Dermatology Research Review™
Special Issue – Focus on Acne
Making Education Easy 2017

In this review:

Welcome to this special issue of Dermatology Research Review, focusing on acne.

We are delighted to have the expertise of Dr Jo-Ann See providing the commentary for this special issue. It is interesting to note that in this month's review of acne journal articles there were certain trends such as the use of light and lasers, revisiting well established treatments such as oral antibiotics and spironolactone as well as those studies supporting new treatments. Several new topical treatments are now or soon to be available. The supporting studies are included for topical dapsone gel, a new fixed combination formulation of adapalene and benzoyl peroxide and the new biophotonic gel. The selected papers begin with acne pathogenesis.

We are pleased to receive any comments or feedback you may have.

Kind Regards,

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Skin expression of mammalian target of rapamycin and forkhead box transcription factor 01, and serum insulin-like growth factor-1 in patients with acne vulgaris and their relationship with diet

Authors: Agamia NF et al.

Summary: These researchers obtained diet questionnaire data and measured skin mTOR (mammalian target of rapamycin), skin Fox (forkhead box transcription factor)-01 and serum IGF (insulin-like growth factor)-1 levels in 40 patients with acne vulgaris and 20 control participants. Compared with controls, patients with acne vulgaris had significantly higher serum IGF-1 levels, greater cytoplasmic FoxO1 expression (with mostly nuclear expression in controls) and more intense cytoplasmic and nuclear mTOR expression. Excess high-glycaemic dietary consumption was significantly associated with higher serum IGF-1 levels and cytoplasmic FoxO1 and mTOR expression.

Comment: NF Agamia *et al.'s* study of 40 acne patients and 20 controls demonstrated higher serum levels of IGF-1 as well as greater cytoplasmic expression of FoxO1 and both cytoplasmic and nuclear expression of mTOR in the acne patients. Excess consumption of a high-glycaemic-load diet was significantly associated with higher serum levels of IGF-1 and cytoplasmic expression of FoxO1 and mTOR. These results suggest that FoxO1, mTOR, serum IGF-1 and a high-glycaemic-load diet may play a role in acne pathogenesis. The role of diet in acne is controversial and the increasing awareness of genetic predisposition makes this article interesting as it is a clue that in some genetically predisposed patients, diet may contribute to acne. The western diet containing hyperglycaemic carbohydrates (high glycaemic load), dairy products that promote increased IGF and saturated fats has been blamed for acne, and this article nicely outlines the science behind why. It also suggests that we recommend nutritional advice for acne sufferers such as normalising total calorie intake, lower glycaemic load and restrict total dairy protein consumption, especially whey protein.

Reference: Br J Dermatol 2016;174(6):1299–1307
Abstract

Recent progress in the research about *Propionibacterium acnes* strain diversity and acne: pathogen or bystander?

Authors: Kwon HH & Suh DH

Summary: The authors of this review sought to provide an update on the recent understanding of research about *Propionibacterium acnes* strain diversity and acne, and evaluated potential implications for clinical applications. They noted that recent phylogenic research that has shed light on the extent to which *P. acnes* impinges on disease formation raises the possibility of the existence of specific virulent strains with increased capacity to cause opportunistic infections. They also highlight the need for further research to clarify the apparent controversy of *P. acnes* in acne and also to develop therapeutic drugs for specific targets of pathogenic strains.

Comment: We know that *P. acnes* plays a role in acne, but now we wonder which *P. acnes*, as research has uncovered many subtypes? This is discussed in this paper, which provides an update on recent research about *P. acnes* strain diversity and acne, analysing the potential implications for future treatment. It suggests that particular *P. acnes* strains play an aetiological role in acne while others are associated with health. Perhaps future research could target treatment by pinpointing specific targets of the pathogenic strain only.

Reference: Int J Dermatol 2016;55(11):1196–204
Abstract

Guidelines of care for the management of acne vulgaris

Authors: Zaenglein AL et al.

Summary: This evidence-based guideline addresses important clinical questions associated with the management of acne vulgaris, including review of issues of acne grading and topical and systemic management. It is the result of work done by a group of 17 recognised acne experts, one general practitioner, one paediatrician and one patient, and a review of 242 papers. The full 62-page paper with all recommendations can be accessed by clicking the 'abstract' link below.

