

## Interleukin-23 in the Pathogenesis and Treatment of Psoriasis

Ramya Kollipara, MD<sup>1</sup>; Christopher Downing, MD<sup>1</sup>; Rachel Gordon, MD<sup>2</sup>; Stephen Tyring, MD, PhD<sup>1</sup>

<sup>1</sup>Center for Clinical Studies, Houston, TX, USA

<sup>2</sup>Department of Dermatology, University of Texas Health Science Center at Houston, Houston, TX, USA

### ABSTRACT

*In the past three decades, major advances have been made in understanding the pathogenesis of psoriasis. The currently accepted theory is that T-cell mediated immune dysregulation triggers keratinocyte hyperproliferation in psoriasis. Recent research indicates that the Th17/interleukin (IL)-23 pathway plays a prominent role in the amplification phase of psoriasis. The discovery of the Th17/IL-23 pathway provides targets for new drug development. This review focuses on the role of IL-23 in psoriasis pathogenesis and the current therapies targeting IL-23 that are in clinical trials.*

**Key words:** cytokine, interleukin-23, IL-23, guselkumab, tildrakizumab, Th17, psoriasis

### Introduction

In the past three decades, major strides have been made in understanding the pathogenesis of psoriasis. While psoriasis pathogenesis originally focused on keratinocyte hyperproliferation, the currently accepted theory is that of T-cell mediated immune dysregulation.<sup>1,2</sup> While the T helper cell (Th) 1/interferon-gamma (IFN- $\gamma$ ) pathway was originally heavily implicated in the amplification phase, recent research indicates that the Th17/interleukin (IL)-23 pathway plays the more dominant role.<sup>3</sup> This review focuses on the role of IL-23 in psoriasis pathogenesis and the current therapies targeting IL-23 that are in clinical trials.

### IL-23

IL-23 is composed of two subunits, p19 and p40, which are linked by a disulfide bond. The p19 subunit is a unique component of IL-23. Alternatively, the p40 subunit is a component of IL-12 as well.<sup>4</sup> IL-23 is produced by keratinocytes and activated antigen-presenting cells (APCs), specifically Langerhans cells, macrophages and dendritic cells. IL-23 is expressed by APCs in the presence of Toll-like receptor (TLR) agonists (lipopolysaccharide, CpG and PolyI:C).<sup>5</sup> The IL-23 receptor is present on memory T cells, natural killer (NK) T cells, macrophages, dendritic cells and naïve T cells.<sup>6</sup>

IL-23 is the key cytokine that propels naïve T cell differentiation to Th17 cells.<sup>6</sup> It is essential in bridging the innate and adaptive immune responses and orchestrating the early local immune response. When IL-23 binds to the IL-23 receptor, the complex activates Jak2 and Tyk, members of the Janus family of tyrosine kinases, leading to phosphorylation of the receptor complex and eventually phosphorylation of signal transducer and activator

of transcription 3 (STAT3). STAT3 phosphorylation triggers differentiation to Th17 cells.<sup>7</sup> Transforming growth factor-beta (TGF- $\beta$ ), IL-6, IL-1 $\beta$  and IL-21 are also needed to coordinate production of Th17 cells.<sup>8</sup> However, IL-23 appears to be the main cytokine in this process as studies have shown that IL-6, IL-1 and TGF- $\beta$  in the absence of IL-23 result in production of regulatory T cells that inhibit inflammation.<sup>9</sup>

### The Th17/IL-23 Pathway in the Immunopathogenesis of Psoriasis

In considering the pathophysiology of psoriasis, it can be divided into two distinct immune-mediated phases: the initial and amplification phases.<sup>5</sup> In the initial phase, trauma to keratinocytes or stimulation of TLR receptors in genetically predisposed skin leads to activation of the innate immune system. This cataclysm of macrophages, dendritic cells and diverse cytokines triggers the production of IL-12 and IL-23. These two cytokines provide the bridge to the amplification phase, which is characterized by the adaptive immune response.<sup>5</sup> The intricacies of this amplification have been the source of much debate over the last three decades, specifically in regards to which Th pathway drives this phase.

In the 1990s, clinical studies demonstrated elevated levels of the p40 subunit in psoriatic lesions. At the time, the high expression of p40 was correlated to elevated levels of IL-12 (a component of the Th1 pathway) because IL-23 had not yet been discovered.<sup>10</sup> This theory further propagated the theory that the Th1 pathway is key in orchestrating the amplification phase of psoriasis. However, recent evidence has revealed that the elevated p40 level in psoriasis is due to IL-23, not IL-12. In a study done by Lee and colleagues, p40 and p19 mRNA were elevated in psoriatic lesions, but p35 mRNA, which is specific to IL-12, was not increased in

lesional skin.<sup>3</sup> Another study highlighted the presence of IL-23-staining cells in palmoplantar pustulosis, hyperkeratotic hand dermatitis and lesional psoriasis biopsies. Furthermore, IL-23 levels in psoriatic skin appear to correspond with the clinical course of the patient.<sup>11</sup> IL-23 injections in mice skin have also induced histological changes seen in psoriatic skin, specifically epidermal acanthosis and parakeratosis. IL-12 injections did not have the same effect.<sup>12</sup> Finally, many genetic studies in psoriasis patients have demonstrated a strong association with genetic loci encoding the IL-23 p19 subunit and IL-12/23 p40 subunit, but not the IL-12 p35 subunit.<sup>13,14</sup> Taken together, this data points to the prevailing role of the Th17/IL-23 pathway in psoriatic disease.

