Retapamulin: What is the Role of this Topical Antimicrobial in the Treatment of Bacterial Infections in Atopic Dermatitis?

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ABSTRACT

In atopic dermatitis (AD), the stratum corneum of patients appears to have alterations that predispose them to colonization and invasion by various bacteria, most notably Staphylococcus aureus (S. aureus). This bacterial co-existence is accepted to be an important factor in AD disease activity. Exactly when to initiate antimicrobial treatment is controversial, but such intervention, when warranted, has repeatedly been demonstrated to improve the course of AD. However, the increase in antibiotic resistance presents a therapeutic challenge in the management of AD patients, which highlights the need for novel mechanism topical antibacterial agents. Retapamulin is a relatively new pleuromutilin antibiotic designed for topical use. In vitro studies have demonstrated its low potential for the development of antibacterial resistance and high degree of potency against Gram-positive bacteria found in skin infections, including many S. aureus strains that are resistant to methicillin, fusidic acid, and mupirocin. Clinical studies exploring the treatment of secondarily infected dermatitis reveal that the efficacy of topical retapamulin is comparable to a 10-day course of oral cephalexin or to topical fusidic acid. Retapamulin appears to be a much needed antimicrobial option for treating the AD population due to their common carriage of bacterial pathogens and frequency of infectious complications.

Key words: antibacterial, atopic dermatitis, retapamulin, skin infections

Atopic dermatitis (AD) is a chronic relapsing inflammatory skin disease that affects approximately 20% of children and 1-3% of adults; incidence is on the rise due to modern environmental factors in addition to genetic predisposition. AD is a condition that encompasses eczematous changes within the epidermis, consisting of a multifaceted underlying etiology including, but not limited to, epidermal barrier dysfunction, atopic diathesis, and an increased incidence of secondary infections. Acute lesions are characterized by erythema, oozing, and crusting, whereas chronic lesions can feature papules and lichenification. Affected individuals experience a decreased quality of life that is secondary to intermittent skin eruptions and difficult-to-control pruritus.

One of the main factors in the pathogenesis of AD involves a compromised function of the natural skin barrier. AD patients are deficient in ceramides, the sphingolipid constituents of protective and potently antimicrobial lamellar sheets in the stratum corneum. A second factor is a reduced amount of antimicrobial peptides in the skin of AD patients. Keratinocytes produce 2 major classes of innate antimicrobials: β-defensins and cathelicidins; both are essential to defend the skin against bacterial invasion. In AD, the high concentrations of interleukin-10 and T2 helper cytokines cause a down regulation in the production of these antimicrobial peptides. Furthermore, the skin of AD patients has decreased moisture content. Together, these alterations in the microenvironment of the skin predispose AD patients to widespread microbial colonization and infection. For instance, it has been reported that AD patients have a 200-fold increase in S. aureus colonization when compared with individuals with healthy skin. On both lesional and nonlesional skin, >90% of AD patients are colonized by S. aureus, whereas the prevalence is only 5-20% in non-AD individuals. Among AD patients, the mean colonization density of S. aureus is markedly higher within the atopic lesions. The presence of such a high microbial load is associated with increased disease severity.

Overview of Standard Treatment

Standard AD care includes topical glucocorticoids as first-line agents, followed by newer options, such as calcineurin inhibitors and anti-IgE antibodies. With regard to secondary
infections, antimicrobial therapy can either be administered orally or topically. Topical antimicrobials are preferentially given due to the fact that administration can be directly targeted to the infected area, therefore reducing the potential for systemic side-effects, such as gastrointestinal distress and undesired drug interactions.\(^1\) Until recently, topical antimicrobials have been limited in availability; the main options include fusidic acid (introduced in 1962) and mupirocin (introduced in 1985). Recent reports indicate that multiple bacterial organisms have successfully developed resistance to these 2 drugs.\(^4,14,15\) This rising prevalence increasingly limits their use to specific conditions, e.g., systemic fusidic acid for severe bone infections and topical mupiricin to eradicate nasal methicillin-resistant *Staphylococcus aureus* (MRSA).\(^14\) However, due to the aforementioned phenomena of increased susceptibility to colonization with microorganisms, combined with a compromised ability to defend against them, the addition to colonization with microorganisms, combined with a compromised ability to defend against them, the addition of antimicrobial therapy to the standard care regimen of AD is recommended in certain clinical circumstances, which include:\(^4\)

- a) early signs of secondary bacterial infection;
- b) AD exacerbation that cannot be otherwise explained; and
- c) AD that is poorly controlled by monotherapy with topical anti-inflammatories.

