AARS HOT TOPICS MEMBER NEWSLETTER

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Industry News

Cassiopea announces FDA submission of new drug application for Clascoterone cream 1%, the first new mechanism of action for acne in nearly 40 years. Cassiopia. August 20, 2019. http://www.cassiopea.com/news-and-media/press-releases/yr-2019/190820.aspx

Cassiopea SpA (SIX: SKIN), a specialty pharmaceutical company developing and commercializing prescription drugs with novel mechanisms of action (MOA) to address long-standing and essential dermatological conditions, announced today that it has submitted a New Drug Application (NDA) to the U.S. Food and Drug Administration (FDA) seeking marketing approval for clascoterone cream 1% for the treatment of acne. Clascoterone cream 1% is under investigation as a first-in-class topical androgen receptor inhibitor for the treatment of acne. Clascoterone is a topically delivered small molecule that penetrates the skin to reach the androgen receptors of the sebaceous gland. It aims to be the first effective and safe topical androgen inhibitor therapy that does not have systemic side effects. Clascoterone cream 1% targets androgen receptors at the site of application, inhibiting the local (skin) effects of dihydrotestosterone (DHT) a key driver of acne lesion development. Laboratory studies show that clascoterone inhibits lipid production from oil producing cells (sebocytes) and reduces proinflammatory cytokines, mediators influenced by androgens. Thus, pathways that foster acne lesion development are disrupted by clascoterone. Unlike oral hormonal therapies for acne, it may be used in both male and female patients. "This is noteworthy because it's been so long since there has been a new, first-in-class molecule for the treatment of acne, particularly given that it is a topical treatment that targets the androgen receptor and works on sebocytes to mediate lipid production and inflammation," said Dr. Lawrence Eichenfield, Chief of Pediatric and Adolescent Dermatology at Rady Children's Hospital–San Diego. "Giving physicians another treatment option for their patients who struggle with acne is tremendously important." Last year, Cassiopea announced topline results from two pivotal phase III clinical trials for clascoterone cream 1% demonstrating highly statistically significant improvements for all primary clinical endpoints. No treatment-related serious adverse events among patients have been recorded during the trials; local skin reactions, if present, were similar to vehicle and predominantly classified as mild. Safety results, announced earlier this year, were confirmed in an open-label safety study for a treatment period of up to one year, with an expanded drug application surface area that included both the face and trunk. The extended duration and coverage of the topically applied drug did not increase the incidence of significant side effects. "If approved, clascoterone cream 1% will be the first new mechanism of action in the treatment of acne in nearly 40 years, offering dermatologists and patients a new and effective therapeutic alternative," said Diana Harbort, CEO of Cassiopea. "We're focused on the urgency to treat skin conditions that can leave not only physical scars, but also emotional scars. That's why innovation is so critical. We are committed to finding a way to treat acne that addresses the root causes of the condition."

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Almirall issues call for grant submissions for development of new immunodermatology therapies. Almirall. July 24, 2019. https://www.almirall.us/pdf/AlmirallShare_PR_20190724.pdf

Almirall is a global pharmaceutical company that leads the fight against skin diseases through medical solutions for health professionals and their patients. The company announced a call for proposals for their open innovation platform, AlmirallShare. AlmirallShare aims to identify collaborations which may lead to innovative targets, pathways, or therapies in medical dermatology. "Immune-inflammatory diseases have a profound impact on patients' lives, which is why our call for proposals is centered around these conditions. Psoriasis, atopic dermatitis and pemphigus vulgaris share common mechanisms, pathways and potential therapies with other diseases, which could inform the

development of new treatments that will help improve patient lives—a core goal for us at Almirall," stated Ayman Grada M.D., Director of US Medical Affairs and R&D at Almirall LLC. The new proposal is seeking novel ideas to identify, validate, or test new targets for the treatment of chronic immune-inflammatory diseases of the skin. The latest call – Immune-Inflammatory Diseases Under Your Skin - will be open from July 25 through October 31, 2019, and is intended for institutions, such as universities, research centers, and start-up biotechnology or pharmaceutical companies worldwide with an interest in pharmaceutical R&D to submit original research ideas. Selected proposals will be considered for grants and/or scientific support for research. To learn more about how to submit your proposal, view the full press release here.

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New Medical Research

Efficacy of 30% azelaic acid peel in the nonpharmacological treatment of facial acne. Szymańska A, Budzisz E, Erkiert-Polguj A. J Dermatolog Treat. 2019 Aug 28:1-6. doi: 10.1080/09546634.2019.1657222. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31455112

Background: Acne is a common, chronic, inflammatory disease of the pilosebaceous unit. It has a significant impact on patient quality of life, especially when lesions occur on cosmetically sensitive areas. Chemical peeling is a well-known option in the treatment of acne vulgaris, but little is known about azelaic acid (AZA) peels. Objectives: To determine the efficacy of 30% AZA peel, in decreasing the amount of secreted sebum, and reducing acne lesions. Methods: The study involved 35 women, with acne lesions on face skin. All the subjects underwent a series of six treatments, performed every 2 weeks. Results: A series of treatments contributed to a statistically significant reduction in the amount of secreted sebum. Similarly, highly significant values determining the overall number of acne lesions and the severity of the disease according to the IGA scale were also changed. The procedure was well tolerated by all participants. Conclusions: Peels with 30% AZA reduced acne lesions and normalized the activity of the sebaceous glands. The reduction of sebum allows us to believe that obtained good results in patients will be stable and long-lasting.