The Th17/IL-23 pathway promotes chronic inflammation. Th17 cells secrete two IL-17 cytokines, IL-17A and IL-F, and also IL-21, IL-22, IL-26 and IFN- $\gamma$ . All of these cytokines activate the inflammatory cascade and provoke irregular cellular replication and maturation in psoriasis.<sup>15</sup> IL-17A is a potent pro-inflammatory cytokine that triggers keratinocyte production of pro-neutrophilic chemokines, including CXCL1, CXCL5, and CXCL8. These chemokines orchestrate neutrophilic migration into psoriatic lesions, which stimulates keratinocyte proliferation.<sup>16</sup> IL-17 also inhibits neutrophil apoptosis, stimulates angiogenesis, augments tissue remodeling and synergistically with tumor necrosis factor-alpha enhances inflammation.<sup>17</sup> IL-22 causes keratinocyte hyperproliferation and increases keratinocyte production of antimicrobial proteins. It is because of these antimicrobial proteins that psoriatic skin lesions are rarely infected.<sup>17</sup> Both IL-17A and IL-22 have also been found to stimulate keratinocyte production of CCL20, a chemokine overproduced in psoriasis. It is hypothesized that CCL20 promotes maintenance of psoriatic lesions by enhancing chemotaxis of CCR6+ Th17 and dendritic cells to diseased skin.<sup>18</sup>

Although there is convincing data about the significant role the Th17/IL-23 pathway plays in late-stage psoriasis, there remain many questions. It is still unclear why IL-23 is preferentially produced in psoriatic skin. Is it a genetic predisposition or a dysregulation of the innate immune response? Furthermore, it is unclear what the specific antigen is that dendritic cells present to antigen-specific Th17 cells. Hypotheses have ranged from an external antigen to an autoantigen.<sup>17</sup>

### Psoriasis Therapies Targeting IL-23

Given the initial discovery of elevated p40 levels in psoriatic skin, novel biologics, specifically ustekinumab and briakinumab, were developed to target this p40 subunit. These agents target the p40 subunit of IL-12 and IL-23 and, thus, both the IL-12/Th1 and Th17/IL-23 pathways.<sup>10</sup> Despite the efficacy and favorable safety profile of ustekinumab, drug development has moved towards solely targeting the IL-23/Th1 pathway given its dominant role in psoriatic disease and the theoretical risk of blocking the IL-12/Th1 pathway.

#### Tildrakizumab

Tildrakizumab, alternatively known as MK-3222 or SCH900222, is a human immunoglobulin G1 (IgG1) monoclonal antibody that targets only the p19 portion of IL-23. Since tildrakizumab does not target the p40 subunit of IL-23, it does not affect IL-12 activity.<sup>19</sup>

The results of a Phase IIb randomized, controlled, dose-ranging study for tildrakizumab were presented at the American Academy of Dermatology 71st Annual Meeting in March 2013. In this study, 335 patients with moderate to severe plaque psoriasis were randomized to receive tildrakizumab 5 mg, 25 mg, 100 mg, 200 mg or placebo at weeks 0, 4, and then every 12 weeks for 52 weeks. The primary endpoint, PASI-75 at week 16, was attained by 33%, 64%, 66%, 74%, and 4% of the 5 mg, 25 mg, 100 mg, 200 mg, and placebo groups respectively. The secondary endpoint, achieving a physician global assessment (PGA) of “clear” or “minimal” at week 16, was achieved by 33%, 58%, 62%, 74%, and 2% of the 5 mg, 25 mg, 100 mg, 200 mg, and placebo groups respectively. The adverse event rate in the treatment groups ranged from 60% to 71% compared to 69% in the placebo group. The most common adverse event was nasopharyngitis. Serious adverse events (including one death) were rare, occurring in only four patients. None of the serious adverse events were linked to tildrakizumab.<sup>19,20</sup>

Of note, data from the proof of concept study demonstrated that 18% of patients treated with three doses of tildrakizumab developed antidrug antibodies. Of these patients with antibodies, 55% had decreased serum drug levels in contrast to patients without antidrug antibodies. However, patients with antidrug antibodies still attained PASI improvement comparable to patients without antidrug antibodies. Similarly, the safety profile did not differ either.<sup>21</sup>

Tildrakizumab is the first anti-IL-23 therapy for psoriasis to enter Phase III trials. There are currently two Phase III trials underway. The projected date for final collection of primary outcome data is June or July 2015 for both trials. This data has yet to be published. The study completion date for both studies is 2019.<sup>21,22</sup>

#### Guselkumab

Guselkumab, or CNTO 1959, is a humanized IgG1 monoclonal antibody that targets the p19 subunit of IL-23.<sup>23</sup>