**Topical Retapamulin**

Retapamulin ointment 1% (*Altabax®/Altargo®, GlaxoSmithKline*) is the first approved pleuromutilin antimicrobial for the treatment of uncomplicated superficial skin infections caused by staphylococcal, streptococcal, and anaerobic Gram-positive organisms; it is not substantially effective against Gram-negative organisms.\(^16,17\) Currently, it is approved for use in the EU for patients with impetigo or small infected wounds, and in the US for impetigo. Retapamulin has not received US FDA approval for MRSA skin infections. However, based on *in vitro* studies and incidental clinical trials data, it holds promise in the treatment of bacterial skin infections owing to its high *in vitro* potency against many common skin pathogens, low potential for development of bacterial resistance, and targeted application to the sites of involvement without significant systemic exposure.\(^13,16,18\)

Retapamulin is a semisynthetic pleuromutilin derivative isolated from *Clitopilus scyphoides* (an edible mushroom) and functions by selectively targeting the 50S subunit of bacterial ribosomes to inhibit protein synthesis.\(^14\) It acts at a site distinct from other available drugs; therefore, cross-resistance is not yet a concern. The *in vitro* minimum inhibitory concentration required to suppress the growth of 90% of organisms (MIC90) by retapamulin was 0.12g/ml against *S. aureus*, including methicillin- and mupirocin-resistant, and *Staphylococcus Epidermidis* isolates. Retapamulin was also shown to be very active against *Streptococcus Pyogenes* (*S. Pyogenes*), approximately 1000 times as potent as mupiricin or fusidic acid.\(^15\)

A large study of over 6500 bacterial isolates, including *staphylococcus* and *streptococcus* from 13 countries, obtained from both hospital and community settings, further demonstrated the *in vitro* efficacy of retapamulin against these bacteria. Between 2005-2006, this Global Surveillance Program found retapamulin to also be effective against strains of *S. aureus* with resistance to methicillin, mupirocin, and fusidic acid.\(^19-21\) Other *in vitro* studies have reported similar findings.\(^18\) In addition to Gram-positive coverage,\(^21\) retapamulin has shown mixed antimicrobial activity against anaerobes\(^14,22\) and exhibited very minimal efficacy against enterococci and Gram-negative bacteria. Despite this *in vitro* data, clinical studies thus far have focused on Gram-positive skin infections. A low potential for the development of bacterial resistance has also been reported with retapamulin, and if resistance does develop, it does so very gradually and by mechanisms distinct from those known to occur against other available antimicrobial options.\(^23,24\) The main mechanisms of resistance are twofold and include mutations in the retapamulin ribosomal binding site and a non-target-specific efflux mechanism.\(^25-27\) These results have been reproduced in both single-step and multistep passage studies.\(^14,23,24\)

**Efficacy of Retapamulin**

The overall findings from multiple trials indicate that retapamulin is a safe therapeutic alternative and it is at least as effective as conventional treatment options.

**Impetigo**

One of the initial retapamulin trials consisted of 7 days of treatment with topical retapamulin 1% vs. placebo in 210 patients. Clinical success rates were significantly higher for the retapamulin-treated group as compared with placebo (85.6% vs. 52.1%). Microbiological success rates were even higher for retapamulin vs. placebo (91.2% vs. 50.9%).\(^28\)

A multicenter trial of noninferiority comparison of retapamulin ointment 1% twice daily for 5 days with sodium fusidate ointment 2% 3 times daily for 7 days was completed. Over 500 adults and children ≥9 months of age with impetigo were treated in this randomized, observer-blinded phase 3 study. The group treated with retapamulin exhibited a 99% clinical success rate vs. 94% in the sodium fusidate treated arm. Cases of MRSA isolated at baseline were treated in the retapamulin group (n=8) and in the sodium fusidate group (n=2); both agents were 100% effective in treating these cases of MRSA impetigo.\(^13\)