The clinical efficacy of ReCell® autologous cell regeneration techniques combined with dermabrasion treatment in acne scars. Chen Q, Yu N, Liu Z, et al. Aesthetic Plast Surg. 2019 Aug 26. doi: 10.1007/s00266-019-01481-8. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31451856

Objective: To evaluate the efficacy of ReCell® autologous cell regeneration techniques combined with dermabrasion treatment on the therapy of acne scars. Methods: We analyzed retrospectively 78 patients with acne scars who presented to the Department of Plastic Surgery at Peking Union Medical College Hospital from May 2015 to May 2017; 30 patients were treated with dermabrasion (Group 1), and the other 48 patients were treated with ReCell® autologous regeneration techniques combined with dermabrasion (Group 2). Efficacy was evaluated through self-evaluation of the patient, third-party evaluation and photographs taken before and after treatment. The wound healing time and postoperative complication rate were also recorded. Results: The study revealed a significant difference in healing time ($P < 0.001$) between patients treated with dermabrasion (Group 1) and patients treated with ReCell® autologous regeneration techniques combined with dermabrasion (Group 2). The average healing time of Group 1 was 12.30 ± 1.725 days, while the average healing time of Group 2 was 5.27 ± 1.086 days. In Group 2, patient self-evaluation and third-party evaluation were more satisfactory than those of Group 1 ($P < 0.001$). Moreover, there were

no postoperative complications in Group 2 such as pigmentation and scar hyperplasia. Conclusion: The ReCell® technique is simple, minimally invasive, biocompatible and effective in the treatment of acne scars. It can shorten healing time and reduce the occurrence of postoperative complications, thereby providing a safe and effective treatment approach for patients with facial acne scars.

Clinical efficacy of herbal extracts in treatment of mild to moderate acne vulgaris: A 8-week, double-blinded, randomized, controlled trial. Yang JH, Moon J, Yoon JY, et al. J Dermatolog Treat. 2019 Aug 19:1-16. doi: 10.1080/09546634.2019.1657792. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31424962

Background: Herbal extracts with fewer adverse effects can be an alternative to these drugs because they can target various molecular pathways of acne pathogenesis. Objectives: To evaluate the clinical efficacy of herbal extracts (mangosteen, Lithospermum officinale, Tribulus terrestris L., Houttuynia cordata Thunb) for the treatment of mild to moderate acne vulgaris Methods: 60 patients were randomized in a 1:1 ratio to receive blinded treatment with herbal extracts or vehicle for 8 weeks. Inflammatory and non-inflammatory acne lesion counts, Investigator's Global Assessment, patient's satisfaction and safety profiles were assessed. We also performed skin biopsy at baseline and week 8 to confirm immunological changes with immunohistochemistry staining. Results: By the end of the study period, both inflammatory and non-inflammatory acne lesion counts were significantly decreased in herbal extracts group ($P < 0.05$). In immunohistochemistry staining, expression of IL-1α, IL-8 and keratin 16 were significantly decreased in herbal extracts group compared to vehicle group from baseline to week 8. There were no serious adverse events in both groups. Conclusion: These herbal extracts can be a new therapeutic option for patients with mild to moderate acne vulgaris who are reluctant to use drugs.

Fractional Erbium-YAG laser and platelet-rich plasma as single or combined treatment for atrophic acne scars: A randomized clinical trial. El-Taieb MA, Ibrahim HM, Hegazy EM, et al. Dermatol Ther (Heidelb). 2019 Aug 16. doi: 10.1007/s13555-019-00318-1. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31420849

Introduction: Acne scarring is a common undesirable complication of acne vulgaris. Fractional erbium-yttrium aluminum garnet (YAG) 2940 nm laser and platelet-rich plasma have been used in treating acne scars with variable outcomes. The objective of this study is to assess the efficacy of fractional erbium-YAG 2940 nm laser and platelet-rich plasma as a single line of treatment in comparison with combined treatment in atrophic postacne scars. Methods: Seventy-five patients were included in this trial and randomized into three equal groups (25 each). Group A was subjected to six sessions of erbium-YAG laser for 6 months, group B was treated with 12 sessions of platelet-rich plasma over the same period, and group C was subjected to six sessions of erbium-YAG laser plus 12 sessions of platelet-rich plasma over the same period. Each subject was evaluated by acne scar grading, photography, and subjective evaluation. Results: Both treatment modalities showed improvement of acne scars, but the improvement with combined treatment was better than that with erbium-YAG laser or platelet-rich plasma alone regarding scar grade improvement ($P = 0.007$ and 0.001), clinical improvement ($P = 0.001$ and 0.001), and patient satisfaction ($P = 0.005$ and 0.001), respectively. Conclusions: The combination of platelet-rich plasma plus erbium-YAG laser is superior to either treatment alone for acne scars, with trivial side effects for all treatment modalities. Trial registration: ClinicalTrials.gov identifier; NCT03933033.