The results of X-PLORE, a Phase IIb randomized, controlled, dose-ranging study for guselkumab, were presented at the American Academy of Dermatology 72nd Annual Meeting in March 2014. In this study, patients with moderate to severe plaque psoriasis were randomized to receive either guselkumab 5 mg, 15 mg, 50 mg, 100 mg or 200 mg, placebo or adalimumab. The guselkumab was given at weeks 0, 4 and then every 12 weeks. The patients in the adalimumab group received an initial dose of 80 mg and then 40 mg every other week (starting one week after the initial dose). The primary endpoint, patients achieving a PGA of “clear” or “minimal” at week 16, was met by 34%, 61%, 79%, 86%, 83%, and 7% of patients in the guselkumab 5 mg, 50 mg, 15 mg, 100 mg, 200 mg, and placebo groups respectively. At week 16, PASI-75 was achieved by 44%, 76%, 81%, 79%, 81%, and 5% of the patients receiving guselkumab 5 mg, 15 mg, 50 mg, 100 mg, 200 mg, and placebo respectively. PASI 90 was achieved by 34%, 34%, 45%, 62%, 57%, and 2% of guselkumab 5 mg, 15 mg, 50 mg, 100 mg, 200 mg, and placebo-treated patients respectively. Comparatively, in the adalimumab group, 58%, 70%, and 44% of patients attained a PGA of “clear” or “minimal”, PASI-75 and PASI-90 respectively at week 16. At week 52, adverse events occurred in 66% of patients treated with guselkumab. Serious adverse events were experienced by 3% of guselkumab-

treated patients. Three patients had either a myocardial infarction or cerebrovascular accident but these were not linked to guselkumab treatment. No serious or opportunistic infections occurred in patients on guselkumab. One patient on guselkumab reported a malignancy (cervical cancer).<sup>24</sup>

Based on the above promising Phase II results, Phase III trials to further assess the efficacy of guselkumab are planned.<sup>25-27</sup> Currently, there is a Phase II trial evaluating guselkumab for palmoplantar pustulosis as well as a Phase I trial to evaluate the pharmacokinetics of guselkumab in lyophilized versus liquid formulations.<sup>28,29</sup> The estimated primary completion date for the palmoplantar pustulosis study is August 2014.<sup>28</sup>

### Other Drugs Targeting IL-23 in the Pipeline

BI655066, manufactured by Boehringer Ingelheim Pharmaceuticals, is another drug targeting IL-23 that is currently in Phase II trials for psoriasis.<sup>30</sup> It is a human IgG1 monoclonal antibody. MP-196, another monoclonal antibody targeting IL-23, is manufactured by TcL Pharma and is in pre-clinical development for psoriasis. Finally, there are several IL-23 receptor antagonists that have been patented but not tested in pre-clinical or clinical trials. Neutralization of the IL-23 receptor is a promising approach for psoriasis management as the IL-23 is only present on developing Th17 cells. Thus, blocking the IL-23 receptor can prevent activation of STAT3 and naïve T cell differentiation to a Th-17 cell.<sup>5</sup>

### Conclusion

The discovery of the Th17/IL-23 pathway adds to the complexity of psoriasis pathogenesis and provides targets for new drug development. Not only are there upstream IL-23 p19 and IL-23 receptor neutralizing drugs in development, there are currently also downstream IL-17 antagonists in trials as well. Although these drugs are still years away from being FDA approved, they offer promise of more targeted, efficacious and safe psoriasis therapy in the future.

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# Male Aesthetics

Terrence Keaney, MD

Washington Institute of Dermatologic Laser Surgery, Washington, DC, USA

## ABSTRACT

*Men are a fast growing segment of the aesthetic industry. A review was performed for publications on gender differences in facial anatomy, behavior, and the use of minimally invasive aesthetic procedures in men. There are substantial facial anatomical differences between genders with men having a larger but unique cranial shape, increased skeletal muscle mass, unique subcutaneous fat distribution, and more severe facial rhytides. Men also exhibit poor behavior that can accelerate aging including poor utilization of preventive health care services, higher rates of smoking, and increased ultraviolet light exposure. Despite gender differences in facial anatomy and behavior, few studies have examined the role of gender in cosmetic procedures. Men require a unique injection technique with botulinum toxin and dermal fillers due to differences in facial anatomy.*

**Key words:** administration and dosage, anatomy, botulinum toxins type A, cosmetic techniques, dermal fillers, face, gender differences, male, neuromuscular agents, skin aging

## Introduction

Men are a fast growing segment of the cosmetic surgery population, representing 9% of all cosmetic procedures in 2012. More than one million minimally invasive procedures were performed in men, an 8% increase from 2011.<sup>1</sup> Despite the increased demand, the scientific community has largely ignored men. The study of beauty and aging typically focuses on the female face. Successful cosmetic treatment of men requires physicians to recognize the gender differences in anatomy, skin biology, skin aging, behavior and rejuvenation goals. The importance of understanding all gender differences is critical in providing a successful cosmetic outcome.

