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IL-12/IL-23 Inhibitors: The Advantages and Disadvantages of this Novel Approach for the Treatment of Psoriasis

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ABSTRACT

Psoriasis is a common chronic inflammatory skin disease that is mediated, in part by the body's T-cell inflammatory response mechanisms. Further insight into the pathogenesis of the disease and the role of various cytokines, particularly interleukin(IL)-12 and IL-23, has led to advances in the treatment of this disease. A relatively new class of drugs that inhibit these interleukins is being developed and studied. Current data regarding the efficacy of these agents show they may have the potential to become the new clinical gold standard for biologic therapy to treat psoriasis.

Keywords: IL-12; IL-23; ustekinumab; psoriasis

The Role of IL-12 & IL-23 in the Pathogenesis of Psoriasis

Psoriasis is a chronic skin disease affecting approximately 2%-3% of the general population and is mediated, at least partially, by the body's T-cell inflammatory response mechanisms. Two interleukins (IL) in particular, IL-12 and IL-23, have been specifically implicated as key players in the pathogenesis of psoriasis secondary to their role in linking the innate and adaptive immune responses.[1] IL-12 and IL-23 are composed of the p40 subunit, which is common to both, as well as the unique subunits, p35 and p19, respectively. The individual subunits facilitate the distinctive biological actions of each molecule. IL-12 functions to induce and sustain TH1 immune responses leading to the secretion of interferon (IFN)-γ and the homing of T cells to the skin via the induction of cutaneous lymphocyte antigen (CLA), whereas, IL-23 functions to maintain chronic autoimmune inflammation via the induction of IL-17, regulation of T memory cells, and direct activation of macrophages.[1-4]

Support for IL-12 and IL-23 Involvement in Psoriasis

Through various approaches, a plethora of studies involving transgenic mice, the human genome, and samples from human psoriatic lesions support the hypothesis that IL-12 and IL-23 have a significant role in the disease process. According to the genome-wide association study (GWAS) conducted by Cargill et al., an association exists between psoriasis and the genes for IL-12 and IL-23. This finding was reproduced by Smith et al. in a study of approximately 600 patients with psoriasis. Additionally, scrapings from psoriatic lesions have exhibited not only increased levels of IL-12 and IL-23, but also higher levels of their downstream effectors, including CLA+ T-cells, IFN-γ, and IL-17.[1,4] Recent findings indicate that people with genetic over-expression of this common p40 subunit have a greater risk for the development of psoriasis, and that psoriatic lesions contain high levels of IL-12, IL-23 and their downstream effectors. In light of these findings, further investigation has been directed towards illustrating not only their specific role in its pathogenesis, but also whether direct inhibition may play an integral role in its treatment.[1-3]

Mechanism of Action

Both IL-12 and IL-23 bind to the β1 receptor of T cells and natural killer cells via their shared p40 subunit.[1,7] This new class of drugs has been designed to function by binding with high affinity to the p40 subunit, thus preventing its binding at the receptor and the subsequent downstream signaling. Currently, at least 2 drugs exist in this class: the first is CNTO-1275 (ustekinumab), which is being developed by Centocor and ABT-874, which is being developed by Abbott.[1,2] Both drugs, given as subcutaneous injections, are fully human monoclonal antibodies targeting

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the shared p40 subunit of IL-12 and IL-23. An oral version of these drugs was introduced by Synta Pharmaceuticals as STA-5326, but this version failed in Phase II clinical trials for the treatment of psoriasis; it is still being tested for the treatment of rheumatoid arthritis and common variable immunodeficiency.[8]

Advantages of IL-12/IL-23 Inhibitors

Four double-blinded, placebo controlled trials, 3 evaluating CNTO-1275 and 1 evaluating ABT-874, have shown that both drugs are very effective in the treatment of psoriasis. These studies all used 3 universal criteria to delineate an adequate response:

1. Psoriasis Area and Severity Index (PASI), which combines assessments of the extent of body surface involvement and the severity of desquamation, erythema, and plaque induration
2. Physician's Global Assessment (PGA), which rates the patient's psoriasis relative to baseline
3. Dermatology Quality of Life Index (DQLI), which is a 10 item questionnaire to assess the patient's perspective on how psoriasis is affecting his or her own quality of life.

