

Therapeutic Advances in Cutaneous T-Cell Lymphoma

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ABSTRACT

A variety of novel therapeutic modalities have recently become available for patients with cutaneous T cell lymphoma (CTCL). In particular, with recent FDA approvals of the three new agents vorinostat (Zolinza[®]), romidepsin (Istodax[®]), and pralatrexate (Foloty[®]) CTCL treatment has been transformed. Here, we offer a brief overview of these agents and discuss their place in the spectrum of current therapies for CTCL.

Key words: CTCL, cutaneous T-cell lymphoma, therapy

Cutaneous T-cell lymphoma (CTCL) is a heterogeneous group of malignancies of mature memory T lymphocytes. Mycosis fungoides (MF) is the most common variant of CTCL, representing about 50% of all cases. Sézary syndrome is a leukemic variant, affecting about 5% of patients with CTCL.¹ Diagnosis is established by skin biopsy, followed by staging work-up, which may include radiologic imaging studies and evaluation of the lymph nodes, blood, bone marrow, and internal organs for systemic involvement, as indicated by initial patient presentation.

While numerous therapeutic options are available and recent reports show improved survival of CTCL patients over historic controls, suggesting the potential benefit of current regimens, no therapy has been shown to be curative. Thus, the goal of therapy is to induce long-term remission without further compromising a patient's immune system or quality of life. In general, MF treatment is divided into two broad categories: skin-directed and systemic therapies. Skin-directed therapy is the key component in management of early disease, while systemic therapy is essential in more advanced cases. Systemic therapy can be further separated into various categories, either based on the mechanism of action of the systemic agent (e.g., biological modifiers such as interferons, retinoids, and rexinoid; histone deacetylase inhibitors; and traditional chemotherapeutic agents, such as doxorubicin and gemcitabine) or by the number of agents used to treat a patient (e.g., monotherapy vs. multiagent combination therapy).

Considering the overall protracted course of CTCL, its indolent character, immunocompromised status of the patient, and absence of definitive therapy, the treatment choices for a particular patient should be made after carefully weighing the risk-benefit ratio. Therapies offering fewer known adverse effects with greater

potential benefits should be attempted first, while aggressive multiagent chemotherapy contributing to immunosuppression should be reserved for end-stage palliation.

Within recent years, there has been an explosion of basic and clinical research in CTCL leading to an escalating number of clinical trials in the field of cutaneous lymphoma. For example, according to a search of ClinicalTrials.gov, from 1996-2000 there were only 66 clinical trials in CTCL, while the number of studies nearly doubled to 121 from 2001-2005, and from 2006-2010 the volume tripled to 219. Within only the last 4 years, the US FDA approved three novel agents (i.e., vorinostat, romidepsin, and pralatrexate) for use in CTCL and/or its variants, whereas within the previous 15 years only two agents (bexarotene and denileukin diftitox) received an official indication for CTCL.

Many other interesting agents currently in clinical trials have already demonstrated efficacy and safety in CTCL. The list includes, but is not limited to, novel histone deacetylase inhibitors (HDIs), novel antibodies (e.g., anti-CD4 and anti-CD30), purine nucleoside phosphorylase (PNP)-inhibitor (forodesine), and immunomodulators (e.g., CpGs). In addition, there are several combination therapies (e.g., pralatrexate and bexarotene, romidepsin and electron beam radiation) under clinical investigation to explore their potential benefits as integrated treatment and to establish the optimal dosing regimen. Our review will focus on new developments in this field.

Skin-Directed Therapies

Various topical agents are not only considered to be mainstays of therapy in cases of CTCL with involvement limited to the skin, but they can also be useful as a palliation treatment in patients with advanced disease (Table 1). Widely used topical therapies include

corticosteroids, nitrogen mustard, carmustine, topical retinoids, and rexinoid (bexarotene), as well as ultraviolet light therapy and body irradiation. These agents/methods may be used alone or in combination with each other.

Drug/Mode of Therapy
Corticosteroids (various potencies)
Nitrogen mustard
Carmustine
Topical retinoids
Topical rexinoid (bexarotene)
Ultraviolet light therapy
• Psoralen + UVA (PUVA), narrowband UVB, and UVB
Electron beam radiation (localized and total skin)
Topical tacrolimus
Imiquimod
Photodynamic therapy (PDT)

Table 1: Skin-directed therapies for CTCL

A number of other skin-directed therapies are available, including topical tacrolimus, imiquimod, and photodynamic therapy (PDT). These treatments are not FDA-approved for use in CTCL, but their effectiveness is well documented in the literature. We will examine only selected newer topical therapies in this review.