**Secondarily Infected Traumatic Lesions**

For the treatment of secondarily infected traumatic lesions, over 1900 patients participated in 2 identical, randomized, double-blind, controlled, multicenter trials of retapamulin 1% ointment twice daily for 5 days vs. oral cephalaxin 500mg twice daily for 10 days.\(^28\) Retapamulin was approximately 90% effective in successfully treating these skin infections compared with 92% for cephalaxin. Compliance rates were
significantly higher in the retapamulin group. Another randomized, double-blind, double-dummy noninferiority trial with 547 adults and children ≥9 months of age with secondarily infected dermatitis (SID) was performed with retapamulin.16 Patients with SID were randomized to treatment with retapamulin ointment 1% twice daily for 5 days or oral cephalexin 500mg twice daily for 10 days. Clinical success rates were 86% and 90%, respectively.

Potential Side-Effects of Retapamulin

The most common adverse event with the use of retapamulin ointment was localized application site irritation (e.g., pruritus), which was reported by less than 2% of all patients. Additionally, there exist 2 newly published case reports detailing allergic contact dermatitis as a result of retapamulin usage.30,31 These patients ranged in age from 6 to 79 years and were all diagnostically worked up via patch testing, which identified retapamulin as the cause and excluded other ingredients in the formulation. While this has been reported as an extremely rare occurrence, no detailed studies have yet been conducted to estimate its true incidence. Nonetheless, a limited duration regimen of topical retapamulin can still ease AD progression and increase compliance vs. other longer term topical treatments or oral regimens. Improved treatment compliance may also contribute to decreased resistance.

The Use of Antibiotics in AD Treatment

Conflicting data exists with regard to the role of antibiotic therapy in the treatment of AD. One controlled study showed that systemic cloxacillin or erythromycin cleared S. aureus with at least 6 months of sustained clinical improvement.32 However, a second study among patients with no overt signs of infection indicated that there was no improvement after fluocloxacinil treatment.33 Numerous open and double-blinded placebo-controlled experiments have since evaluated the combination of corticosteroids with topical antimicrobials in AD treatment. The majority of findings from these studies have shown significant benefit (1 of these studies specified benefit only in the case of severe disease), which included decreased colonization density and at least partial improvement of skin lesions. However, 1 study showed only marginal improvement and 2 showed no benefit.7,8,10,34-37

Bacterial Decolonization

A meta-analysis by Birnie et al. investigated whether or not interventions to decrease S. aureus colonization in AD patients should be prescribed.1 They looked at 21 studies and analyzed different eradication mechanisms, and concluded that treatment simply to decrease the colony load of S. aureus in AD patients without an overt infection was not recommended. However, the study team stated that this conclusion is limited by multiple factors, such as poor study design, improper reporting of results, and failure to include outcome findings related to quality of life and long-term improvement. The investigators do recommend further research in this area.

Conclusion

Finite topical antimicrobial therapy (for approximately 2 weeks) can be an important addition to the standard treatment of AD in many instances, especially when there are overt signs of a secondary infection or if manifestations cannot be well controlled with anti-inflammatories alone. Data is conflicting as to exactly when antimicrobials should be introduced for the treatment of AD, but following their use, overall improvement in disease course has been shown in multiple studies. Considering that resistance to current topical antimicrobials is increasing, leading to further challenges in treating skin infections, the need for new treatment options is very real. The advent of retapamulin offers a safe, effective, and distinct alternative to its predecessors, and can serve as an adjunctive therapeutic option in specified AD patients. While no clinical trials with retapamulin have been performed specifically for AD, its safety and efficacy are proven in uncomplicated superficial skin infections involving the same bacterial isolates, notably S. aureus, MRSA, and S. pyogenes.