The Four Studies

Krueger et al.[3] evaluated the efficacy of 4 dosing regimens of CNTO-1275:

- one 45mg dose
- one 90mg dose
- 4 weekly 45mg doses
- 4 weekly 90mg doses.

At least 75% improvement from the baseline PASI was seen in more than 50% (54%-81%) of subjects at 12 weeks in all 4 treatment arms. A higher dose of drug correlated with a higher percentage of subjects with a PASI-75 or better. This degree of improvement was seen in only 2% of those who received placebo. With regards to the PGA and DQLI, all active-treatment groups significantly improved when compared with the placebo group.

The PHOENIX 1 and 2 trials[9,10] also evaluated the efficacy of CNTO-1275 by considering 2 treatment arms:

- one 45mg dose at week 0 and week 4, followed by one 45mg dose every 12 weeks
- one 90mg dose in the same dosing schedule.

Both trials illustrated improvement of at least 75% from baseline in more than 50% of both CNTO-1275 arms (66.4% and 63.1% in the 45mg arms, and 66.4% and 72% in the 90mg arms). In the PHOENIX 1 trial, patients who had achieved a satisfactory PASI-75 by weeks 28 or 40 were then rerandomized to a withdrawal vs. maintenance phase. Those who received the maintenance dose did much better than those who were withdrawn.[9] Furthermore, in both PHOENIX trials, after the primary efficacy data was collected at week 12, patients originally allocated to the placebo arm were again randomized into either 45mg or 90mg dosing every 12 weeks. The results of these crossover randomizations paralleled those of the original treatment groups.

Kimball et al.[2] conducted a similar study evaluating the efficacy of 5 dosing regimens of ABT-874:

- one 200mg dose at week 0
- 100mg every other week for 12 weeks
- 200mg weekly for 4 weeks
- 200mg every other week for 12 weeks
- 200mg every week for 12 weeks.

Ninety percent of the patients in the ABT-874 multiple-dose arms exhibited improvement of at least 75% from baseline vs. only 3% in the placebo group.

These studies exhibited a dose-response phenomenon, and response rates declined across all dosages after treatment was discontinued for more than 12 weeks.[3] Additional support for this drug class as a treatment option for psoriasis includes a short response latency and sustainable efficacy. Response time for both drugs was very rapid, measured by PASI-50 at week 2 and PASI-75 by week 4.[2,9,10] The PHOENIX 1 trial continued for a total follow-up time of 76 weeks, and the PHOENIX 2 trial for 52 weeks, illustrating that maintenance dosing every 8-12 weeks ensures a sustained response. This further indicates that IL-12 and IL-23 inhibitors have the potential to provide a treatment regimen that is not only successful but also convenient.[12] Data further showed that maximum effects were reached by week 20, and that response rates had stabilized by week 28. They were successfully maintained throughout the remainder of the study at the dosage frequency of 1 dose (either the 45mg or 90mg originally assigned) every 8-12 weeks.[9,10]

Disadvantages of IL-12/IL-23 Inhibitors

For studies using CNTO-1275, there were no significant differences in adverse events (AEs) between the treatment groups and placebo groups.[3,9,10] However, for ABT-874, Kimball et al.[2] reported a higher percentage of AEs in the treatment group vs. the placebo group.[2]

Patients receiving any dose of ABT-874 were significantly more likely to experience an AE than those in the placebo group, 36.1% vs. 10%, respectively. The AEs in the ABT-874 treated group were most commonly related to reactions at the injection site (erythema, pruritus, and irritation), but also included nasopharyngitis (12.0%) and upper respiratory tract infections (10.7%), followed by bronchitis and viral infection (both 2.7%). The incidences of other AEs were not statistically significantly different in the ABT-874 treatment group compared with placebo-treated patients.