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Evaluation of PSP technique including dot peeling, subcision and intradermal injection of PRP in the treatment of atrophic post-acne scars. Ibrahim ZAE, Elgarhy L. Dermatol Ther. 2019 Aug 15:e13067. doi: 10.1111/dth.13067. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31414709

Background: Atrophic post-acne scars are common complications of acne. Many modalities are proposed but each does not yield satisfactory clinical outcomes. Objective: To evaluate the therapeutic effect of PSP technique including dot peeling, subcision and intradermal injection of autologous platelet rich plasma (PSP) for treatment of atrophic post-acne scars. Patients and methods: 20 patients with different types of atrophic acne scars on the face were included. All patients received PSP technique in the form of dot peeling then after two weeks subcision and intradermal PRP injection were done simultaneously. PSP technique was performed for each patient every month for 3 months. Results: After three months of the last session, 30% out of 20 patients had excellent improvement, 20% of patients had good improvement, 20% of patients had moderate improvement and 30% of patients had mild improvement. There was statistically significant difference after treatment (p=<0.001). Side effects were mild and tolerable and included erythema, ecchymosis and hyperpigmentation. All types of scars showed significant improvement with no significant difference between them. Conclusion: PSP technique was found to be safe and cost-effective treatment option for atrophic acne scars.

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A cross-sectional study of rosacea and risk factors in women with frontal fibrosing alopecia. Porriño-Bustamante ML, Fernández-Pugnaire MA, Arias-Santiago S. Acta Derm Venereol. 2019 Aug 13. doi: 10.2340/00015555-3286. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31408181

Frontal fibrosing alopecia has been related to some autoimmune diseases, but the association with rosacea is not clear. The objective of this study was to analyze the prevalence of rosacea in a group of patients with frontal fibrosing alopecia. A cross-sectional study, including 99 women with frontal fibrosing alopecia and 40 controls, was performed, in which clinical, dermoscopic and hormonal data were analyzed. Women with frontal fibrosing alopecia presented a higher prevalence of rosacea than did controls (61.6% vs. 30%, p = 0.001), especially those with severe grades of alopecia (77.8% in grade V vs. 33.3% in grade I, p = 0.02). Binary logistic multivariate analysis showed that perifollicular erythema (odds ratio (OR) 8.5; 95% confidence interval (95% CI) 1.73-42.30), higher body mass index (OR 1.16; 95% CI 1.01-1.34) and lower progesterone levels (OR 0.15; 95% CI 0.028-0.89) were associated with a higher risk of rosacea in patients with frontal fibrosing alopecia. In conclusion, patients with frontal fibrosing alopecia presented a higher prevalence of rosacea than did controls. Perifollicular erythema, higher body mass index and lower progesterone levels were associated with a higher risk of rosacea in the group with frontal fibrosing alopecia.

Intralesional corticosteroid injection for the treatment of hidradenitis suppurativa: A multicentre retrospective clinical study. García-Martínez FJ, Vilarrasa Rull E, Salgado-Boquete L, et al. J Dermatolog Treat. 2019 Aug 12:1-19. doi: 10.1080/09546634.2019.1655524. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31402725

Background and objectives: Hidradenitis suppurativa (HS) is a chronic inflammatory disease of the follicular unit characterized by recurrent, painful, skin lesions including inflammatory nodules, abscesses, tunnels and mutilating scarring. Intralesional corticosteroids injection (ICI) for HS has received little attention in scientific literature. We evaluate the clinical response of ICI in acute and chronic HS lesions and aim to identify new applications of ultrasound assisted procedures in HS management. Patients and methods: An observational, retrospective, multicenter study of HS patients treated with ICI was conducted from January 1 to August 1, 2015 We collected 98 HS patients. 135

individual lesions were infiltrated, including non-inflammatory nodules, inflammatory nodules abscesses and fistulous tracts. Results: Complete response was reached in 95 lesions (70.37%), 34 showed partial response (25.19%) and 6 (4.44%) were non-response. 105 individual lesions underwent sonographic scan before ICI. Conclusion: Clinical experience supported the use of ICI for individual lesions. Our results showed that ICI is a useful treatment to control in acute and recalcitrant HS lesions. Response rates improves significantly if lesions are previously evaluated with HFUS.

Multimodal clinical imaging assessment of the outcome in mild-to-moderate acne: A prospective study. Kyrgidis A, Becker M, Zampeli V, et al. Dermatology. 2019 Aug 7:1-7. doi: 10.1159/000501272. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31390623

Background: The quality of outcome assessment in acne studies has been either subjective/insufficient or time consuming through the ordinary lesion counting. Objective: To evaluate the application of multimodal clinical imaging (MCI), a combination of imaging technology and computation, in the assessment of acne lesions in a clinical study setting. Methods: A prospective, monocentric, single-group open study designed to evaluate the efficacy and tolerance of a cosmetic product (IP/SG) in subjects with mild-to-moderate facial acne by classical clinical counting (CCC) - change in the total/inflammatory/noninflammatory acne lesion number compared with baseline (D0) - Investigator Global Assessment (IGA) and self-reported outcomes. Concomitantly, MCI was administered. The study was performed for 12 weeks (D84) with a 4-week follow-up (D112). Results: Mean age of patients (n = 49) was 18.2 ± 3.7 years (range 13-25). The mean acne duration was 3.8 ± 2.8 years. The total number of lesions did not differ significantly between D0/D84 by both CCC and MCI. However, the Cardiff Acne Disability Index (CADI) and uncomfortable feeling improved at D28/D0, the perception of oily skin improved at D14/D0, and the perception of sticky skin improved from D28/D0 to D56/D0. Deterioration was detected between D84/D0 and D112/D0, namely after product discontinuation. Interestingly, a change in trend was recorded for acne lesions at D14/D0 by MCI but not by CCC. Conclusion: MCI, applied for the first time in a small clinical study setting, is at least as reliable as CCC and may allow for a sensitive longitudinal evaluation of single acne lesions and their response to products, especially in conditions where clinical evaluation reaches its limits.