Topical Tacrolimus

Topical tacrolimus (Protopic®) has been approved for use in atopic dermatitis. It is as effective as mid- to low-potency glucocorticoids and is used on facial skin and intertriginous areas in patients with MF. A major advantage of tacrolimus when compared with steroids is that it does not suppress collagen synthesis, and therefore, does not cause skin atrophy.^{2,3} However, because therapy with calcineurin inhibitors in CTCL is controversial, tacrolimus should be limited to short-term use on small areas of skin.

Imiquimod

Imiquimod (Aldara®) is a relatively new topical immunomodulator that is extremely effective in the treatment of condylomata acuminata (genital warts), actinic keratoses, basal cell carcinomas, keratoacanthomas, and other cutaneous malignancies. Several groups have reported the effectiveness of imiquimod in early patch MF.^{8,9} It should be used three times per week for 3 months. The time to response in some patients can be as short as 2 weeks. Long-term follow-up data is not available at this time.

Photodynamic Therapy

Photodynamic therapy (PDT) is a photochemistry-based modality utilizing the properties of photosensitizers (PS) to induce singlet oxygen and reactive oxygen species upon light irradiation. Out of the broad chemical spectrum of PS, only a PS precursor, 5-aminolevulinic acid (ALA) and its derivative (methyl aminolevulinate hydrochloride), have FDA approval for use in dermatology and have been tested for CTCL. Several investigations have appraised ALA-PDT as a prospective

modality for CTCL. Orenstein et al. observed that malignant cells in CTCL plaques have a greater ability to convert ALA into protoporphyrin IX than peripheral blood lymphocytes.⁴ High expression of CD71 (transferring receptor) on the surface of the malignant lymphocyte may be a reason for higher production of protoporphyrin IX due to higher turnover of iron.⁵ The benefit of PDT for CTCL is considerably modest, and hence, it is generally reserved as forth-line therapy. While PDT is efficient for patch/plaque stage of MF, ALA-PDT is not useful for the tumor stage of CTCL, due to insufficient penetration of PS and light during topical application.⁶ It may be useful for resistant cases of localized plaques, particularly on the head.⁷

Systemic Therapies

Several novel systemic agents have been recently added to the assortment of therapies available for CTCL. Previous FDA-approved therapies include oral bexarotene and denileukin diftitox. Here, we will focus on agents that have been recently approved for CTCL or demonstrated some promising preliminary results in clinical trials.

Histone Deacetylase Inhibitors (HDIs)

Epigenetic modulation is an important mechanism of regulation in gene expression. Histone deacetylase inhibition increases acetylation of lysine residues that form the octomeric histone core of chromatin, thereby decreasing the ability of the histones to bind to DNA. This decreased binding allows chromatin expansion, permitting transcription of the tumor suppressor genes. However, HDIs affect acetylation globally and may have wider effects on various cellular functions. Two novel HDIs (vorinostat and romidepsin) were recently approved by the US FDA for use in patients with CTCL.^{10,11}

Vorinostat

Vorinostat (suberoylanilide hydroxamic acid, Zolinza®) is the first HDI approved by the US FDA in October 2006 for cutaneous manifestations of CTCL in patients with progressive, persistent, or recurrent disease on or following two systemic therapies.¹ The clinical response endpoint in a pivotal phase II clinical trial was exclusively improvement in skin manifestations of the disease, as measured by a Modified Severity Weighted Assessment Tool (mSWAT) score. In this clinical trial, formal assessment of the disease in the lymph nodes, blood, and visceral organs was not done for calculation of the clinical response rate. This trial demonstrated an overall response rate (ORR) of 32%; for patients with advanced CTCL it was slightly less (30%).¹² Of the responding patients, 98.6% exhibited a partial response (PR). Median time to response (TTR) was 56 days; time to progression (TTP) was 168 days. Overall, 32% of patients experienced pruritus relief. The most common drug-related adverse events were diarrhea, fatigue, nausea, and anorexia. Bexarotene failure was one of the inclusion criteria for this clinical trial. Many patients were refractory to other therapies (on average, patients failed 3.5 prior therapies). Therefore, vorinostat appears to work in a manner that is different and non-cross resistant to other CTCL treatments. Vorinostat is not an immunosuppressive agent, though some degree of bone marrow suppression may occur. Vorinostat has been shown to be safe and effective, with acceptable tolerability, when used long-term.^{10,13}