The most commonly encountered AE was infection, which, surprisingly, did not show a significant dose-related trend. One major difference noted between CNTO-1275 and ABT-874 was the rate of AEs at the injection site. Such

events occurred at a much higher frequency with ABT-874. Injection site reactions occurred in 16.7% of patients in the study arms treated with ABT-874[2] vs. only 1.2%-2% in the CNTO-1275 studies.[3,9,10] In all 4 studies the occurrence of adverse injection reactions among the placebo groups was 0%-2%. The development of antibodies to the drugs also remains a concern with these treatments.

Krueger et al.[3] reported AEs in 51 of 64 patients (79%) in the treatment group vs. 46 of 64 patients (72%) in the placebo group (p=0.19). Three of these patients (4%) developed antibodies to CNTO-1275. AEs leading to hospitalizations and discontinuation of treatment occurred in 3 patients in the treatment group vs. 1 in the placebo group (p=0.69). Among the patients in the groups receiving treatment who experienced a serious AE, 2 of them were hospitalized for infections (1 for cellulitis and 1 for pneumonia).

The PHOENIX 1 trial[9] reported AEs in 54% of patients in either treatment arm and in 48% of patients in the placebo arm. Of the patients who were getting CNTO-1275, 5.1% developed antibodies to this formulation. Serious AEs occurred in 1.2% of treatment groups vs. 0.8% in the placebo group.

The PHOENIX 2 trial[10] reported AEs at an equal frequency among the treatment and placebo arms, both measuring in at approximately 50%. Twelve percent of patients developed antibodies to CNTO-1275. For the most part, these antibodies were found to be neutralizing. Serious AEs occurred in 2% of treatment groups vs. 0% in the placebo group.

Prior to the use of IL-12 and IL-23 inhibitors for the treatment of psoriasis, concern arose because of unrelated studies involving people and transgenic mice with IL-12 deficiencies. Populations of people with a congenital deficiency of the IL-12 p40 subunit or the IL-12 receptor were found to have an increased susceptibility to intracellular pathogens, including tuberculosis, *Toxoplasma gondii* and *Leishmania major*, as well as defective delayed type hypersensitivity reactions. Furthermore, IL-12 plays an integral role in immunity against multiple viruses, including herpes simplex virus, vesicular stomatitis virus, and murine aquired immunodeficiency syndrome (MAIDS).[7] These specific concerns have not yet been proven to be an issue in the trials, but due to the tuberculosis concern, an exclusion criterion common to all 4 studies outlined that no person with active disease would be allowed to participate. Ultimately, long-term consequences of IL-12 and IL-23 inhibitor usage beyond 76 weeks have yet to be determined as the clinical trials are very recent.

Various studies involving autoimmune diseases in non-human models have shown that targeting IL-23 alone instead of targeting both may be a better strategy.[1] Specifically, a study by Chan et al. showed that direct intradermal administration into mice of IL-23 alone, but not IL-12 alone, initiates a psoriatic type reaction. This TNF-mediated spectrum of events culminates in erythema, and acanthosis with parakeratosis that is accompanied by a mixed dermal infiltrate.

Another important consideration is the cost of these drugs. Although the exact market cost has not yet been established, biologic agents tend to be very expensive, and IL-12 and IL-23 inhibitors will likely not be an exception to this trend.