## Discussion

### Biologic Differences

Gender anatomical differences are wide ranging and are reflected in the differences in external genitalia, greater musculature and a larger skeletal anatomy of males relative to females.<sup>2</sup> Sexual dimorphism in facial anatomy and cutaneous physiology is well documented, yet these differences are rarely accounted for in clinical practice.<sup>3</sup>

Male skin is thicker at all ages with the extent varying with anatomical region.<sup>4</sup> Male cutaneous appendages also show greater activity with men having an increase in sebum and sweat production. There are significant differences in hair distribution because the growth of sexual hair is dependent on androgens. Androgens convert small, straight, nonpigmented vellus hairs into coarse, pigmented, terminal hairs. Androgen-dependent areas include the chin, upper lip, chest, breasts, abdomen, back, and anterior thighs.

Subcutaneous structures are important to consider when evaluating a male cosmetic patient. The male skull is not only unique in its overall larger size,<sup>5</sup> but also in its unique shape. Men tend to have a large forehead with prominent supraorbital ridges,<sup>6</sup> wide glabella,<sup>7</sup> square orbit and a prominent protruding

mandible. Men have increased skeletal muscle mass<sup>8</sup> including facial masticatory muscles.<sup>9</sup> Men also have a highly vascularized face due to the vascular plexus supporting the beard hairs.<sup>10</sup> The greater density of facial vasculature may make men more prone to develop bruising with injectables, particularly in the lower face.

The subcutaneous adipose layer is thinner in men irrespective of age, but men have higher rates of visceral abdominal adipose.<sup>11</sup> The facial subcutaneous fat also exhibits sexual dimorphism. Facial soft-tissue assessments by using three-dimensional (3D) reconstructed models have demonstrated that men have less soft tissue in the cheek area.<sup>12,13</sup> Women have 3 mm more subcutaneous tissue in the medial malar area when compared with men.<sup>14</sup> Clinically, this difference corresponds to flatter, more angular cheeks in men.

### Male Aging

The anatomical variations between genders result in differences in aging. The aging male face is unique and must be approached and treated differently. Men have more severe facial rhytides except in the perioral area.<sup>15,16</sup> The loss of subcutaneous adipose with age results in deeper expression lines in men because of the thicker skin and more prominent facial musculature, as opposed to the superficial rhytides that women tend to develop. The prominent volume loss makes men appear older than their age when compared to women.<sup>17</sup>

### Behavioral Differences

It is important that physicians do not overlook the behavioral differences, which also need to be acknowledged when evaluating male aesthetic patients. Men are generally poor consumers of health care and dermatology services. Men consistently underutilize preventive health care services compared with women, regardless of income or ethnicity even when reproductive services are accounted for.<sup>18</sup> In regards to their cutaneous health, men are less likely to see a dermatologist, participate in a skin cancer screening, or perform self-skin exams.

Extrinsic aging factors range from exposure to sunlight, pollution, cigarette smoke, repetitive muscle movements, and diet.<sup>19</sup> The two greatest extrinsic aging factors are smoking and exposure to ultraviolet (UV) light.<sup>20</sup> Men smoke more often, increasing their risk for cutaneous aging. In 2012, the worldwide prevalence of smoking in men was 31.1% and 10.6% in women.<sup>21</sup> Smoking is an independent risk factor for the development of elastosis among both men and women, although smoking was strongly associated with men given their higher incidence of smoking.

Not only are men more likely to smoke, but they are more likely to be exposed to UV radiation. The highly gendered nature of employment results in men being more likely to be employed in outdoor occupations resulting in greater UV light exposure.<sup>22</sup> When men are in the sunlight, they are less likely to adopt sun protective behaviors.<sup>23</sup> Men use sunscreen less frequently than women.<sup>24</sup> One study found that 41% of men never apply sunscreen.<sup>25</sup> While females are more likely to sunbathe and indoor tan more frequently than males, men are more likely to develop sunburns.<sup>26</sup>

### Aesthetic Procedures in Men

Injectable botulinum toxin type A and dermal fillers are the main drivers of any cosmetic dermatology practice. Injection technique varies in male patients due to differences in anatomy and patient goals. Success in using dermal fillers and botulinum toxin in men requires a balancing act between masculinizing and feminizing the face, as excessive use of either may result in an undesired cosmetic outcome.

Treatment with botulinum toxin is the single most common cosmetic procedure performed in men.<sup>1</sup> Given the anatomic differences, botulinum toxin injections should be tailored to the male face. When treating the frontalis muscle, a flat injection technique is recommended to minimize brow arching and maintain the normal flat male eyebrow position. The lateral aspect of the frontalis also must be treated in order to avoid lateral frontalis contraction leading to arching of the eyebrows. Extra caution is required when treating the inferior portion of the frontalis muscle. Because eyebrow ptosis occurs when the eyebrow falls significantly below the orbital rim, there is not much room for error in men given their naturally low eyebrow position. More injections may be required to ensure complete and balanced treatment of the frontalis muscle due to the larger surface area of the male forehead. Careful inspection and treatment of the superior frontalis muscle in men with androgenic alopecia and high hairlines are needed to avoid unnatural movement in the areas of alopecia. When treating the lower face in men, the perioral area is not a common injection site due to the relative lack of perioral rhytides. Caution is advised in the treatment of masseter hypertrophy in male patients to ensure that a true muscular hypertrophy exists (rather than normal lateral flaring of the mandible).

