.6% (mean 16.3%), and the appearance of adverse events from 9.1% to 38.3% (mean 21.9%). The most common adverse events were gastrointestinal (GI) disturbances (diarrhea, vomiting, abdominal pain, dyspepsia) followed by cutaneous rash, vaginitis, nonspecific pain and arthralgias. A better understanding of the reasons for poor adherence and adverse events associated with treatment may help dermatologists to better advise patients, potentially allowing prevention of some side effects. We designed a descriptive, observational, retrospective multicentric study to determine the prevalence of interruption of clindamycin plus rifampicin before ten weeks in HS patients. A retrospective chart review was performed including patients aged ³ 18 years, Hurley stage II or III, who were receiving clindamycin plus rifampicin for the first time. Patients simultaneously receiving other systemic therapies for HS, were excluded. We enrolled 509 patients from 14 Spanish hospitals (table 1); 135 (26.5%) interrupted antibiotic treatment. We did not observe differences between the proportion of men (26.6%) and women (26.5%) who interrupted their treatment. After dividing the study population into quartiles by age (n=133: ≤30 years, n=127: 31-38 years, 98 n=125: 39-49 years, n=124: ≥50 years), we observed that older age was associated with treatment interruption. Compared to the youngest age group, the odds ratio (OR) for treatment interruption in patients aged 50 or older was 1.9 (95% confidence interval [CI] 1.1–3.3, P =.03). Ever-smokers had 1.5 times the odds of interrupting their treatment as compared to never-smokers (95% CI 1.1–2.1, P =.02). In multivariable analysis, these associations remained significant (smoking: OR 1.7, 95% CI 1.0-2.7, P =.033; and age ≥50: OR 1.8, 95% CI 1.0–2.7, P =.048). We did not observe any association between treatment interruption and any other feature (table 2). There were 182

adverse effects in 145 (28.5%) patients, the most frequent being GI disturbances (n=108; 21.2%), followed by non-specific aches or pains (n=19; 3.7%) and mucocutaneous Candida albicans infections (n=12; 2.4%). None of the patients with GI disturbances presented Clostridium difficile colitis, and all responded well to conservative management. Association between adverse events and any of the demographic or disease characteristics considered were not observed. In conclusion, to our knowledge, this is the largest reported series of patients treated with combination clindamycin plus rifampicin for HS. We observed higher treatment interruption and prevalence of adverse effects than previously reported. Patients aged 50 years or older and smokers were more prone to interrupt their treatment. GI disturbances were the most frequent adverse effects in our population. Physicians may consider prescribing probiotics to these patients at higher risk for GI side effects.

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Novel tretinoin 0.05% lotion for once-daily treatment of moderate-to-severe acne vulgaris in a Hispanic population. Cook-Bolden FE, Weinkle SH, Guenin E, Bhatt V. J Drugs Dermatol. 2019 Jan 1;18(1):32-38. https://www.ncbi.nlm.nih.gov/pubmed/30681791

Background: Acne vulgaris (acne) is the most common dermatologic disease seen in a racially, geographically, politically, culturally, and socioeconomically diverse Hispanic population. Despite their growing demographics in the US, there are few studies evaluating acne treatment in this population. Potential for skin irritation and dryness, as well as pigmentary changes are key concerns. The first lotion formulation of tretinoin was developed using novel polymerized emulsion technology to provide an important alternative option to treat these acne patients who may be sensitive to the irritant effects of other tretinoin formulations. Objective: To determine the efficacy and safety of tretinoin 0.05% lotion in treating moderate-to-severe acne in a Hispanic population. Methods: Post hoc analysis of two multicenter, randomized, double-blind, vehicle-controlled Phase 3 studies in moderate or severe acne. Hispanic subjects (aged 11 to 50 years, N=766) were randomized (1:1) to receive tretinoin 0.05% lotion or vehicle, once-daily for 12 weeks. Efficacy assessments included changes in baseline inflammatory and noninflammatory lesions and treatment success (at least 2-grade reduction in Evaluator's Global Severity Score [EGSS] and clear/almost clear). Safety, adverse events (AEs), and cutaneous tolerability were evaluated throughout using a 4-point scale where 0=none and 3=severe. Results: At week 12, mean percent reduction in inflammatory and noninflammatory lesion counts were 60.1% and 53.0%, respectively, compared with 51.1% and 38.7% with vehicle (P≤0.001) in the Hispanic population. Treatment success was achieved by 19.6% of subjects by week 12, compared with 12.7% on vehicle (P=0.015). The majority of AEs were mild and transient. There were four serious AEs (SAEs) reported (two each group) unrelated to treatment. Incidence of treatment-related AEs with tretinoin 0.05% lotion was lower than in the overall study population; the most frequently were application site pain (2.0%), dryness (1.4%), and erythema (1.2%). Local cutaneous safety and tolerability assessments were generally mild-to-moderate at baseline and improved by week 12. There were slight transient increases in scaling and burning over the first four weeks. Hyperpigmentation severity reduced progressively with treatment. Conclusions: Tretinoin 0.05% lotion was significantly more effective than its vehicle in achieving treatment success and reducing inflammatory and noninflammatory acne lesions in a Hispanic population. The new lotion formulation was well-tolerated, and all treatment-related AEs were both mild and transient in nature.