Conclusions

IL-12 and IL-23 inhibitors remain on the forefront of treatment options for inflammatory diseases such as psoriasis, Crohn's disease, multiple sclerosis, and rheumatoid arthritis. Although the current data does not provide insight into the long-term effects of these drugs, results have been extremely encouraging. In light of the current research and results, IL-12 and IL-23 inhibitors are a very promising option in the treatment of psoriasis. While the therapeutic effects were shown to have a dose-response relationship, the AEs illustrated no such trend. Furthermore, although the rate of AEs was higher in the ABT-874 treatment groups, these events were reported to be generally tolerable, easily managed, and did not cause a significant percentage of subjects to be discontinued from the study.[2] The current standard of care for psoriasis includes the use of broad spectrum anti-T-cell agents with accompanying immunosuppression,[12] and often necessitates early discontinuation and subsequent psoriatic flares. With the introduction of the IL-12 and IL-23 inhibitors, there is new hope for patients battling psoriasis, as these formulations offer a favorable balance between disease treatment, resolution, tolerable side-effects, and an overall improved quality of life.

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Notice of Inadvertent Duplicate Publication

Skin Therapy Letter announces the recent discovery of an inadvertent duplicate publication. Three articles[1-3] have 1 or more authors in common and content similarities without acknowledgement by or to the article published in Skin Therapy Letter.[1]

The author, Dr. Gilchrest, is one of the few experts who has written and spoken extensively on the subject of vitamin D sufficiency and sun protection. Each of these 3 articles were written independently, and while there is some overlap, each was directed at a different audience and each makes reference to points that were not included in the other 2. The other 2 articles[2,3] were individually transcribed, more or less verbatim, from talks that Dr. Gilchrest gave and were submitted for publication with conference proceedings.

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The Role of Cosmeceuticals in Antiaging Therapy

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ABSTRACT

As baby boomers get older, they have shown an increasing interest in maintaining a youthful appearance. As a result, there has been a corresponding increase in topical antiaging formulations, which are commonly referred to as cosmeceuticals. These products come with a seemingly limitless number of key active ingredients and claims of reducing the signs of aging and/or maintaining a youthful appearance. This paper reviews the more common cosmeceutical ingredients.

Key Words: Cosmeceuticals; alpha hydroxy acids; antioxidants; botanicals; exfoliants; depigmenting agents; moisturizers; retinoids; sunscreens

As baby boomers begin to reach retirement age, there has been an increased interest in antiaging preparations, or cosmeceuticals, and their purported ability to enhance a person's more youthful appearance. Antiaging topicals, with their multiple claims, seemingly limitless key active ingredients, and complex formulations are leading the way in this huge growth industry of cosmeceuticals, especially as this segment of the population opts for less invasive, non-surgical alternatives to slow the effects of aging on the skin. Market trends in the US for cosmeceuticals and antiaging products project sales of more than $16 billion by 2010.[1]

The term cosmeceutical was introduced by Albert Kligman in 1984 to refer to substances that exerted both cosmetic and therapeutic benefits.[2] Many contain biologically active ingredients, and in general, cosmeceuticals undergo tests to determine safety, but claims of efficacy are largely unsubstantiated.[3] Efforts have only recently been initiated to address the issues surrounding quality control and to establish industry standards and regulations. Demonstrating the skin effect of a cosmeceutical can be difficult; there are no placebos because anything that is applied to the skin will have an effect.

This term is not applied to the same products universally (e.g., sunscreen is considered to be an over-the-counter drug in North America, but a cosmeceutical in Europe), and the term "cosmeceutical" is not recognized by the US FDA. Categorization and regulation will depend upon how product claims are presented to the public.

Vehicles

One of the most important parts of any cosmeceutical is the vehicle that carries the active ingredient into the skin.[4] Vehicle delivery systems can:

- augment the efficacy of the active ingredient
- inactivate the active ingredient
- improve the skin barrier
- provoke allergic contact dermatitis.[4]

In some skin conditions, the vehicle may be as good as the active preparation, and it may take 3 months or more to see a difference.

Cosmeceutical Research

There is limited research being done on cosmeceuticals in academic dermatology, and there have been no NIH grants available for cosmeceutical research to date. As a result, the best research comes from industry sponsored studies.