Despite gender differences in facial anatomy, the use of botulinum toxin in men is inadequately studied with regards to dosing, efficacy and safety. A review on the use of botulinum toxin in men found only two studies that accounted for gender in either the study design or subgroup analysis and only one dose-ranging study.<sup>27</sup> The studies that accounted for gender in their study

design found abobotulinumtoxinA (Dysport®) to be less effective in men compared with women at similar doses. The dose ranging study suggested that higher doses of onabotulinumtoxinA (Botox®) were more efficacious in treatment of the male glabella. Although there are no studies examining the use of botulinum toxin elsewhere in the male face, this data suggests that men require a higher total dose.

Dermal fillers can be very useful in male patients who struggle with volume loss given their relative lack of subcutaneous fat. Volume replacement with dermal fillers carries the risk of feminization. Mid face augmentation should account for the male cheek anatomy. Fillers should be injected laterally along the zygomatic arch, carefully avoiding too much volume in the anterior and medial cheeks. In contrast to women, for whom lip augmentation is a leading use of fillers, the upper lip is generally avoided in men due to the risk of feminizing.

### Conclusion

Men may represent a small proportion of cosmetic patients, but they are a growing segment of the cosmetic industry. Males are an untapped patient population that could serve as an area for growth in aesthetic practices. As the number of male patients seeking treatment increase, physicians need to account for gender when evaluating and treating a cosmetic patient. It would also behoove the medical community to expand our understanding of the male face and its appropriate treatment with minimally invasive cosmetic procedures.

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# Skin Treatments Introduced in 2014

Type/Class of Therapy	Generic/Trade/ Company Names	Indication	Approving Regulatory Agency
Anti-acne Agents	<b>Clindamycin phosphate 1.2% + benzoyl peroxide 3.75% gel</b> <i>Onexton</i> <sup>™</sup> Valeant Pharmaceuticals	Approval was granted to this once-daily topical treatment of comedonal (noninflammatory) and inflammatory acne. This fixed combination of a lincosamide antibacterial agent and an antimicrobial is indicated for the treatment of acne vulgaris in patients ≥12 years of age.	US FDA
	<b>Doxycycline hyclate tablets</b> <i>Acticlate</i> <sup>™</sup> Aqua Pharmaceuticals Almirall	This tetracycline-class antimicrobial agent was approved for treating a number of infections including adjunctive therapy in severe acne. Several dosing options are available with film-coated round 75 mg tablets and oval-shaped dual-scored 150 mg tablets.	US FDA
	<b>Tretinoin gel microsphere 0.08%</b> <i>Retin-A Micro</i> <sup>®</sup> Valeant Pharmaceuticals	Approval of a Supplemental New Drug Application (sNDA) was granted for Retin-A Micro <sup>®</sup> gel microsphere 0.08% for the topical treatment of acne vulgaris. Retin-A Micro <sup>®</sup> gel is already available in 0.04% and 0.1% strengths.	US FDA
Antibacterial Agents	<b>Dalbavancin IV injection</b> <i>Dalvance</i> <sup>™</sup> Durata Therapeutics	Dalbavancin, a novel second generation lipoglycopeptide antibiotic, was approved for the treatment of adults with skin infections. Treatment is indicated for acute bacterial skin and skin structure infections (ABSSSI) caused by designated susceptible strains of Gram-positive microorganisms, such as <i>Staphylococcus aureus</i> (including methicillin-susceptible and methicillin resistant strains) and <i>Streptococcus pyogenes</i> .	US FDA
	<b>Oritavancin IV infusion</b> <i>Orbactiv</i> <sup>™</sup> The Medicines Company	Approval was granted for this novel semi-synthetic glycopeptide antibiotic for treating adults with ABSSSI caused by certain susceptible bacteria, including <i>Staphylococcus aureus</i> (including methicillin-susceptible and methicillin resistant strains), various <i>Streptococcus</i> species and <i>Enterococcus faecalis</i> .	US FDA
	<b>Tedizolid phosphate tablets &amp; IV injection</b> <i>Sivextro</i> <sup>™</sup> Cubist Pharmaceuticals	Tedizolid, a novel oxazolidinone-class antibacterial agent, was approved for the treatment of adult ABSSSI caused by susceptible Gram-positive bacteria, including methicillin-resistant <i>Staphylococcus aureus</i> (MRSA).	US FDA
	<b>Metronidazole 1.3% vaginal gel</b> Actavis plc Valeant Pharmaceuticals	A New Drug Application (NDA) for metronidazole 1.3% vaginal gel, a nitroimidazole antibiotic, was approved for the treatment of bacterial vaginosis (BV) in non-pregnant women. This preparation of metronidazole offers a convenient single-dose treatment for BV that is packaged in a pre-filled disposable applicator.	US FDA
Antifungal Agents	<b>Efinaconazole 10% topical solution</b> <i>Jublia</i> <sup>®</sup> Valeant Pharmaceuticals	Approval was granted to this antifungal compound for the treatment of mild to moderate onychomycosis. It is the first topical triazole antifungal agent developed for distal lateral subungual onychomycosis (DLSO).	US FDA
	<b>Naftifine HCl 2% gel &amp; cream</b> <i>Naftin</i> <sup>®</sup> Merz Dermatology	Naftin <sup>®</sup> (naftifine HCl) 2% gel and cream formulations received approval for the treatment of interdigital type tinea pedis in pediatric patients aged 12-17 years. This pediatric approval expands the previous labelling that indicated use in patients >18 years of age.	US FDA
	<b>Tavaborole 5% topical solution</b> <i>Kerydin</i> <sup>™</sup> Anacor Pharmaceuticals	Tavaborole, the first oxaborole antifungal agent, was approved for the topical treatment of onychomycosis of the toenails caused by <i>Trichophyton rubrum</i> or <i>Trichophyton mentagrophytes</i> . This clear, colorless, alcohol-based solution is applied with a dropper to the infected toenail once daily for 48 weeks.	US FDA