References


Predictive Testing of the Melanocortin 1 Receptor for Skin Cancer and Photoaging

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ABSTRACT

Genetic predisposition to melanoma and nonmelanoma skin cancer extends far beyond the Fitzpatrick phenotype classification scheme. Specific alleles of the gene that codes for the melanocortin 1 receptor are predictive of skin cancer risk independent of skin type and hair color. The ability to identify high risk patients independent of the red hair phenotype may help to modify routine sun and skin monitoring behaviors. In addition, as this increased skin cancer risk is likely due to impaired UV A and UVB defence mechanisms, consideration of genetic predisposition may also be appropriate for patients undergoing psoralen + UVA (PUVA) or UVB treatments for various cutaneous disorders, such as psoriasis, eczema, and vitiligo. Testing aimed at improving prognostication may serve to limit the influence of certain risk factors.

Key Words: melanocortin 1 receptor, melanoma, MC1R, photoaging, skin cancer

It has long been known that cutaneous pigmentation is our principal photoprotective defence against the carcinogenic and aging effects of ultraviolet radiation (UVR). Recent evidence, however, indicates that much of the defence provided by eumelanin is independent of pigmentation. This photoprotective mechanism, therefore, is determined not only by the quantity of eumelanin in the skin, but also by the variants of eumelanin.

Melanocortin 1 Receptor (MC1R)
The melanocortin 1 receptor (MC1R or alpha melanocyte-stimulating hormone receptor) is a key protein regulating skin and hair pigmentation. Melanin synthesis is largely modulated by the agonistic binding of alpha-melanocortin (alpha-MSH) and adrenocorticotropic hormone (ACTH) to MC1R. This initiates the cAMP mediated pathway required for UV-induced tanning and ultimately yields the black-brown pigment (eumelanin). Total melanin content (quantity and variety), as well as the relative amounts of eumelanin and phaeomelanin, are important determinants for skin color, hair color and photoprotection.

Melanin-containing granules (melanosomes) form supranuclear caps in keratinocytes, thus shielding the nuclear deoxyribonucleic acid (DNA) from UVR. In dark skin, melanosomes are found throughout the epidermis, but in fair skin they are absent from the suprabasal layer, allowing for increased UVR penetration and DNA damage. Eumelanin is also a scavenger for reactive oxygen species (ROS). On the other hand, phaeomelanin may contribute to UV-induced skin damage due to its potential to generate singlet oxygen and hydroxyl radicals in response to UVR. Furthermore, it is also known that the chromophore backbone of eumelanin is responsible for the absorption and scattering of UVR; however, there are several different chromophore monomer units and not all perform this function equally well. As such, it is clear that eumelanin does much more than pigment our skin and there are potential clinical outcomes associated with the eumelanin mix that we are genetically coded to produce.

More than 120 genes have been shown to regulate pigmentation, with a key gene being HomoloGene 1789 (locus: Chr.16:q24.3). This gene encodes the MC1R, a 7-transmembrane G protein-coupled receptor (GCR) expressed on the surface of melanocytes. The modulation of MC1R function regulates melanin synthesis both qualitatively and quantitatively. The human MC1R gene is highly polymorphic with over 70 identified alleles. Certain allelic variants are associated with the red hair phenotype (red hair, fair skin, lack of tanning ability, and propensity to freckle), melanoma, and nonmelanoma skin cancer. The MC1R gene is, of course, not the only gene that is associated with skin cancer risk, but it has been widely studied. As well, 7 identified risk alleles, independent of skin type and hair color, appear to confer a greater risk of nonmelanoma skin cancer, melanoma, and photoaging.

Exposing cultured human melanocytes to increasing doses of UVR has shown that total melanin and eumelanin content (MC and EC) correlate inversely with the extent of UVR-induced growth arrest, apoptosis, and induction of cyclobutane pyrimidine dimers (CPD). Melanocytes with loss-of-function MC1R, regardless of their MC or EC, sustained more UVR-induced apoptosis and CPD, and exhibited reduced CPD repair. MC, mainly EC, and MC1R function are therefore independent determinants of UVR-induced DNA damage in melanocytes. This may help to explain why the predictive value for skin cancer and photaging from alleles that code for the MC1R receptor are independent of skin type and hair color.