Some Common Types of Cosmeceutical Ingredients

- Alpha Hydroxy Acids
- Antioxidants
- Botanicals
- Depigmenting Agents
- Exfoliants
- Moisturizers
- Peptides
- Retinoids
- Sunscreens

Alpha Hydroxy Acids (AHAs)

Also referred to as fruit acids, they are a common ingredient found in cosmeceutical products. Examples include:

- Citric acid
- Glycolic acid
- Lactic acid
- Malic acid
- Pyruvic acid
- Tartaric acid

AHAs improve skin texture and reduce the signs of aging by promoting cell shedding in the outer layers of the epidermis and by restoring hydration. The mechanism of action is not completely understood. One hypothesis suggests that AHAs reduce the calcium ion concentration in the epidermis and, through chelation, remove the ions from the cell adhesions, which are thereby disrupted, resulting in desquamation. This is enhanced by cleavage of the endogenous stratum corneum chymotryptic enzyme on the cadherins, which are otherwise protected from proteolysis by conjugation with calcium ions. The resulting reduction of the calcium ion levels tends to promote cell growth and slow cell differentiation, thus giving rise to younger looking skin.[5]

Antioxidants

Antioxidants reduce free-radical damage, thereby preventing impairment at the cellular level. They inhibit inflammation, which leads to collagen depletion, and they offer protection against photodamage and skin cancer.

However, there is no completely satisfactory agent available for humans. Explanations for this could include the fact that:

- Reactive oxygen species (ROS) affect different pathways in different situations and an antioxidant focused on 1 such pathway may be ineffective in a redundant pathway.
- ROS pharmacokinetics in the target tissue may not relate to that of the antioxidant.
- Bioavailability and target organ concentration of the antioxidant may be a limiting issue.[6]

Common antioxidants include alpha-lipoic acid (ALA), L-ascorbic acid (vitamin C), niacinamide (vitamin B3), N-acetyl-glucosamine (NAG), α-tocopherol, and ubiquinone (CoQ10).

Alpha-lipoic Acid (ALA)

Alpha-lipoic acid has anti-inflammatory properties and acts as an exfoliant. In a split face study, topical 5% ALA applied b.i.d. for 12 weeks reduced skin roughness, lentigines and fine wrinkles.[7] This agent does not protect against UV-induced erythema or reduce the number of sunburn cells.

L-Ascorbic Acid (Vitamin C)

There is clinical data to support the use of topical vitamin C to improve fine lines and reduce both pigmentation and inflammation,[8] and many cosmeceutical formulations contain this antioxidant. However, many of these formulations are not effective on the skin because:

- the concentration of L-ascorbic acid is too low.
- exposure of the product to air and light compromises the stability of the product.
- the L-ascorbic acid molecule (in the form of an ester or a mixture of isomers) cannot be absorbed or metabolized effectively by the skin.

In high enough concentrations (i.e., at least 10%) of the nonesterified, optimal isomer, this antioxidant does inhibit UV damage.[9] It is important to note that stabilizing ascorbic acid presents many formulary challenges; however, a formulation that has an acid pH of approximately 3.5 may optimize vitamin C absorption.[9] Newer formulations of stabilized ascorbic acid derivatives may prove to be more efficacious.

Niacinamide (Vitamin B3)

Niacinamide is a potent antioxidant that is generally well tolerated. It improves the lipid barrier component of the epidermis, thus reducing transepidermal water loss, and acts as an inhibitor of melanosome transfer, resulting in reduced hyperpigmentation. Studies have revealed significant reduction in fine lines and wrinkles, hyperpigmented spots, red blotchiness, and skin sallowness, as well as improved skin elasticity.[10,11]

N-Acetyl-Glucosamine (NAG)