Antiparasitic Agent	<b>Miltefosine capsules</b> <i>Impavido</i> <sup>®</sup> Paladin Labs Inc. Knight Therapeutics Inc.	Approval was granted to this oral alkylphosphocholine antiparasitic agent for the treatment of three main types of leishmaniasis: visceral leishmaniasis (affects internal organs), cutaneous leishmaniasis (affects the skin) and mucosal leishmaniasis (affects the nose and throat). It is intended for use in patients ≥12 years of age. <i>Impavido</i> <sup>®</sup> is the first FDA-approved drug to treat cutaneous or mucosal leishmaniasis.	US FDA
Antiviral Agent	<b>Human papillomavirus 9-valent vaccine, recombinant</b> <i>Gardasil</i> <sup>®9</sup> Merck	This 9-valent human papillomavirus (HPV) vaccine was approved for use in girls and young women 9-26 years of age for the prevention of cervical, vulvar, vaginal, and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52 and 58, pre-cancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, and genital warts caused by HPV types 6 and 11. <i>Gardasil</i> <sup>®9</sup> is also approved for use in boys 9-15 years of age for the prevention of anal cancer caused by HPV types 16, 18, 31, 33, 45, 52 and 58, precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, and genital warts caused by HPV types 6 and 11. <i>Gardasil</i> <sup>®9</sup> includes the greatest number of HPV types in any available HPV vaccine.	US FDA
Dermal Filler	<b>Hyaluronic acid-based dermal filler</b> <i>Restylane</i> <sup>®</sup> <i>Silk</i> Valeant Pharmaceuticals (In July 2014, all rights to <i>Restylane</i> <sup>®</sup> were sold by Valeant to Galderma)	Marketing clearance was granted for <i>Restylane</i> <sup>®</sup> <i>Silk</i> injectable gel with 0.3% lidocaine, a device indicated for submucosal implantation for lip augmentation and dermal implantation for the correction of perioral rhytids in patients >21 years of age.	US FDA
Dupuytren's Contracture	<b>Collagenase clostridium histolyticum for injection</b> <i>Xiaflex</i> <sup>®</sup> Auxilium Pharmaceuticals BioSpecifics	A supplemental Biologics License Application (sBLA) was approved for this novel, first-in-class biologic for the treatment of up to two Dupuytren's contracture cords in the same hand during a single treatment visit. <i>Xiaflex</i> <sup>®</sup> obtained FDA approval in 2010 as the first and only nonsurgical treatment for adult Dupuytren's contracture patients with a palpable cord in the palm.	US FDA
Hemangioma	<b>Propranolol hydrochloride oral solution</b> <i>Hemangeol</i> <sup>™</sup> Pierre Fabre Dermatologie	The first and only beta-blocker formulation was approved for the treatment of proliferating infantile hemangioma requiring systemic therapy. <i>Hemangeol</i> <sup>™</sup> , specifically developed for use in pediatric patients, was studied in infants aged 5 weeks to 5 months (at therapy initiation). The treatment protocol of 3 mg/kg/day for 6 months demonstrated a 60.4% success rate vs. 3.6% in the placebo group, achieving the primary endpoint of complete or nearly-complete resolution.	US FDA
Hereditary Angioedema	<b>C1 esterase inhibitor IV infusion</b> <i>Ruconest</i> <sup>®</sup> Pharming Group NV Salix Pharmaceuticals	The first recombinant human C1 esterase inhibitor was approved for the treatment of acute angioedema attacks in adult and adolescent patients with acute hereditary angioedema (HAE).	US FDA
	<b>Ecallantide SC injection</b> <i>Kalbitor</i> <sup>®</sup> Dyax Corp.	Ecallantide, a peptide inhibitor of plasma kallikrein, was approved for the treatment of HAE attacks. This drug is the first and only subcutaneous therapy available to treat acute attacks of HAE in patients ≥12 years of age.	US FDA
	<b>Icatibant SC injection</b> <i>Firazyr</i> <sup>®</sup> Shire Canada	A Notice of Compliance was issued for icatibant acetate ready-to-use injection for the treatment of acute attacks of HAE in adults with C1-esterase inhibitor deficiency via blockade of bradykinin at the bradykinin B2 receptor.	Health Canada