In clinical practice, the standard approach is to use a combination of therapeutic agents to achieve an optimal outcome. However, no clinical studies have been conducted to test the most effective combinations. A recent practical review of CTCL patients treated with vorinostat in combination with various other therapeutic modalities, including narrowband UVB, bexarotene, and interferon, demonstrated better clinical outcomes in 6 of 14 patients. Importantly, 11 of 14 patients experienced significant improvement in their pruritus score, which is one of the major issues affecting quality of life.¹⁴ We have also previously described a patient with refractory Sézary syndrome who responded well to the combination of vorinostat with extracorporeal photopheresis; the clinical response may be theoretically explained through the further induction of cell cycle arrest and apoptosis of malignant T lymphocytes.¹⁵

Romidepsin

Romidepsin (depsipeptide, FK-228, Istodax®) is a cyclic peptide that selectively inhibits histone deacetylase isotypes 1, 2, 4 and 6. Romidepsin, like other HDIs, was shown to induce cell cycle arrest in both G1 and G2/M phases of DNA replication and to trigger apoptosis in several cell lines.¹⁶ Generally, romidepsin is well tolerated; common side-effects include fatigue, nausea, vomiting, and transient thrombocytopenia and neutropenia.¹⁷ A recent phase II multicenter clinical trial examining response rates in patients with MF (stage IB-IV) resulted in US FDA approval of this drug for clinical practice.¹¹ Romidepsin was evaluated in two international multicenter open-label phase II clinical studies involving a total of 167 patients. In pooled analysis, the ORR was 35% based on evaluation of response in all parameters (i.e., skin, nodes, blood, and visceral involvement); with median response duration of 14 months in one study and 11 months in the other study. Complete responses (CR) were observed in 6% of those studied.¹¹ Side-effects included nausea, fatigue, anorexia, electrocardiograph T-wave changes, anemia, dysgeusia, neutropenia, and leucopenia. However, romidepsin monotherapy may not be sufficient for maximal benefit, and hence, the continued search for adjuvant measures capable of providing synergistic effects is needed. We have observed durable and prolonged clinical responses at the radiotherapy site in patients receiving local electron beam therapy while enrolled in the romidepsin clinical trial. Such synergy may find a clinical application, although further clinical trials should be performed to formally test the efficacy and safety of this combination.

Monoclonal Antibodies

Alemtuzumab (Campath-1H, Campath®) is a humanized IgG1 monoclonal antibody that targets the CD52 antigen. An ORR of 50% in a small cohort of patients has been reported.^{18,19} Low-dose alemtuzumab is safe and effective in very elderly Sézary syndrome patients.²⁰ Alemtuzumab effectively depletes leukemic cells from the blood of these patients. Subcutaneous (SC) administration of low doses on an as needed basis has been effective in Sézary syndrome patients.²¹ A recent update of this therapeutic schema for patients with Sézary syndrome was proposed by Quaglino et al.²² The authors have suggested starting with 3 mg of SC alemtuzumab on day 1, then administering 10 mg on alternating days until the circulating Sézary cell count drops below 1000/mm³. Once the Sézary cell count rises above 2000/mm³, another SC alemtuzumab dose of 10 mg can be administered.

Such an approach can help to avoid complete obliteration of the lymphocytes and reduce the rate of opportunistic infections.