NAG is a more stable form of glucosamine, and may prevent new signs of photodamage from occurring, and fade existing imperfections by interrupting the chemical signals that promote melanin production. A placebo-controlled study comparing 3.5% NAG with the combination of 3.5% NAG plus 3.5% niacinamide on hyperpigmented spots showed a superior reduction in pigmentation in the combination treatment group vs. both the placebo and NAG only groups. When combined they produced synergistic effects.[12]

α-Tocopherol (Vitamin E)

When taken orally, α-tocopherol protects membrane lipids from peroxidation. It has been shown to reduce sunburn cells after UV exposure, neutralize free radicals, and act as a humectant.[13] Its activity can be renewed by combining it with a vitamin C preparation. As a component in topical formulations, it, like unmodified L-ascorbic acid, has shown some limited efficacy; however, when a stable formulation delivers a high concentration of the nonesterified, optimal isomer of this antioxidant, vitamin E does inhibit the acute UV damage of erythema, sunburn, and tanning, as well as chronic UV photoaging and skin cancer.[9] Because vitamin C regenerates oxidized vitamin E, the combination in a cosmeceutical formulation is synergistic - particularly with regard to UV protection.[9]

Ubiquinone (CoQ10)

Ubiquinone is a naturally occurring, fat-soluble antioxidant and there is good in vitro evidence that it can suppress fibroblast production of UVA-induced collagenase, thereby reducing collagen breakdown.[14] It has been shown to be effective against UVA mediated oxidative stress in human keratinocytes. Ubiquinone was also able to significantly suppress the expression of collagenase in human dermal fibroblasts following UVA irradiation.[15] Another study showed that ubiquinone can strongly inhibit oxidative stress in the skin induced by UVB.[16] It is an effective antioxidant protecting the dermal matrix from both intrinsic and extrinsic aging.[14]

Botanicals

Botanicals comprise the largest category of cosmeceutical additives found in the marketplace today. Their use is unregulated and often unsupported by science and their purported therapeutic properties remain largely unexplored.

Some botanicals that may benefit the skin include: green tea extract, ferulic acid, and grape seed extract.

Green Tea Extract
Research has shown that green tea (*Cammelia sinensis*) polyphenols are potent suppressors of carcinogenic activity from UV radiation and can exert broad protection against other UV-mediated responses, such as sunburn, immunosuppression, and photoaging.[17]

Ferulic Acid
This compound, which is derived from plants, is considered to be a potent antioxidant, and has been shown to provide photoprotection to skin.[17,18] Furthermore, when ferulic acid is combined with vitamins C and E, the product has been shown to provide substantial UV protection for human skin.[19,20] Moreover, Murray et al. report that because its mechanism of action is different from sunscreens, ferulic acid could be expected to supplement the sun protection provided by sunscreens.[20]

Grape Seed Extract
This botanical has been established as a potent antioxidant and has been shown to speed wound contraction and closure.[21] Topical application of grape seed extract has also been shown to enhance the sun protection factor in humans.[22]

Depigmenting Agents
Skin-lightening agents added to product formulations have become increasingly popular. Common depigmenting ingredients include hydroquinone, ascorbic acid (vitamin C), kojic acid, and licorice extract (glabridin).

Hydroquinone
Hydroquinone has been the agent of choice for skin lightening. However, there are concerns over exogenous ochronosis and permanent depigmentation, as well as possible carcinogenicity,[23] and it has been banned as an over-the-counter depigmenting agent in Europe, Australia and Japan.[24] The US FDA has proposed concentrations between 1.5% and 2% in skin lighteners.[25] A recent report suggested that this concern has been based mainly on studies with animal models utilizing long-term exposure at high dosages. Routine topical application may pose no greater risk than that from levels present in common foods.[26]

Ascorbic acid (Vitamin C)
Ascorbic acid is a naturally occurring antioxidant found in citrus fruits and leafy green vegetables. It is hydrophilic, so skin penetration is low.