Furthermore, in helping to explain the independence of photoprotection and pigmentation, it has been demonstrated that melanocortins reduce the generation of hydrogen peroxide and enhance repair of DNA photoproducts independently of pigmentation. Natural expression of certain MC1R allelic variants sensitizes melanocytes to the cytotoxic effect of UVR and increases the burden of DNA damage and oxidative stress.
It is clear, therefore, that the Fitzpatrick classification of skin type and hair color is insufficient to predict susceptibility to the photo consequences of UVR. While there is no doubt that Fitzpatrick skin type I is more susceptible to burning, skin cancer, and photoaging, the large number of melanoma and nonmelanoma skin cancer patients seen in clinical practice presenting with Fitzpatrick skin types II, III, and IV suggest that additional diagnostic tools are required to identify the spectrum of at-risk patients.

Early work performed in the UK identified a dosage effect of MC1R alleles on sensitivity to UVR (degree of tanning after repeated sun exposure). Given that red hair approximates an autosomal recessive trait and that there is a higher risk for sun sensitivity amongst heterozygotes of certain allelic variants of the MC1R, this gene is likely associated with diversification in the skin’s response to UVR in a majority of the population without red hair. As heterozygotes for the MC1R gene are common, this suggests that the MC1R gene may be regarded with substantial importance as a susceptibility gene for sunburn, photoaging, and skin cancer.

**Studies of MC1R Associated Skin Cancer Risk**

In 2000, an Australian investigation across 859 subjects showed MC1R variants in 72% of individuals with cutaneous malignant melanoma (CMM), whereas only 56% of the control individuals carried at least 1 variant (P<0.001). These findings were independent of family history of melanoma. Three active alleles (Arg151Cys, Arg160Trp, and Asp294His), previously associated with red hair, doubled the risk for CMM for each additional allele carried (odds ratio [OR]=2.0; 95% confidence interval [CI] 1.6-2.6).

In 2001, a broader Dutch study across 961 subjects showed that numerous MC1R gene variants predisposed individuals to cutaneous melanoma. In stratified analyses, the genetic predisposition was shown to be largely independent of skin type and hair color. The ORs, after adjusting for skin type, were 3.6 (95% CI 1.7-7.2) for 2 variants and 2.7 (95% CI 1.5-5.1) for 1 variant. The Asp84Glu variant appeared to confer the highest risk.

As the tendency to sunburn and inability to tan after sun exposure are known risk factors for both melanoma and nonmelanoma skin cancer, the interest to further investigate the MC1R gene as a predictive indicator for nonmelanoma skin cancer was pursued.

A second Australian study investigated 220 individuals [111 high risk and 109 low risk for basal cell (BCC) and squamous cell carcinomas (SCC)]. Comparative allele frequencies for 9 MC1R variants were determined. An association was demonstrated between the prevalence of BCC, SCC, and solar keratosis (OR=3.15; 95% CI 1.7-5.82) and 3 alleles with a known association with skin UV sensitivity and melanoma. It was concluded that the presence of at least 1 variant allele was informative in predictive risk beyond that gained from observation of pigmentation phenotype.

A larger study involving 838 subjects (453 with nonmelanoma skin cancer and 385 with no skin cancer) found that the presence of 2 variant alleles indicated increased risk of developing cutaneous SCC (OR=3.77; 95% CI 2.11-6.78), nodular BCC (OR=2.26; 95% CI 1.45-3.52), and superficial multifocal BCC (OR=3.43; 95% CI 1.92-6.15) when compared with carriers of 2 wild type alleles. Furthermore, when stratified by skin type and hair color, the analysis demonstrated that these factors did not materially alter the relative risks.

It is important to note that all observed odds ratios are expressed as multiples of some baseline level of risk; in this report, it is defined as the level or risk seen with that of none of the studied MC1R risk alleles being present.

**Epidemiology**

With respect to melanoma, public awareness is increasing, but its incidence is rising at an annual rate of 4.5%. The melanoma incidence in Australia is the highest in the world, exceeding 50 per 100,000 individuals. The lifetime risk of developing melanoma in the US is 1 out of 52 in men and 1 out of 77 in women. In the US in 2005, 59,000 people were diagnosed with melanoma and 7700 died of the disease, which translates to about 1 melanoma death per hour.