Comment: This paper by the American Academy of Dermatology is a good reference point as a 'big picture view to acne treatment'. These guidelines published in J Am Acad Dermatol are evidence based and are an update from the 2007 guidelines. They provide strength of recommendation, level of evidence and comprehensive referencing for classification, investigation as well as topical and oral treatments for acne. It is a good refresher and you can easily skip sections to gain an insight into the area you are interested in.

Reference: J Am Acad Dermatol 2016;74(5):945–73
Abstract

Oral spironolactone for acne vulgaris in adult females

Authors: Layton AM et al.

Summary: This hybrid systematic review included ten randomised controlled trials and 21 case series reporting on benefits and harms of oral spironolactone for treating acne in women; all the included trials were assessed as being at high risk of bias, with low or very low quality evidence. One crossover trial reported that oral spironolactone 200 mg/day was significantly superior to placebo for reducing lesion inflammation. Data from the remaining trials were unhelpful for evaluating efficacy of lower oral spironolactone doses compared with active comparators or placebo. Oral spironolactone 200mg was also associated with more menstrual effects, although they were less frequent when combined oral contraceptives were taken concomitantly. Pooled data on serum potassium levels support the recommendation that routine monitoring is not required for women receiving oral spironolactone.

Comment: Many older treatments go out of fashion and although used for decades are not 'evidenced based' despite widespread usage and seeming efficacy. Spironolactone is one of these and discussed in this paper. This systematic review of ten randomised controlled trials and 21 case series identified evidence of limited quality to underpin the expert endorsement of spironolactone at the doses typically used (≤100 mg/day) in everyday clinical practice. Data were unhelpful in establishing the degree of efficacy of lower doses <100 mg/day and menstrual side effects were significantly more common with the 200mg dose, which could be significantly reduced by concomitant use of a combined oral contraceptive. Pooling of results for serum potassium levels supported the recent recommendation that routine monitoring is not required in this patient population. This article shows us that what we do in everyday practice and what seems to work is not necessarily evidenced based and acceptable to those evidence-based medicine types! It shows us more studies are needed.

Reference: Am J Clin Dermatol 2017;18(2):169–91
Abstract

Oral antibacterial therapy for acne vulgaris

Authors: Bienenfeld A et al.

Summary: This evidence-based review of 41 articles comparing oral antibiotics with placebo, another oral therapy, topical therapy or alternate dose or duration found that tetracyclines, macrolides and trimethoprim/sulfamethoxazole were effective and safe for moderate-to-severe inflammatory acne, and that combining oral antibiotics with topical therapy was better than oral antibiotic therapy alone. The authors were not able to determine superior efficacy of one antibiotic type or class over others, so they advise that antibiotic choice should generally be based on the adverse effect profile.

Comment: While oral antibiotics have been the mainstay of acne therapy for years, no one antibiotic or dose has been considered 'the best' or most effective. This is yet another evidence-based review of 41 articles. It provides a systematic evaluation of the scientific evidence of the efficacy of oral antibiotics for acne. However, due to heterogeneity in the design of the trials, there is insufficient evidence to support one type, dose or duration of oral antibiotic over another in terms of efficacy. Ideally we would have liked a simple answer to the question – which antibiotic, at what dose and for how long? Alas, this article does not give us the answer!

Reference: Am J Clin Dermatol; Published online March 2, 2017
Abstract

Dapsone 7.5% gel: a review in acne vulgaris

Authors: Al-Salama ZT & Deeks ED

Summary: These authors reviewed the use of topical 7.5% dapsone gel (Aczone®) once daily for its indicated use in patients aged ≥12 years with acne vulgaris. Two 12-week phase 3 trials in such patients showed that 7.5% dapsone gel applied once daily led to reduced acne severity and lesion counts compared with vehicle only, with benefits seen as early as week 2 for inflammatory lesion count and from week 4 or 8 for the other outcomes. There were few treatment-related adverse events, most of which were administration-site reactions and mild-to-moderate in severity.

Comment: Dapsone 7.5% gel is a new once-daily topical acne treatment for patients aged ≥12 years. Dapsone is a sulfone antibacterial with anti-inflammatory actions with improvements seen as early as week 2 for inflammatory lesions. The gel was well tolerated with the convenience of once-daily application, which will make it a novel option for those acne sufferers who often have skin dryness, erythema or irritation with topical treatments. It may be very useful for adult acne patients or those with sensitive skin.