Clinical Reviews

The frequency of off-label prescribing in the treatment of dermatologic disease. Feldman SR. Practice Update. August 28, 2019. https://www.practiceupdate.com/c/87958/2/4/?elsca1=emc_enews_daily-digest&elsca2=email&elsca3=practiceupdate_derma&elsca4=dermatology&elsca5=newsletter&rid=MjE2NTI0OTk2NDk2S0&lid=10332481

Expert Comment: Chu et al used a nationally representative survey of outpatient medical practice in the United States and found that off-label prescribing is common for uncommon skin conditions. These data support that off-label prescribing is simply part of the standard of care for managing skin diseases. FDA-approved drug labels don't necessarily reflect how drugs are best used. I'm reminded of a television commercial for a topical clotrimazole cream that said that the cream was approved for use anywhere on the foot, whereas topical terbinafine was only approved for use between the toes. This commercial gave what I thought was a misleading impression that the clotrimazole cream was a better choice for treating foot fungus. Despite the difference in their FDA-approved labels, I believe topical terbinafine is a more potent anti-fungal on any part of the foot. Chu et al make an important point that FDA approval may be used as a criterion for insurance coverage. Hopefully, payers will recognize appropriate uses rather

than solely FDA approvals as the appropriate criterion for basing drug coverage decisions, just as we recognize appropriate uses rather than solely FDA approvals as the appropriate criterion for basing our drug prescribing decisions. Comment on: The frequency of off-label prescribing in the treatment of dermatologic disease: 2006-2015. Chu B, Fleischer A Jr, Barbieri JS. J Am Acad Dermatol. 2019 Jul 18. pii: S0190-9622(19)32398-9. doi: 10.1016/j.jaad.2019.07.038. [Epub ahead of print] Off-label prescribing is the use of a drug for an indication not approved by the Food and Drug Administration (FDA), often driven by low financial incentives to seek regulatory approval for every possible indication, particularly for uncommon diseases. Off-label prescribing is often used in the treatment of skin diseases, with the frequency of off-label prescribing for several common skin diseases ranging from 17-73% during the 1990s. However, little is known about the frequency of off-label prescribing for uncommon conditions and whether the frequency of off-label prescribing has changed with the introduction of new FDA-approved treatments.

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A systematic review of factors influencing treatment adherence in chronic inflammatory skin disease - strategies for optimizing treatment outcome. Eicher L, Knop M, Aszodi N, et al. J Eur Acad Dermatol Venereol. 2019 Aug 27. doi: 10.1111/jdv.15913. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31454113

Adherence describes how a patient follows a medical regime recommended by a healthcare provider. Poor treatment adherence represents a complex and challenging problem of international health care systems, as it has a substantial impact on clinical outcomes and patient safety and constitutes an important financial burden. Since it is one of the most common causes of treatment failure, it is extremely important for physicians to reliably distinguish between non-adherence and non-response. This systematic review aims to summarize the current literature on treatment adherence in dermatology, focusing on chronic inflammatory skin diseases such as psoriasis, atopic dermatitis and acne. A systematic literature search was performed using the PubMed Database, including articles from 2008 to 2018. Low treatment adherence is a multidimensional phenomenon defined by the interplay of numerous factors and should under no circumstances be considered as the patient's fault alone. Factors influencing treatment adherence in dermatology include patient characteristics and beliefs, treatment efficacy and duration, administration routes, disease chronicity and the disease itself. Moreover, the quality of the physician-patient relationship including physician-time available for the patient plays an important role. Understanding patients' adherence patterns and the main drivers of non-adherence creates opportunities to improve adherence in the future. Strategies to increase treatment adherence range from reminder programs, to simplifying prescriptions or educational interventions. Absolute adherence to treatment may not be realistically achievable, but efforts need to be made to raise awareness in order to maximize adherence as far as possible.

Promising plant-derived secondary metabolites for treatment of acne vulgaris: A mechanistic review. Soleymani S, Farzaei MH, Zargaran A, et al. Arch Dermatol Res. 2019 Aug 26. doi: 10.1007/s00403-019-01968-z. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31448393

Acne vulgaris is the most common skin condition associated with inflammation of pilosebaceous unit. Since conventional therapies have not demonstrated desirable effectiveness and possess remarkable side effects, there is a growing interest in the use of herbal medicines for the management of acne vulgaris. In this study, plant-derived molecules investigated in acne vulgaris have been reviewed and their possible underlying mechanisms of action were discussed. For this purpose, different electronic databases including PubMed, Scopus, Cochrane library and Google Scholar were searched to obtain any in vitro, in vivo, or human studies evaluating the phytochemicals in the

management of acne vulgaris. Data were collected from 1980 to 2018 (up to October). Most of the phytochemicals investigated in acne were from the category of polyphenols including resveratrol, myricitrin, schisandrin, terchebulin, alpha-mangotin, curcumin, ellagic acid and epigallocatechin 3-gallate. Moreover, alkaloids and terpenoids such as berberine, ursolic acid, lupeol were evaluated in acne vulgaris with less abundance. Various molecular mechanisms were involved in effects of phytochemicals including antioxidant (through down-regulation of H2O2, MDA, ROS and upregulation of SOD), anti-inflammatory (through reduction of proinflammatory cytokines, i.e., IL-1ß, IL-6, IL-8, TGF-β, TNF-α, NF-κB), immunomodulatory, antibacterial (against Propionibacterium acnes and Propionibacterium granulosum), antiandrogenic, reducing sebum production, and lipogenesis inhibitory activities. Therefore, phytochemicals seem to be a precious source for identifying new medicines for treatment of acne vulgaris; however, since most of studies are preclinical, further clinical studies are needed to achieve more conclusive and reliable results.