Kojic acid
Kojic acid is a less commonly used bleaching agent. When combined with dipalmitate, there is improved skin penetration and greater stability, but there is little research to support its efficacy.[27]

Licorice Extract (Glabridin)
Several studies on melasma have shown good efficacy with only mild irritation that disappeared with discontinuation.[25]

Exfoliants
Exfoliants promote skin turnover by removing adherent cells in the stratum corneum. Common exfoliants found in cosmeceutical preparations include salicylic acid (SA), lactic acid, and glycolic acid. There are concerns that repeated use of SA and AHAs could cause the dermis and epidermis to be more vulnerable to penetration by UV radiation. Therefore, patients should be advised to use adequate sun protection. The Cosmetic Ingredient Review Expert Panel concluded that SAs are safe to use when formulated to avoid skin irritation and to be non-photosensitizing, or when directions for use include the daily application of sun protection.[28] Sufficient data is not available to establish a limit on SA concentration or to identify the minimum pH of formulations to inhibit skin irritation.

Moisturizers
Moisturizers restore water content to the epidermis, and provide a soothing protective film. They improve the appearance and tactile properties of dry and aging skin, restore the normal barrier function of the skin, and reduce the release of inflammatory cytokines. Moisturizers comprise an important therapeutic component in the management of various skin conditions (e.g., eczema, psoriasis, pruritus, and aged skin)[29]

Topical Peptides
Topical peptides are regarded as cellular messengers that are formed from amino acids and are designed to mimic peptide fragments with endogenous biologic activity. These pentapeptides (e.g., KTTKS) are comprised of a subfragment of type I collagen propeptide, and play a role in signalling fibroblasts to produce collagen in the skin,[30] which can improve the appearance of wrinkles. One variation, the palmitoyl pentapeptide known as Pal-KKTKS (Matrixyl™, Sederma) was tested in a controlled, double-blind, left-right randomized, split-face study of 93 women between 35 and 55 years of age who had Fitzpatrick I-III type skin. Pal-KTTKS concentration was 3ppm; both groups were treated twice daily for 12 weeks. Improvements in wrinkle appearance and length were observed.[31]

Retinoids
Retinoids are among the most common ingredients found in cosmeceuticals. In fact, they are the most studied and have the most data behind them. They consist of natural and synthetic derivatives of vitamin A that reduce hyperpigmentation and inhibit enzymes from breaking down collagen. Many of their cosmeceutical claims are based on data derived from

studies on tretinoin and other classes of retinoid drugs. Some key retinoids include retinoic acid (tretinoin), retinol, retinaldehyde.

Retinoic Acid (Tretinoin)

There is extensive literature on the use of tretinoin, which is considered to be one of the most potent compounds for treating the signs of aging and/or photodamaged skin, including fine lines, hyperpigmented spots, and wrinkles.[32-34] However, side-effects such as burning and scaling have limited its acceptance. In order to minimize these side-effects, various novel drug delivery systems are being developed.[34]

Retinol (Vitamin A)

Retinol is oxidized into retinaldehyde and then into retinoic acid, the biologically active form of vitamin A. *In vivo* studies showed that topical retinol had only a modest retinoid-like biologic activity compared with topical retinaldehyde and retinoic acid.[32] Two randomized, controlled trials reported significant improvement in fine wrinkles after 12 and 24 weeks of treatment, respectively.[35,36]

Retinaldehyde

Retinaldehyde is viewed in a large part as an intermediate form during the conversion of retinol to retinoic acid. Studies have shown that it does have activity in human skin.[33] Moreover, some studies have reported that this retinoid can produce significant clinical improvement in the appearance of fine and deep wrinkles.[32,37]

Sunscreens

Sunscreens are the single most important cosmeceutical, because they protect skin against solar radiation, which is the most important damaging environmental agent. As a result, they help to prevent the signs of aging. To be effective, sunscreens should provide broad spectrum coverage that includes both UVA and UVB blocking agents to inhibit photoaging and be part of a daily skin care regimen. Sunscreens contain active ingredients that act as ultraviolet filters. The recommended application is 2mg/cm^2, though this is rarely achieved in real-life practice.[38] Labeling changes proposed by the US FDA on sunscreen products are forthcoming.[39]