Reference: Am J Clin Dermatol 2017;18(1):139–45
Abstract

Moderate and severe inflammatory acne vulgaris effectively treated with single-agent therapy by a new fixed-dose combination adapalene 0.3%/benzoyl peroxide 2.5% gel

Authors: Stein Gold L et al.

Summary: Patients with inflammatory acne were stratified by acne severity (50% moderate and 50% severe) and randomised to receive 0.3% A/BPO (0.3% adapalene and 2.5% benzoyl peroxide; n=217), 0.1% A/BPO (benchmark; n=217) or vehicle (n=69) once daily for 12 weeks. Compared with vehicle, 0.3% A/BPO was associated with a greater proportion of participants rated 'clear' or 'almost clear' with a ≥2-point improvement in IGA (Investigator's Global Assessment) score at week 12 (33.7% vs. 11.0%), greater reductions from baseline in inflammatory and noninflammatory lesion counts (27.0 vs. 14.4 and 40.2 vs. 18.5, respectively) and percentage reductions from baseline in inflammatory and noninflammatory lesion counts (68.7% vs. 39.2% and 68.3% vs. 37.4%, respectively; p<0.001 for all). Among participants with severe inflammatory acne, 0.3% A/BPO was significantly superior compared with vehicle, but the difference in success rate for 0.1% A/BPO did not reach statistical significance. Treatment with 0.3% A/BPO was safe and well tolerated.

Comment: The results of this clinical trial of 503 subjects demonstrate the significantly greater efficacy of 0.3% A/BPO topical gel compared with vehicle, as well as a good safety profile, in the treatment of moderate-to-severe inflammatory non-nodulocystic acne. Patients were randomised, with 217, 217 and 69 subjects in the 0.3% A/BPO, 0.1% A/BPO and vehicle groups, respectively, and in those subjects with severe inflammatory acne (IGA score 4), 0.3% A/BPO demonstrated significantly greater efficacy (p=0.029), requiring a ≥3-point IGA improvement. The bottom line is that this formulation of Epiduo Forte may be an option to patients who are considering oral isotretinoin, especially if combined with an oral antibiotic.

Reference: Am J Clin Dermatol 2016;17(3):293–303
Abstract

A multicenter, randomized, split-face clinical trial evaluating the efficacy and safety of chromophore gel-assisted blue light phototherapy for the treatment of acne

Authors: Antoniou C et al.

Summary: This trial enrolled 98 patients with moderate-to-severe acne vulgaris to receive 6 weeks of twice weekly treatment with an LED blue-light device using specific photoconverter chromophores (KLOX BioPhotonic System) applied to a randomly selected hemiface, but not the contralateral hemiface; all participants also applied a cleanser and a noncomedogenic cream with ultraviolet protection to their entire face during the treatment period, and were followed for a further 6 weeks. At 12 weeks, IGA (Investigator's Global Assessment) scale severity scores had reduced by ≥2 grades in 51.7% of participants, with 45.3% and 61.1% of those with baseline IGA grades of 3 and 4, respectively, experiencing this level of improvement. Lesion count decreases of >40% were seen in 81.6% of treated hemifaces at 12 weeks. The participants also reported a decrease of acne-related pain and improved quality of life at 6 weeks. There were no serious adverse events or adverse event-related study discontinuations.

Comment: This is one of the first studies that describes the 12-week clinical trial to evaluate the efficacy and safety of the KLOX BioPhotonic System, also known under the Leo Pharma Kleresca brand. It is an LED blue-light device using specific photoconverter chromophores, in the treatment of moderate-to-severe acne vulgaris. The randomly selected hemiface received 6 weeks of treatment (twice weekly) and the patients were followed 6 weeks later. A reduction of at least two grades in IGA scale severity was demonstrated in 51.7% of patients at week 12. Furthermore, at week 12, subjects with a baseline IGA grade of 3 (moderate) demonstrated a success rate (2 or greater grade drop) of 45.3%, whereas patients with a baseline IGA grade of 4 (severe) demonstrated a success rate of 61.1%. This LED blue-light phototherapy and photoconverter treatment was found to be efficacious and safe, with a sustained clinical response at 12 weeks for moderate-to-severe facial inflammatory acne. This may prove to be a safe alternative for those not wanting to take oral antibiotics, the oral contraceptive or oral isotretinoin. There is also some suggestion that there is a longer term benefit after week 12 for those that have used it already in clinical practice.