PAPA and FMF in two siblings: Possible amplification of clinical presentation? A case report. Maggio MC, Ceccherini I, Grossi A, et al. Ital J Pediatr. 2019 Aug 23;45(1):111. doi: 10.1186/s13052-019-0705-z. https://www.ncbi.nlm.nih.gov/pubmed/31443670

Background: Familial Mediterranean Fever is a monogenic autoinflammatory disease, typically characterized by recurrent attacks of fever, serositis, aphthous of oral mucosa, erythema. "Pyogenic arthritis, pyoderma gangrenosum and acne syndrome" is a rare autoinflammatory disease with variable expression and typically involving joints and skin. Both the diseases are linked by the overproduction of IL-1. Case presentation: We report on the case of two siblings affected by recurrent attacks of fever, oral aphthous stomatitis, abdominal pain, arthritis, undefined dermatitis at the hands, associated with increased AST, ALT, C-reactive protein, erythrocyte sedimentation rate, serum amyloid A, leucocytosis with neutrophilia. Infectious diseases were excluded. The genetic study for Familial Mediterranean Fever, tumor necrosis factor receptor-associated periodic syndrome, Mevalonate kinase deficiency, showed the homozygous mutation p.M680I of exon 10 in MEFV. Their parents were heterozygous for the same mutation p.M680I, however, the mother showed severe symptoms of FMF (recurrent attacks of fever, arthralgia and arthritis, abdominal pain, thoracic pain), the father showed recurrent pustulosis prevalent on the hands and limbs, with arthralgia and abdominal pain. Both the patients started colchicine, with an improvement in clinical manifestations and a reduction of serum amyloid A. For the atypical dermatologic signs present in the two siblings and in the father, the study of other autoinflammatory syndromes was performed with next generation sequencing and showed the heterozygous rare missense mutation of unknown significance: p.(Val408Ile) of PSTPIP1 gene in the two siblings and in the mother, the father was negative. Canakinumab treatment was started in the younger patient, with the resolution of the clinical symptoms and the normalization of serum amyloid A. Conclusions: Further studies are needed to better describe the correlation between genotype and phenotype in patients with PAPA syndrome and with PAPA syndrome associated with FMF, considering that the presence of mutations in both genes may amplify clinical presentation and evolution of both diseases.

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Hyperhidrosis affects quality of life in hidradenitis suppurativa: A prospective analysis. Hua VJ, Kuo KY, Cho HG, Sarin KY. J Am Acad Dermatol. 2019 Aug 23. pii: S0190-9622(19)32651-9. doi: 10.1016/j.jaad.2019.08.046. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31449904

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disorder characterized by painful nodules and scarring of the apocrine gland-bearing areas. Antibiotics and immunosuppressive agents form the mainstay of treatment, but

treatments are often ineffective, and a subset of patients cannot tolerate systemic medications. Additionally, patients frequently suffer from co-associated conditions, leading to significant morbidity levels. Given the apocrine distribution of HS, we hypothesized that hyperhidrosis could be a comorbidity that contributes to disease activity and morbidity. This hypothesis was supported by five case reports demonstrating excellent response of HS in six patients (of whom three demonstrated clinical remission) who were treated with botulinum toxin A (BoNT-A), a U.S. FDA-approved treatment for hyperhidrosis. Half of these patients presented with hyperhidrosis or increased sweat production. Using cross-sectional data from IBM® MarketScan® Research Databases, representing approximately 50% of the U.S. population with employer-sponsored insurance, we identified 10,469 patients with 3-year continuous enrollment from 2013-2015 with a minimum of two ICD-9-CM codes for HS, as well as an age- and gender-matched control cohort of 104,690 patients. We performed age- and gender-adjusted multivariable logistic regression and observed a 3.61-fold (95% CI 2.83-4.61, p-value<.0001) increased risk of hyperhidrosis in HS, demonstrating a novel association between hyperhidrosis and HS. We therefore sought to confirm the efficacious treatment of HS by BoNT-A, as demonstrated by the five case reports. To investigate this, we conducted a prospective analysis to assess the effectiveness of one-time treatment of BoNT-A (100 units, 2.5 units per 1.5 cm) in five HS patients at the Stanford Department of Dermatology. All patients were female and endorsed excessive sweating, with an average age of 38.6 years and Hurley stages I-III. The Dermatology Life Quality Index (DLQI), visual analogue score (VAS) for pain, and number of active nodules were recorded at baseline and follow-up (≥ 6 weeks) (Table 1). In contrast to prior case reports demonstrating excellent response of HS to BoNT-A, our data remarkably did not exhibit an improvement in any of the metrics for HS disease activity, including the nodule number, which decreased in only one patient, or VAS for pain, which instead increased in three patients. However, 80% (4/5) of patients noted an improvement in their hyperhidrosis, and the only patient who demonstrated no improvement suffered from severe HS (Hurley III). Nevertheless, of the patients with mild to moderate HS (Hurley I-II), 75% (3/4) reported an improvement in DLQI and 100% (4/4) elected to undergo a second round of treatment. 100% (5/5) of patients tolerated the treatment well, without side effects. Our study did not demonstrate a notable improvement in HS following BoNT-A treatment, contrary to prior published case reports investigating BoNT-A efficacy in HS. This may be the result of positive selection reporting bias in case reports. However, our study demonstrates that hyperhidrosis is significantly increased in individuals with HS, and that BoNT-A has a meaningful impact on the quality of life of patients with lesions of concurrent HS and hyperhidrosis activity, likely in part due to its efficacious treatment of hyperhidrosis. Our results support the need for a larger controlled study in patients with HS to determine which patients are most likely to benefit from BoNT-A therapy. The implications on quality of life and its psychosocial consequences are critical considerations, as the psychiatric burden of HS supersedes that of even psoriasis. Moreover, in contrast to the systemic treatments of HS, BoNT-A is well-tolerated, with no side effects reported in any of our patients. We therefore propose that clinicians would benefit from not only screening HS patients for hyperhidrosis, but also considering BoNT-A as a safe and noninvasive therapeutic option to reduce morbidity in patients with concurrent HS and hyperhidrosis.