Melanoma	<b>Trametinib tablet + Dabrafenib capsule</b> <i>Mekinist® + Tafinlar®</i> GlaxoSmithKline plc	Accelerated approval was granted to trametinib in combination with dabrafenib for the treatment of patients with unresectable or metastatic melanoma with BRAF V600E or V600K mutations. These mutations must be detected by the FDA-approved THxID™ BRAF test. Approval of the combination therapy is based on the demonstration of response rate and median duration of response in a multicenter, open-label, randomized, active-controlled, dose-ranging Phase 1/2 trial, which compared combination trametinib and dabrafenib to dabrafenib monotherapy. The overall response rate was 76% (95% confidence interval [CI]; 62, 87) with combination therapy compared to 54% (95% CI; 40, 67) with dabrafenib alone.	US FDA
	<b>Nivolumab IV infusion</b> <i>Opdivo®</i> Ono Pharmaceutical Co.	Manufacturing and marketing approval was granted to this programmed death-1 (PD-1) monoclonal antibody for the treatment of unresectable melanoma. It is the first PD-1 immune checkpoint inhibitor to gain regulatory approval. Opdivo® received accelerated US FDA approval in December 2014.	MHWL (Japan)  US FDA
	<b>Pembrolizumab IV injection</b> <i>Keytruda®</i> Merck & Co., Inc.	Accelerated approval was granted to pembrolizumab for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF V600 mutation positive, a BRAF inhibitor. The drug acts by targeting the PD-1 receptor. Pembrolizumab is a monoclonal antibody that binds to the PD-1 receptor and blocks its interaction with programmed cell death 1 ligand 1 (PD-L1) and PD-L2, thereby releasing PD-1 pathway-mediated inhibition of the immune response, including anti-tumor immune response.	US FDA
Photo-dermatosis	<b>Afamelanotide 16 mg SC bioresorbable implants</b> <i>Scenesse®</i> Clinuvel Pharmaceuticals	The European Medicines Agency (EMA) approved afamelanotide 16 mg implants for treating the genetic disorder erythropoietic protoporphyria (EPP), a painful photodermatosis. This photo-protective agent belongs to a family of drugs known as melanocortins and is the first ever treatment developed for EPP. Afamelanotide provides prophylactic treatment through its antioxidant effects and activation of melanin in skin, thereby providing patients with a biological barrier between their skin and the various wavelengths of light that trigger phototoxic reactions.	European Commission
Psoriasis	<b>Apremilast tablets</b> <i>Otezla®</i> Celgene Corporation	This orally available, first-in-class, small molecule inhibitor of phosphodiesterase-4 (PDE4) was approved for the treatment of patients with moderate to severe plaque psoriasis who are candidates for phototherapy or systemic therapy. Inhibition of PDE4 suppresses both TNF- $\alpha$ production and immune responses, which play important roles in the chronic inflammation associated with the development of skin symptoms in psoriasis.	US FDA  Health Canada
	<b>Calcipotriene 0.005% + betamethasone dipropionate 0.064% topical suspension</b> <i>Taclonex®</i> Leo Pharma Inc.	An expanded indication was granted for this topical combination treatment for plaque psoriasis of the scalp in patients 12-17 years of age. It is the first indication for adolescent patients aged $\geq 12$ years with scalp plaque psoriasis among commercially available treatments.	US FDA
	<b>Methotrexate SC injection</b> <i>Rasuvo™</i> Medac Pharma	Approval was granted to this SC injectable methotrexate therapy delivered in an auto-injector for rheumatoid arthritis, polyarticular-course juvenile idiopathic arthritis, and psoriasis.	US FDA
Psoriatic Arthritis	<b>Apremilast tablets</b> <i>Otezla®</i> Celgene Corporation	Approval was granted to the first oral therapy for the treatment of adults with active psoriatic arthritis (PsA). Apremilast is an oral small molecule inhibitor of PDE4 specific for cyclic adenosine monophosphate (cAMP). PDE4 inhibition results in increased intracellular cAMP levels, thereby suppressing immune responses.	US FDA