Melanoma represents one of the most common types of cancer occurring in young adults; it is the leading cause of skin cancer death among this population. Recent data from Cancer Research United Kingdom has shown that skin malignancies have overtaken cervical cancer as the most prevalent cancer striking British women in their 20s. Although women in this age group represent only a small percentage of patients diagnosed with melanoma, nearly one-third of all cases occur in those younger than 50 years.

In the US, there has been a 15-fold increase in the incidence of melanoma over the last 40 years, which is a more rapid rate of growth than any other malignancy. As early metastasis is possible and late stage disease usually fatal, prevention and early detection are crucial. The potential cost savings to the health care system resulting from implementation of these measures in both melanoma and nonmelanoma skin cancer can be significant. It is well known that adopting sun awareness, safer “in sun” behaviors, and greater vigilance, as well as diagnostic advances, can save lives and reduce health care costs. Consequently, screening for specific MC1R allelic variants that could identify patients at higher risk for skin cancer and photoaging independent of their skin type or hair color has generated great interest.

**Genomic Testing of MC1R**

It is now possible to accurately assess the MC1R receptor using a noninvasive skin sample taken with an epithelial swab. A commercial test is presently available in Canada (and soon in other countries) that identifies the 7 high-risk genetic markers associated with MC1R for melanoma, nonmelanoma skin cancer, and photoaging that are...
independent of skin type and hair color. The gene assays are performed by a central laboratory and results are generally return to the doctor’s office in 14 days.

**Clinical Implications of the MC1R Test**

Genomic tests (diagnostic or prognostic) are becoming increasingly popular and mainstream, but many are plagued by 3 potential deficiencies including:

- Identification of disease for which nothing can be done to prevent its onset or minimize severity.
- Identification of risk alleles does not necessarily convey actual risk, as environmental factors are not considered.
- Marketing directly to the public without providing sufficient interpretation of the results by a qualified health care professional can negate the test’s relevancy.

With skin cancer and photoaging, identification of higher risk individuals may significantly improve health outcomes by providing the opportunity for earlier detection and intervention. Identified patients will likely have a greater incentive to practice safer sun behaviors, undertake self examination with more diligence, and seek professional help for abnormal skin changes earlier than they would otherwise, which appears to be the case with the early Canadian experience. Preliminary findings from a recent Australian study of 119 individuals showed healthy psychological, behavioral, and cognitive adjustments after participation in genetic testing for melanoma risk. Being able to personalize an otherwise ambiguous risk by showing patients their genetic markers can assist physicians in encouraging modification of sun protection behaviors, identifying higher risk patients, and individualizing treatment. Patients who do not possess the MC1R risk alleles have a lower probability, but are not entirely safe from developing UV-related cutaneous neoplasms, and thus, should be counselled accordingly. As the clinical consequences of specific MC1R alleles are believed to be the result (in part) of impaired absorption and scattering of UVR, the utility of the MC1R genomic test as a pre-treatment screening tool for patients undergoing PUVA or UVB treatment is an interesting consideration.

**Conclusion**

This test is not available to the public save through the physician’s office, which is intended to assure proper interpretation of results that is accompanied by appropriate counselling. Campaigns aimed at increasing public awareness are important in shaping attitudes, but evidence demonstrates that sun behavior by the general population is not changing sufficiently, as reflected by the rising incidence of skin cancer. Because assessing an individual’s genetic markers personalizes risk, the goal is to motivate changes in sun behavior and assist clinicians in tailoring treatment regimens for patients at higher risk of skin cancer and photoaging. Ultimately, the genetic and chemical assessment of melanin synthesis is poised to become a superior indicator over skin color alone for determining skin cancer risk.