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Hidradenitis suppurativa: Current understanding, diagnostic and surgical challenges, and developments in ultrasound application. Elkin K, Daveluy S, Avanaki KM. Skin Res Technol. 2019 Aug 18. doi: 10.1111/srt.12759. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31423654

Background: Hidradenitis suppurativa (HS) is debilitating, costly, chronic disease for which no cure exists and which often precipitates greater health concerns. While we are making advances in understanding, HS remains an area of attention which is evidenced by a 400% increase in research studies involving HS in the past 5 years. This includes research regarding the advantages and limitations of ultrasound (US) imaging and its ability to enhance the surgical

treatment and medical management of HS. Herein, we describe the diagnostic and surgical obstacles that HS presents, the foremost of which is detection of subclinical information, and perform an in-depth synthesis of current knowledge regarding the use of US imaging to mitigate these obstacles. Materials and methods: A comprehensive literature review of US imaging in HS patients and a supplementary review of the current state of HS were conducted. Conclusion: Ultrasound imaging is a powerful tool in the diagnosis, monitoring, clinical management, and preoperative assessment of HS. However, it also has relevant limitations that necessitate additional consideration. Significance: Hidradenitis suppurativa is a disabling skin disease that presents a diagnostic and surgical challenge. The invaluable advantages and relevant limitations that US imaging offers are beginning to be understood, leading to standardization and increased implementation. US imaging has the potential to drastically improve patient care and merits further attention.

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The effects of isotretinoin therapy on serum homocysteine, folate and vitamin B12 levels in patients with acne: A meta-analysis and meta-regression. Tsai TY, Hsieh TS, Yang TH, et al. J Eur Acad Dermatol Venereol. 2019 Aug 16. doi: 10.1111/jdv.15886. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31419342

Isotretinoin, one of the most effective treatments for acne, has various adverse effects with the most common being mucocutaneous dryness. Other rarer adverse effects include hepatic dysfunction and hypertriglyceridemia. Studies have revealed changes in the serum level of homocysteine, folate and vitamin B12 in patients with acne receiving isotretinoin treatment; however, the results were incosistent. Hyperhomocysteinemia and deficiency of folate and vitamin B12 following isotretinoin therapy may potentially increase cardiovascular and neuropsychiatric risks. We sought to examine this potential side effects by conducting a meta-analysis and meta-regression.

SAPHO syndrome of the temporomandibular joint associated with trismus: A case report and review of the literature. Kotaki S, Gamoh S, Yoshida H, et al. Oral Radiol. 2019 Aug 14. doi: 10.1007/s11282-019-00405-1. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31414280

Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome is a disorder characterized by pustular skin lesions and osteoarticular lesions. Mandibular involvement occurs in approximately 10% of the cases and is often seen as recurrent mandibular osteitis with bone sclerosis, mainly involving the body of the mandible in the head and neck region. Middle cranial base with temporomandibular joint (TMJ) involvement in SAPHO syndrome can be diagnostically challenging because of its rarity. Herein, we present a case of a 37-year-old man who suffered from trismus and dull pain in the left TMJ region. The initial panoramic image revealed spotty osteolysis around the left condylar head. Computed tomography (CT) images showed an osteosclerotic change in the middle cranial base including the TMJ. Magnetic resonance images showed a cortical bone change in the left TMJ without anterior disk displacement, with spotty low signal intensity in the left condyle bone marrow on T2- weighted images. Our initial diagnosis was osteomyelitis of the middle cranial base including the TMJ region. However, antimicrobial therapy, training for TMJ opening, and a surgical procedure were not effective. A detailed medical interview, careful check for skin lesions, and further imaging examinations including bone scintigraphy and chest CT led to the diagnosis of SAPHO syndrome. The possibility of SAPHO syndrome should be considered in patients suspected of osteomyelitis of the middle cranial base including the TMJ with unknown etiology.