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Clinical Reviews

Topical retinoids in acne vulgaris: A systematic review. Kolli SS, Pecone D, Pona A, et al. Am J Clin Dermatol. 2019 Jan 23. doi: 10.1007/s40257-019-00423-z. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/30674002

Background: Topical retinoids are a first-line treatment for acne vulgaris. Objective: This systematic review aims to evaluate the efficacy, safety, and tolerability of topical retinoids approved in the United States for the treatment of acne vulgaris. Methods: A PubMed and Embase search was conducted using the search terms 'adapalene,' 'tretinoin,' 'tazarotene,' and 'acne vulgaris.' Selection of articles fit the following inclusion criteria: clinical trials evaluating both efficacy and safety/tolerability of topical retinoids approved in the United States for the treatment of acne vulgaris and published between January 1, 2008 and September 1, 2018. Exclusion criteria included clinical trials involving 20 subjects or fewer, subjects under 12 years of age, and topical retinoid combination therapies with moisturizers or aloe vera. Of 424 search results found, a total of 54 clinical trials were chosen based on selection criteria. Results: Topical retinoids are superior to vehicle in improving Investigator Global Assessment and Investigator's Static Global Assessment (24.1-28.8% and 13.3-17.3%, respectively; $p < 0.001$). A topical retinoid combined with benzoyl peroxide led to IGA improvement compared with vehicle (26.1-34.9% vs 7-11.8%; $p < 0.001$) at Week 12. Topical retinoid plus an oral antibiotic was superior to vehicle in reducing lesion counts (64-78.9% vs 41-56.8%, $p < 0.001$). There was no significant difference in efficacy between tretinoin and tazarotene. Tretinoin 0.05% resulted in 62% of patients experiencing AEs compared with adapalene 0.1% (19%) and adapalene 0.3% (40%). More patients receiving adapalene were tolerant of the AEs compared with tazarotene (55.4% vs 24.4%; $p < 0.0012$). Conclusions: Topical retinoids are safe and efficacious for the treatment of acne vulgaris. They should be used in combination with benzoyl peroxide to optimize results in patients. The differences in efficacy of topical retinoids appears minor; therefore, the type of topical retinoid is not as important as choosing a particular strength of topical retinoid and combining it with an antimicrobial agent. Adapalene has a superior tolerability profile amongst topical retinoids.

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Use of isotretinoin and risk of depression in patients with acne: A systematic review and meta-analysis. Li C, Chen J, Wang W, et al. BMJ Open. 2019 Jan 21;9(1):e021549. doi: 10.1136/bmjopen-2018-021549. https://www.ncbi.nlm.nih.gov/pubmed/30670500

Objective: This study aimed to investigate the association between the use of isotretinoin and the risk of depression in patients with acne. Design: This was a meta-analysis in which the standardised mean difference (SMD) and the relative risk (RR) were used for data synthesis employing the random-effects model. Setting: Studies were identified via electronic searches of PubMed, Embase and the Cochrane Library from inception up to 28 December 2017. Participants: Patients with acne. Interventions: Studies comparing isotretinoin with other interventions in patients with acne were included. Results: Twenty studies were selected. The analysis of 17 studies showed a significant association of the use of isotretinoin with improved symptoms compared with the baseline before treatment (SMD = -0.33, 95% CI -0.51 to -0.15, $p<0.05$; $I^2=76.6\%$, $p<0.05$)). Four studies were related to the analysis of the risk of depression. The pooled data indicated no association of the use of isotretinoin with the risk of depressive disorders (RR=1.15, 95% CI 0.60 to 2.21, p=0.14). The association of the use of isotretinoin with the risk of depressive disorders was statistically significant on pooling retrospective studies (RR=1.39, 95% CI 1.05 to 1.84, p=0.02), but this association was not evident on pooling prospective studies (RR=0.85, 95% CI 0.60 to 2.21, p=0.86). Conclusions:

This study suggested an association of the use of isotretinoin in patients with acne with significantly improved depression symptoms. Future randomised controlled trials are needed to verify the present findings.

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Trends in oral antibiotic prescription in dermatology, 2008 to 2016. Barbieri JS, Bhate K, Hartnett KP, et al. JAMA Dermatol. 2019 Jan 16. doi: 10.1001/jamadermatol.2018.4944. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/30649187