**References**

A recent study by Kenter et al.* explored the efficacy of a human papillomavirus (HPV) vaccine in 20 women with precancerous vulvar lesions. Vulvar intraepithelial neoplasia is chronic and caused by high-risk types of HPV, especially type 16 (HPV-16). The objective of the trial was to assess the immunogenicity and efficacy of a synthetic long-peptide vaccine in women with HPV-16-positive, high-grade vulvar intraepithelial neoplasia. Patients were vaccinated 3-4 times. At 3 months after the last vaccination, 60% of patients showed clinical responses and reported relief of symptoms. Five women had complete regression of the lesions, and 57% showed partial regression. The complete response rate was maintained at 24 months of follow-up. All patients had vaccine-induced T-cell responses; retrospective analyses indicate that subjects demonstrating a complete response at 3 months experienced a significantly stronger induction of HPV-16-specific immunity, when compared with patients without a complete response. This study shows that it may be possible to vaccinate against and treat HPV-induced premalignance. If validated by larger trials, this novel therapeutic approach has the potential to reduce the need for more intensive treatments, such as cryotherapy and laser surgery.


At variance are reports linking psoriasis with lymphohematopoietic malignancies (e.g., leukemia and lymphoma) and solid cancers. In an observational study using the UK General Practice Research Database, cancer incidence was compared between patients with and without psoriasis; duration of disease and treatments used were also examined. Among 67,761 patients, 1703 had incident cancer, with 54% having had a history of psoriasis. Incidence rate ratios for lymphohematopoietic and pancreatic cancers were 1.81 (95% CI 1.35-2.42) and 2.20 (95% CI 1.18-4.09), respectively. In a nested case-control analysis with this cohort, adjusted odds ratios (ORs) for cancer overall were 1.50 (95% CI 1.30-1.74) for psoriasis of >or=4 years duration and 1.53 (95% CI 0.97-2.43) for patients receiving systemic therapy. Findings revealed that highest risk for lymphohematopoietic malignancies was associated with systemic treatment. The OR for patients without systemic treatment was 1.59 (95% CI 1.01-2.50) for psoriasis of <2 years and 2.12 (95% CI 1.45-3.10) for that of >or=2 years duration. Increased risk of bladder/kidney and colorectal cancers correlated with longer-duration psoriasis. Although further study is necessary, longer-term and more severe psoriasis appears to confer an increased, but not significant, risk for certain cancers.