Rosacea	<p><i>European Commission:</i>  <b>Brimonidine 3 mg/g gel</b>  <i>Mirvaso</i><sup>®</sup>  Galderma International</p> <p><i>Health Canada:</i>  <b>Brimonidine tartrate 0.33% topical gel</b>  <i>Onreltea</i><sup>®</sup>  Galderma Canada Inc.</p>	<p>This alpha-adrenergic receptor agonist received approval for the topical treatment of facial erythema (redness) of rosacea in adults ≥18 years of age. It is not indicated for the treatment of inflammatory lesions (papules and pustules). Brimonidine constricts dilated facial blood vessels to reduce the redness of rosacea. This drug has a rapid onset of action, with effects occurring as quickly as 30 minutes after application and lasting up to 12 hours. Brimonidine tartrate 0.33% gel (<i>Mirvaso</i><sup>®</sup>) was US FDA approved in August of 2013.</p>	<p>European Commission</p> <p>Health Canada</p>
	<p><b>Ivermectin 1% cream</b>  <i>Soolantra</i><sup>®</sup>  Galderma Laboratories, L.P.</p>	<p>Ivermectin 1% cream was approved for the once-daily topical treatment of inflammatory lesions, or bumps and pimples, of rosacea. The exact cause of rosacea is unknown, but multiple triggers have been implicated. Recent evidence suggests that rosacea may be caused by the over-proliferation of <i>Demodex</i> mites in the skin. Ivermectin has both anti-inflammatory and antiparasitic activities.</p>	<p>US FDA</p>
Urticaria	<p><b>Omalizumab SC injection</b>  <i>Xolair</i><sup>®</sup>  Genentech, Inc.  Novartis</p>	<p>Omalizumab (a recombinant humanized monoclonal antibody that blocks the high-affinity Fc receptor of immunoglobulin E) was approved for the treatment of chronic idiopathic urticaria (CIU), also referred to as chronic spontaneous urticaria (CSU). The new use (already approved for asthma) is for patients ≥12 years of age who remain symptomatic despite H1-antihistamine therapy. Treatment is not indicated for other forms of urticaria (hives).</p>	<p>European Commission</p> <p>Health Canada</p> <p>US FDA</p>

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## Update on Drugs

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Name/Company	Approval Dates/Comments
<b>Human papillomavirus 9-valent vaccine, recombinant</b> <i>Gardasil®9</i> Merck	In December 2014, the US FDA approved this 9-valent human papillomavirus (HPV) vaccine for use in girls and young women 9-26 years of age for the prevention of cervical, vulvar, vaginal, and anal cancers caused by HPV types 16, 18, 31, 33, 45, 52 and 58, pre-cancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, and genital warts caused by HPV types 6 and 11. It is also approved for use in boys 9-15 years of age for the prevention of anal cancer caused by HPV types 16, 18, 31, 33, 45, 52 and 58, precancerous or dysplastic lesions caused by HPV types 6, 11, 16, 18, 31, 33, 45, 52 and 58, and genital warts caused by HPV types 6 and 11. Gardasil®9 includes the greatest number of HPV types in any available HPV vaccine.
<b>Ivermectin 1% cream</b> <i>Soolantra®</i> Galderma Laboratories	The FDA approved ivermectin 1% cream in December 2014 for the once-daily topical treatment of inflammatory lesions, or bumps and pimples, of rosacea. The exact cause of rosacea is unknown, but multiple triggers have been implicated, including the over-proliferation of <i>Demodex</i> mites in the skin. Ivermectin has both anti-inflammatory and antiparasitic activities. Phase 3 clinical investigations observed onset of action as early as week 2 with continuous improvement. In long-term extensions to 12-week studies, ivermectin 1% cream demonstrated safety and tolerability for an additional 40 weeks (up to 52 weeks in total).
<b>Naftifine HCl 2% gel &amp; cream</b> <i>Naftin®</i> Merz Dermatology	The FDA approved a pediatric indication for naftifine HCl (an allylamine antifungal) 2% cream and gel formulations in December 2014 for the treatment of interdigital type tinea pedis in patients aged 12-17 years.
<b>Nivolumab IV infusion</b> <i>Opdivo®</i> Bristol-Myers Squibb Company	The FDA approved this human programmed death receptor-1 (PD-1) blocking monoclonal antibody in December 2014 for the treatment of patients with unresectable or metastatic melanoma and disease progression following ipilimumab (Yervoy®) and, if BRAF V600 mutation positive, a BRAF inhibitor. This indication was granted under accelerated approval based on tumor response rate and durability of response.
<b>Polymethylmethacrylate collagen dermal filler for acne scars</b> <i>Bellafill®</i> Suneva Medical, Inc.	The FDA approved this dermal filler in January 2015 for the treatment of acne scars. Bellafill® is the only injectable filler sanctioned for this indication. The product was studied extensively prior to gaining regulatory approval and shown to be safe and effective for the correction of moderate to severe, atrophic, distensible facial acne scars on the cheek in patients >21 years of age.
<b>Secukinumab SC injection</b> <i>Cosentyx™</i> Novartis Pharmaceuticals	The FDA approved secukinumab in January 2015 for the treatment of moderate to severe plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy, or a combination of both. Secukinumab is a fully human monoclonal antibody that inhibits the proinflammatory cytokine interleukin 17A (IL-17A). It is the first approved antipsoriatic agent to selectively bind to IL-17A and inhibit interaction with the IL-17 receptor, thereby suppressing inflammatory responses. The approval is based on the efficacy and safety outcomes from ten Phase 2 and Phase 3 studies, including over 3,990 adult patients with moderate to severe plaque psoriasis, which demonstrated that secukinumab resulted in clear or almost clear skin in the majority of patients and had an acceptable safety profile.