Importance: Dermatologists prescribe more oral antibiotic courses per clinician than any other specialty, and this use puts patients at risk of antibiotic-resistant infections and antibiotic-associated adverse events. Objective: To characterize the temporal trends in the diagnoses most commonly associated with oral antibiotic prescription by dermatologists, as well as the duration of this use. Design, setting, and participants: Repeated cross-sectional analysis of antibiotic prescribing by dermatologists from January 1, 2008, to December 31, 2016. The setting was Optum Clinformatics Data Mart (Eden Prairie, Minnesota) deidentified commercial claims data. Participants were dermatology clinicians identified by their National Uniform Claim Committee taxonomy codes, and courses of oral antibiotics prescribed by these clinicians were identified by their National Drug Codes. Exposures: Claims for oral antibiotic prescriptions were consolidated into courses of therapy and associated with the primary diagnosis from the most recent visit. Courses were stratified into those of extended duration (>28 days) and those of short duration (≤28 days). Main outcomes and measures: Frequency of antibiotic prescribing and associated diagnoses. Poisson regression models were used to assess for changes in the frequency of antibiotic prescribing over time. Results: Between 2008 and 2016 among 985 866 courses of oral antibiotics prescribed by 11 986 unique dermatologists, overall antibiotic prescribing among dermatologists decreased 36.6% (1.23 courses per 100 visits) from 3.36 (95% CI, 3.34-3.38) to 2.13 (95% CI, 2.12-2.14) courses per 100 visits with a dermatologist (prevalence rate ratio for annual change, 0.931; 95% CI, 0.930-0.932), with much of this decrease occurring among extended courses for acne and rosacea. Oral antibiotic use associated with surgical visits increased 69.6% (2.73 courses per 100 visits) from 3.92 (95% CI, 3.83-4.01) to 6.65 (95% CI, 6.57-6.74) courses per 100 visits associated with a surgical visit (prevalence rate ratio, 1.061; 95% CI, 1.059-1.063). Conclusions and relevance: Continuing to develop alternatives to oral antibiotics for noninfectious conditions, such as acne, can improve antibiotic stewardship and decrease complications from antibiotic use. In addition, the rising use of postoperative antibiotics after surgical visits is concerning and may put patients at unnecessary risk of adverse events. Future studies are needed to identify the value of this practice and the risk of adverse events.

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Acne, the skin microbiome, and antibiotic treatment. Xu H, Li H. Am J Clin Dermatol. 2019 Jan 10. doi: 10.1007/s40257-018-00417-3. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/30632097

Acne vulgaris is a chronic skin disorder involving hair follicles and sebaceous glands. Multiple factors contribute to the disease, including skin microbes. The skin microbiome in the follicle is composed of a diverse group of microorganisms. Among them, Propionibacterium acnes and Malassezia spp. have been linked to acne development through their influence on sebum secretion, comedone formation, and inflammatory response. Antibiotics targeting P. acnes have been the mainstay in acne treatment for the past four decades. Among them, macrolides, clindamycin, and tetracyclines are the most widely prescribed. As antibiotic resistance becomes an increasing concern in clinical practice, understanding the skin microbiome associated with acne and the effects of antibiotic use on the skin

commensals is highly relevant and critical to clinicians. In this review, we summarize recent studies of the composition and dynamics of the skin microbiome in acne and the effects of antibiotic treatment on skin microbes.

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Models for acne: A comprehensive study. Kanwar IL, Haider T, Kumari A, et al. Drug Discov Ther. 2018;12(6):329-340. doi: 10.5582/ddt.2018.01079. https://www.ncbi.nlm.nih.gov/pubmed/30674767

Acne vulgaris (AV) is the familiar chronic skin ailment affecting most of the individuals. This multifarious, disease involves the bacterium gram-positive, anaerobic Propionibacterium acnes (P. acnes) which resides on skin microflora and participated in acne inflammation and acne lesions. The object of this review is to discuss presently available in vitro, ex vivo, and in vivo models to evaluate the cosmetic formulations that are developed for dealing and prevention of acne formation. These various available models offer new chances for further research on biologically active materials, drugs & pharmaceutical as well as cosmetics for acne treatment.

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Patient Counseling/Communication

What Italians think about acne: Results of a survey on 2.327 patients and 2.327 mothers. Tavecchio S, Barbareschi M, Veraldi S. G Ital Dermatol Venereol. 2019 Jan 8. doi: 10.23736/S0392-0488.18.05920-5. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/30621386

Background: The psychological impact of acne is comparable to that experienced by patients with severe diseases; however, most of the people does not consider acne as a true disease. We evaluated beliefs, sources of information and knowledge about acne in Italian adolescents and their mothers. Methods: This survey was carried out in 2.327 acne patients and their mothers (=4.654 subjects) by means of a self-administered questionnaire. The questionnaire was based on ten questions: seven questions for the patients and three questions for their mothers. Results: All the 2.327 patients and their mothers completed the survey. Approximately 75% of patients declared that acne has a negative influence on their self-esteem and relationships; furthermore, 87% of patients stated that acne limits their social life. Finally, 65% of patients declared that they are under treatment, but only in 20% of cases the treatment was prescribed by a dermatologist. The mothers considered pollution, wrong diet and hyperseborrhoea as the most important aetiological factors. They considered the treatment suggested by a cosmetologist and contraceptive pill as the best one; only 8% of mothers reported that they regularly took their children to the dermatologist. Conclusions: In order to improve the treatment and the quality of life in acne patients, there is a need to improve awareness about this disease and its causes and to highlight the role and importance of dermatologists.