Reference: Int J Dermatol 2016;55(12):1321–8
Abstract

Topical minocycline foam for moderate to severe acne vulgaris

Authors: Shemer A et al.

Summary: Patients with moderate-to-severe acne vulgaris were randomised to receive a topical foam formulation of 1% (n=46) or 4% (n=47) minocycline (FMX-101) or vehicle (n=46) applied once daily to the face for 12 weeks in this phase 2 trial. Compared with vehicle, 4% minocycline foam was associated with greater mean percentage reductions from baseline in inflammatory and noninflammatory lesion counts at 12 weeks (–71.7% vs. –50.6% [p=0.0001] and –72.7% vs. –56.5% [p=0.0197], respectively) and significant improvements in IGA (Investigator's Global Assessment) scores; 0.1% minocycline foam only significantly reduced inflammatory lesions (–66.6% vs. –50.6% [p=0.0072]) and had no significant impact on IGA scores.

Comment: The objective of the study was to evaluate the safety, tolerability and efficacy of two strengths of FMX-101 (1% and 4%) versus vehicle in subjects with moderate-to-severe facial acne. A once daily application of foam for 12 weeks showed treatment with 4% FMX-101 (rather than 1%) led to a greater mean percentage reduction from baseline in lesion count versus vehicle at 12 weeks for both inflammatory and noninflammatory lesions. The significant reduction in inflammatory lesions was observed as early as week 3 and persisted until the study end. The formulation was well tolerated and safe, with no drug-related systemic side effects or serious adverse events. FMX-101 4% is the appropriate strength for further evaluation in phase 3 trials and may be a safer way for patients to use topical minocycline without the systemic side effects. Recent studies suggest that inflammation may be the driving factor in acne pathogenesis and therefore antibiotics play an anti-inflammatory role. Oral minocycline is an effective treatment but should not be used long term, so maybe this will be a new option with no systemic side effects. Of course, antibiotic resistance needs to be considered for the future.

Reference: J Am Acad Dermatol 2016;74(6):1251–2
Abstract

The extinction of topical erythromycin therapy for acne vulgaris and concern for the future of topical clindamycin

Authors: Austin BA & Fleischer Jr AB

Summary: This retrospective review of US National Ambulatory Medical Care Survey data for the period 1993–2012 identified that around 94.5 million visits were for a primary diagnosis of acne vulgaris. During this period, erythromycin prescriptions significantly decreased to almost near zero while clindamycin prescriptions significantly increased. These changes significantly correlated with declining and increasing results of literature searches for 'erythromycin AND resistance' and 'clindamycin AND resistance', respectively. There were >100 papers on erythromycin resistance in 1983 and on clindamycin resistance in 2003, which roughly corresponded to the interval between reports of their utility in acne.

Comment: This is a reminder of prescribing trends and warnings for the future. This study evaluated changes in topical antibiotic prescribing trends for acne by retrospectively reviewing the National Ambulatory Medical Care Survey data from 1993 to 2012 for all visits in which acne vulgaris was the primary diagnosis. The analysis showed that over time erythromycin use declined and clindamycin use rose. Current recommendations discourage topical antibiotic monotherapy in favour of combination therapy with benzoyl peroxide and topical retinoids, and are a reminder that we must be ever vigilant as prescribers. It also makes us think of other nonantibiotic treatments that are available to us.

Reference: J Dermatolog Treat 2017;28(2):145–8
Abstract

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Selection of papers and comments are provided by Dr Jo-Ann See, M.B.B.S. (Hons), F.A.C.D., a dermatologist in private practice in Sydney, Australia. After obtaining her medical degree from the University of New South Wales, she completed her Dermatology training at both Prince of Wales and St Vincent's Hospitals in Sydney. Dr See has served on the State and Federal boards of the Australasian College of Dermatologists as well as having been a guest examiner for the Fellowship examinations. Her practice covers a broad spectrum of cases which often times require innovative methods of treatment. Her key interests are skin care, sun damage, skin cancer and acne. She is co-chair of All About Acne, an online acne resource as well as a regular national and international speaker on acne. She is a key opinion leader regarding acne and chairs several advisory boards looking at new acne treatments as well as education resources for the public and doctors. She appears regularly in the media talking about acne and skin care.