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<td>3:6</td>
<td>Embrel®</td>
<td>2:6</td>
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<td>Arbelic™</td>
<td>5:6</td>
<td>Epigallocatechin gallate</td>
<td>5:4</td>
<td></td>
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<tr>
<td>Atazanor sulphate</td>
<td>1:6</td>
<td>Erythromycin</td>
<td>1:4;3:6</td>
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</tr>
<tr>
<td>Atopic dermatitis</td>
<td>6:6;8:4-5</td>
<td>Etenaccept</td>
<td>2:6</td>
<td></td>
<td></td>
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<tr>
<td>Autologous collagen</td>
<td>3:8</td>
<td>Eretinate</td>
<td>3:3</td>
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<td></td>
</tr>
<tr>
<td>Azelaic acid</td>
<td>2:1</td>
<td>Evolence®</td>
<td>7:8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin</td>
<td>3:6</td>
<td>B</td>
<td>8:2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azulene</td>
<td>4:8</td>
<td>C</td>
<td>2:2;6;4:5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td>D</td>
<td>7:2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BD</td>
<td>5:1-3</td>
<td>E</td>
<td>8:4-5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzoyl peroxide</td>
<td>2:2;3;6;4:5</td>
<td>Efalizumab</td>
<td>1:6;2:6;3:8;4:8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzyl alcohol</td>
<td>4:8;6;6</td>
<td>Eflornithine hydrochloride</td>
<td>7:3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bexarotene</td>
<td>3:2</td>
<td>Eflornithine hydrochloride</td>
<td>7:3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Biaxin®</td>
<td>1:4</td>
<td>Elidel®</td>
<td>2:2;3:2;4:5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bimatoprost</td>
<td>2:6</td>
<td>Embrel®</td>
<td>2:6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body piercing</td>
<td>7:4-7</td>
<td>Epigallocatechin gallate</td>
<td>5:4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botox®</td>
<td>3:4;4:8;5:6:8</td>
<td>Erythromycin</td>
<td>1:4;3:6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botox Cosmetic®</td>
<td>7:8</td>
<td>F</td>
<td>8:2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botulinum toxin</td>
<td>3:4;4:8;5:6:8</td>
<td>Farnesoid</td>
<td>8:2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bowen’s disease</td>
<td>6:1-3</td>
<td>Farnesoid</td>
<td>8:2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>RPO</td>
<td>2:2;2:6;4:5</td>
<td>Farnesoid</td>
<td>8:2</td>
<td></td>
<td></td>
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<tr>
<td>C</td>
<td></td>
<td>Farnesoid</td>
<td>8:2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcineurin inhibitors</td>
<td>2:2;3:2</td>
<td>Farnesoid</td>
<td>8:2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcipotriol + Betamethasone dipropionate</td>
<td>4:1-4</td>
<td>Farnesoid</td>
<td>8:2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcitriol</td>
<td>3:8</td>
<td>Farnesoid</td>
<td>8:2</td>
<td></td>
<td></td>
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<tr>
<td>Cefotibiprole</td>
<td>1:6;2:6</td>
<td>Farnesoid</td>
<td>8:2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CelCept®</td>
<td>3:3;8:6</td>
<td>Farnesoid</td>
<td>8:2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cervical cancer vaccine</td>
<td>3:8</td>
<td>Farnesoid</td>
<td>8:2</td>
<td></td>
<td></td>
</tr>
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<td>Childhood eczema</td>
<td>8:4-5</td>
<td>Farnesoid</td>
<td>8:2</td>
<td></td>
<td></td>
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<tr>
<td>Ciclopirox</td>
<td>1:2</td>
<td>Farnesoid</td>
<td>8:2</td>
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<td></td>
</tr>
<tr>
<td>Claravis®</td>
<td>1:4</td>
<td>Farnesoid</td>
<td>8:2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clarithromycin</td>
<td>1:4;3:6</td>
<td>Farnesoid</td>
<td>8:2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cindamycin</td>
<td>2:1-2</td>
<td>Farnesoid</td>
<td>8:2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cindamycin phosphate</td>
<td>2:6</td>
<td>Farnesoid</td>
<td>8:2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
PCOS 7:1
PDT 6:1-3;6:6
Pediatric dermatitis 8:4-5
Pemphigus 4:7
Penciclovir 8:1-2
Peripheral T-cell lymphoma 4:8
Permethrin 2:2
Phenylalanine 1:6
Photography 5:4-5
Photodynamic Therapy 6:1-3;6:6
Photopheresis 3:8
Phototherapy 3:2;3:7;4:6
Pimecrolimus 2;2;3:2;4:5
Psoriasis 3:6-7
PML 3:8;4:8
Polycystic ovary syndrome 7:1
Poly-L-lactic acid 7:8
Psoralen + UVA 6:1
Proliferative retinopathy 5:6
Progressive multifocal leukoencephalopathy 3:8;4:8
Protoporphyrin IX 2:2;3:2;4:5-7
Protophophyrin IX 6:1
Psoralen + UVA 3.3
Psoriasis 4:1;4:8
Psoriatic arthritis 5:6
PUVA 3:8
Recurrent herpes labialis 8:1-3
Retinoids 3.2-4;6:4-5
REYATAZ® 1:6
Rheumatoid arthritis 5:6
Romidepsin 8:6
Rosacea 2:1
SBCC 6:1-3;6:6
SBII-087 5:6
Scalp psoriasis 4:1-4
Sculptra Aesthetic® 7:8
SELZENTRY® 2:6
Simponi™ 5:6
Skin infections 2:1
SLE 3:6
Sodium sulfacetamide + Sulfur 2:2
Solar radiation 5:4-5
Sorafenib 6:6
Soriatane® 3:3
Sotret® 1:4
Spironolactone 7:2
Sporanox® 1:4
Stelara® 3:8;8:6
Stevens-Johnson syndrome 1:6
Sumycin 1:4
Superficial basal cell carcinoma 6:1-3;6:6
Systemic lupus erythematosus 5:6
Toxic epidermal necrolysis 1:6
Traditional Chinese medicine 6:6
Tri-Luma® 8:6
UV protection 5:4-5
UVB 3:2;4:6
Valacyclovir 3:2;4:6
Vaniq® 3:3
Vitiligo 4:1-4
Xamiol® 4:1-4
Zeftera® 1:6
Zeranol® 7:8
Zovirax® 1:4
Zevalin® 7:8