Formulation Considerations and Conclusions

Although some product claims for the active ingredients used in cosmeceutical formulations are evidence-based, consumers often place their confidence in the claims made by the manufacturer. Without testing to assess the efficacy of key active ingredients in relation to overall product content, it is possible that at inadequate concentrations, any beneficial effect will become inapparent. Ensuring consistency of formulations is also an area that has been neglected and necessitates regulation.

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Update on Drugs

Name/Company	Approval Dates/Comments
Bimatoprost Ophthalmic Solution 0.03% *Lumigan*® Allergan, Inc.	The US FDA will be receiving a new drug application for this synthetic prostaglandin analog by the end of 2008 for a new indication. Bimatoprost is currently indicated for the reduction of elevated intraocular pressure in patients with glaucoma or ocular hypertension. In clinical studies, patients reported significant eyelash growth when the drug was applied directly to the eyelash bases. FDA approval is anticipated in 2009.
Ustekinumab (CNTO-1275) Centocor	The US FDA extended the review timeline for the Biologic License Application for this subcutaneous biologic therapy by 3 months to December 2008 in order to provide additional time to review amendments to the application. This application seeks marketing approval for the treatment of adult patients with chronic moderate-to-severe plaque psoriasis. Ustekinumab is also under review by the European Medicines Agency (EMEA).
p53 tumor suppressor therapy *ADVEXIN*® Introgen Therapeutics	The EMEA accepted for review a Marketing Authorization Application in August 2008 for this p53 tumor suppressor therapy for the treatment of recurrent, refractory squamous cell carcinoma of the head and neck. If approved, this will be the first gene therapy product approved for use in Europe.
Shingles Vaccine *Zostavax*® Merck Frosst	Health Canada approved this vaccine in August 2008 for the prevention of shingles in individuals aged 60 years or older. This vaccine is expected to become available sometime in 2009.
Calcipotriene 0.005% + betamethasone dipropionate 0.064% *Xamiol*® *Gel* LEO Pharma	The EMEA approved this gel in August 2008 for the treatment of scalp psoriasis. The gel is expected to become available in Europe by late 2008.
Etanercept *Enbrel*® Wyeth	The EMEA approved this product in a 50mg once weekly dosage regimen as an alternative to the currently approved etanercept 25mg twice weekly regimen for the treatment of patients with moderate-to-severe plaque psoriasis.

Drug News

The US FDA announced in September 2008 that the manufacturers of Humira® (adalimumab, Abbott Laboratories), Cimzia® (certolizumab pegol, UCB), Enbrel® (etanercept, Amgen-Wyeth), and Remicade® (infliximab, Centocor) must strengthen the existing warnings in the Warnings and Precaution sections of each drug's Prescribing Information and Medication Guide to include information about the risk of developing opportunistic fungal infections. Based on reports reviewed by the US FDA, health care professionals are not consistently recognizing cases of histoplasmosis and other invasive fungal infections, leading to delays in treatment and as a result, some patients with invasive fungal infections have died. These drugs are known as tumor necrosis factor-α blockers and are approved to treat a variety of conditions, which may include rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, plaque psoriasis, ankylosing spondylitis, and Crohn's disease.

In a small study published in a recent issue of the British Journal of Dermatology*, Perrett et al. found that azathioprine treatment was associated with an increase in ultraviolet A and solar-stimulated radiation sensitivity and a significant reduction in the minimal erythema dose. In addition, they also found that DNA from the skin of these patients contained 6-thioguanine, which supports the hypothesis that DNA 6-thioguanine interacts with UVA, resulting in abnormal cutaneous photosensitivity.
* Perrett CM, et al. *Br J Dermatol* 159:198-204 (2008).