Onychocryptosis and asymptomatic external urethritis as complications of oral isotretinoin therapy. Sivaraj K, Friedman J, Morrell D. BMJ Case Rep. 2019 Aug 13;12(8). pii: e231387. doi: 10.1136/bcr-2019-231387. https://www.ncbi.nlm.nih.gov/pubmed/31413063

This case report presents a patient who, while undergoing oral isotretinoin therapy for acne vulgaris, developed onychocryptosis and asymptomatic external urethritis. These uncommon adverse events are not well-documented in medical literature. While his urethritis spontaneously resolved, his onychocryptosis symptoms necessitated surgical intervention. This report illustrates both cosmetic and functional adverse effects of isotretinoin and provides insight into the progression of these reactions over time.

The role of IL-17 in papulopustular rosacea and future directions. Amir Ali A, Vender R, Vender R. J Cutan Med Surg. 2019 Aug 12:1203475419867611. doi: 10.1177/1203475419867611. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31402691

Rosacea is a chronic, progressive, inflammatory condition phenotypically subtyped into diagnostic features, major features, and minor/secondary features. There is currently no cure for rosacea, and it carries a significant negative psychosocial burden for afflicted patients. While there are a number of treatment modalities at the disposal of the clinician, clinical experience has suggested a need for updated treatments. The pathogenesis of rosacea is multifactorial; however, this paper will focus on the pivotal role of interleukin 17 (IL-17) in the development and progression of the disease. Furthermore, this paper will explore the mechanism of action of standard rosacea treatments and their effect on different stages of the IL-17 pathway. The standard treatments for rosacea are usually effective in controlling the symptoms of the disease in its mild-to-moderate form; however, their efficacy is diminished in the setting of severe and treatment-resistant rosacea. We hypothesize that IL-17 inhibitors, currently used successfully in psoriasis and psoriatic arthritis, could perhaps be used to treat severe and treatment-resistant papulopustular rosacea in the future; however, clinical trials and case reports will be needed to dictate expanded indications of IL-17 inhibitors. Furthermore, the high cost of IL-17 inhibitors presently prevents their use in disease states other than psoriasis or psoriatic arthritis.

Targeting the gut-skin axis - probiotics as new tools for skin disorder management? Szántó M, Dózsa A, Antal D, et al. Exp Dermatol. 2019 Aug 6. doi: 10.1111/exd.14016. [Epub ahead of print] https://www.ncbi.nlm.nih.gov/pubmed/31386766

The existence of a gut-skin axis is supported by increasing evidence, but its translational potential is not widely recognized. Studies linked inflammatory skin diseases to an imbalanced gut microbiome, hence, the modulation of the gut microbiota to improve skin condition seems to be a promising approach. Today there is a growing interest in natural products as alternatives to synthetic drugs. In this respect, oral probiotics could be a simple, safe and cheap modality in the therapeutic management of skin inflammation. Unfortunately, very few studies have looked how probiotic supplementation influence inflammatory skin disorders. The results of probiotic use, although beneficial, are difficult to implement into clinical practice due to the heterogeneity of the applied supplemental regimen. In this Viewpoint we aim to encourage the conduction of more research in that direction to explore unambiguously the therapeutic potential of oral probiotics in dermatology. We focus on the most common inflammatory skin diseases (atopic dermatitis, psoriasis, rosacea, acne vulgaris) with gut dysbiosis, but we also discuss some less common and very serious skin pathologies (e.g. erythema nodosum, pyoderma gangrenosum, hidradenitis suppurativa) that are possibly linked to an imbalanced gut microbiome. We dissect the possible mechanisms along the gut-skin axis and highlight novel points where probiotics could interfere in this communication in the diseased state.

Consumer safety considerations of skin and oral microbiome perturbation. McBain AJ, O'Neill CA, Amezquita A, et al. Clin Microbiol Rev. 2019 Jul 31;32(4). pii: e00051-19. doi: 10.1128/CMR.00051-19. Print 2019 Sep 18. https://www.ncbi.nlm.nih.gov/pubmed/31366612

Microbiomes associated with human skin and the oral cavity are uniquely exposed to personal care regimes. Changes in the composition and activities of the microbial communities in these environments can be utilized to promote consumer health benefits, for example, by reducing the numbers, composition, or activities of microbes implicated in conditions such as acne, axillary odor, dandruff, and oral diseases. It is, however, important to ensure that innovative approaches for microbiome manipulation do not unsafely disrupt the microbiome or compromise health, and where major changes in the composition or activities of the microbiome may occur, these require evaluation to ensure that critical biological functions are unaffected. This article is based on a 2-day workshop held at SEAC Unilever, Sharnbrook, United Kingdom, involving 31 specialists in microbial risk assessment, skin and oral microbiome research, microbial ecology, bioinformatics, mathematical modeling, and immunology. The first day focused on understanding the potential implications of skin and oral microbiome perturbation, while approaches to characterize those perturbations were discussed during the second day. This article discusses the factors that the panel recommends be considered for personal care products that target the microbiomes of the skin and the oral cavity.

Synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome with destructive spondylitis: A case report. Nakamae T, Yamada K, Tsuchida Y, et al. Spine Surg Relat Res. 2018 Jul 25;3(3):267-269. doi: 10.22603/ssrr.2018-0035. eCollection 2019. https://www.ncbi.nlm.nih.gov/pubmed/31440687

Introduction: Spinal lesions in synovitis, acne, pustulosis, hyperostosis, and osteitis (SAPHO) syndrome generally have a good prognosis and rarely cause structural destruction or neurological deterioration. We described a surgical case of posterior instrumented surgery without anterior reconstruction and bone graft in a patient with SAPHO syndrome with destructive spondylitis and reviewed the literature on surgical treatment for this entity. Case report: We describe the case of a 73-year-old male who presented with palmoplantar pustulosis. He experienced progressive low back and leg pain for the past 3 months. Destructive spondylitis and lumbar canal stenosis were detected with magnetic resonance imaging (MRI), and aspiration biopsy was used to exclude pyogenic spondylitis and spinal tumors. He underwent posterior decompression and fixation surgery without anterior reconstruction and bone grafting. Low back and leg pain improved after surgery. Postoperative radiography and computed tomography showed boney bridge between vertebral bodies, and MRI showed the decrease of bone marrow edema. Conclusions: Posterior fusion without anterior reconstruction produced a bony bridge between the vertebral bodies. Taking the pathophysiology of SAPHO syndrome into consideration, anterior reconstructed fusion for patients with SAPHO syndrome might not be needed.

Acne treatment alternatives to know. Lisette Hilton. Dermatology Times, July 3, 2019. https://www.dermatologytimes.com/acne/acne-treatment-alternatives-know

In dermatology the first line of defense against acne vulgaris has largely been the use of antibiotics. However, the need to limit antibiotic use means acne treatment protocols are starting to shift. “We’re trying to limit the amount of antibiotics people are taking, as well as the number of people who are taking antibiotics,” says William James, M.D., professor and chair of dermatology at Penn Medicine. “There’s been a major push over the past few years to do that. So, it changes how we treat people, particularly women in many cases.” It’s no secret that antibiotics have been successful in treating and controlling most acne cases. The efficacy has led dermatologists to be among the highest prescribers of antibiotics. However, frequent and long-term antibiotic use can also present problems, such as the

development of antibiotic resistance in patients over time. Additionally, existing research indicates long-term use can also be associated with irritable bowel syndrome. Consequently, the American Academy of Dermatology's standing recommendation is to limit antibiotic use to less than three months. To abide by this suggestion and to comply with the non-antibiotic treatment paradigm shifts, says Dr. James who addressed acne treatment options at the American Academy of Dermatology's (AAD) 2019 spring meeting in Washington, D.C., dermatologists must consider alternative therapies. In particular, he says, providers should examine spironolactone or isotretinoin as options to treat moderate-to-severe acne. Spironolactone for acne - Originally designed as a high blood pressure medication, spironolactone is frequently used off-label to treat moderate-to-severe acne in women. It's inappropriate for men because it blocks the function of male hormones. "This is an excellent medication for acne, and many women respond very well to it," he says. "And, dermatologists should be more comfortable prescribing it." According to existing research, a 200-mg daily dose — lower than levels needed to control high blood pressure — has been shown to reduce acne levels equivalent to those seen with antibiotics. Patients treated with spironolactone also experience low relapse rates, and few report discontinuing use. Overall, spironolactone is well tolerated with few side effects, according to Dr. James. Fatigue, increased urination, irregular periods, breast tenderness, muscle pain and irregular heartbeat are possible. Additionally, dermatologists should ask patients if they have low blood pressure before writing the prescription. Despite evidence of efficacy, however, some dermatologists remain reticent to recommend spironolactone, he says. Based on older research, the medication carries a black box label warning, cautioning providers that the medication is associated with several types of tumors. However, the warning is based on studies that included doses from 10-to 500-times the highest dose given to humans, Dr. James says. And, additional research has shown little-to-no evidence that the medication causes tumors. Sharing this updated information, Dr. James says, will, hopefully, encourage more dermatologists to pivot toward spironolactone rather than antibiotics. "This discussion is alerting dermatologists that spironolactone is available and safe," Dr. James says. "It's been around for many years, so it's not new. But it's a matter of trying to make people aware of these newer studies that indicate its safety and efficacy, so more people feel comfortable using it." Isotretinoin for acne - Previously known on the market as Accutane, isotretinoin has been considered the topline in efficacy for treating acne, according to Dr. James. But, historically, it has not been the initial defense due to many concerns. "In the past, if people weren't responding to antibiotics, they might go to isotretinoin as a final effort to control acne," he says. "Now, as dermatologists are trying to utilize antibiotics less and less, they're turning to isotretinoin for more and more people." This move stems from recent research that shows patients treated with isotretinoin experience roughly the same level of efficacy as those who undergo an antibiotic regimen. Normally, patients receive a 120 mg/kg to 150 mg/kg dose, and they must complete the full course even if they achieve 100% acne clearing. However, lower beginning doses can be recommended to help side-step initial acne flares. Researchers have also found the body best absorbs isotretinoin when patients take it with a high-fat meal. Updated studies also reveal a need to potentially change conventional complete blood panel monitoring practices. Traditionally, dermatologists have performed these tests as frequently as once a week. Instead, new data indicates lipids, liver function and triglycerides can be checked roughly once a month. This change is both convenient and cost-effective for patients. Ultimately, Dr. James says, he wants dermatologists to have new information about how to best treat acne. "I think it would be good to consider spironolac tone when treating women for acne. You'll be able to improve outcomes for a wider array of women while limiting the use of antibiotics. And, I think of isotretinoin similarly," he says.

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