Extracorporeal Photopheresis

Extracorporeal photopheresis (ECP) is an approved palliative treatment for CTCL. The novel continuous flow separation (CFS) system (THERAKOS™ CELLEX™) has been developed based on the current UVAR®XTS™ device and is designed to reduce treatment times and extracorporeal volumes. A safety and efficacy study assessed patients receiving ECP with the novel UVAR® CFS system for up to 6 months in their previously established regimen. Thirteen patients were enrolled and 12 completed the study; 155 ECP treatments were initiated and 153 were completed. This new ECP system improved treatment times and decreased extracorporeal volumes while demonstrating an acceptable safety profile in the treatment of Sézary syndrome patients.²³

Chemotherapy

Neither single agent nor multiagent therapy is curative in MF. Additionally, single or multiagent chemotherapy results in a higher incidence of transformation to large cell lymphoma, which carries a worse prognosis than the original diagnosis.²⁴ Because ORR and disease free survival are generally higher after combination therapy, single agent chemotherapy is rarely used. However, use of multiagent chemotherapy results in increased immunosuppression and higher risk of serious infections, leading to death in a majority of patients who develop these complications.²⁵ A number of single agent chemotherapeutic agents have been reported to be effective in CTCL. For example, gemcitabine (Gemzar®) demonstrated high clinical efficacy in advanced and refractory CTCL, with a 70.5% response rate,²⁶ while pegylated doxorubicin used in advanced MF has resulted in an even higher overall response of 88%.²⁷

Pralatrexate

Pralatrexate (Folotyn®) is a new antifolate analogue that is FDA-approved for relapsed or refractory peripheral T-cell lymphoma. The relative specificity of antifolates for malignant cells is a result of over-expression of their receptor, reduced folate carrier-1 (RFC-1). Pralatrexate was specifically designed to have significantly higher affinity to RFC-1 as compared with other antifolates. In addition, polyglutamylation of pralatrexate secures retention of this drug within the cancer cell. The interference with dihydrofolate reductase affects synthesis of deoxythymidine and the purine DNA nucleotides, which ultimately results in arrest of the cell cycle.^{28,29}

Pralatrexate was evaluated in a pivotal phase II non-randomized, open-label international study. The trial enrolled 115 patients, 111 of whom received intravenous pralatrexate 30 mg/m² weekly for 6 weeks every 7 weeks, supplemented with B12 and folic acid; 109 patients were evaluable for efficacy. The ORR was 27% with a CR of 10%, and a PR of 17%. The majority of responses were observed after the first cycle. Adverse events included mucosal inflammation and thrombocytopenia.³⁰

Lenalidomide

Lenalidomide (Revlimid®), a thalidomide analogue, is an immunomodulatory agent with antiangiogenic and antineoplastic properties. Querfeld et al. reported an ORR of 28% in CTCL patients who received a median of nine cycles of therapy consisting of 25 mg lenalidomide daily for 21 days of a

28-day cycle. Median TTR was 6 months. However, high toxicity symptoms (i.e., anemia, fatigue/malaise, skin burning, pruritus, diarrhea, and lower leg edema) resulted in discontinuation of the drug in 40% of patients.^{31,32}

Bortezomib

Bortezomib (Velcade®) is a reversible 26S proteasome inhibitor approved by the US FDA for the treatment of multiple myeloma and mantle cell lymphoma. A phase II trial demonstrated considerable clinical efficacy of bortezomib (the ORR was 67%) as single agent therapy in patients with relapsed or refractory CTCL.³³

Stem Cell Transplant

The lifetime expectation for transformed MF and Sézary syndrome is less than 2.5 years.³⁴ Stem cell transplantation (SCT) is a promising approach aimed at providing a cure or increasing life expectancy. Autologous SCT showed very limited efficacy in most patients with CTCL, since 60% of these patients experienced an early relapse (median time to relapse was 120 days).³⁵ In another study, relapse occurred in 50% of patients in less than 100 days.³⁶ The CR of 58% in the first US study by Duvic et al.³⁷ is similar to the 60.5% reported by Duarte et al.³⁸ The relapse rate was shown to be lower after allogeneic SCT (39% of patients), however, time to relapse was shorter (50 days).³⁷ Nevertheless, SCT carries a risk of significant toxicity and fatal complications, particularly in older patients. Careful patient selection and proper timing of SCT are critical factors in successful therapy.

Conclusion

Because CTCL is an indolent malignancy of T cells with excellent prognosis in early stages, the treatment approach should be conservative with skin-directed therapies (nitrogen mustard, topical glucocorticoids, topical bexarotene, and imiquimod) combined with light therapy, low-dose interferon, low-dose methotrexate, other biologics, or single agent chemotherapy. The survival of patients treated with aggressive chemotherapy is not different from the survival of patients treated conservatively, but aggressive chemotherapy results in greater toxicity. Because no curative therapy exists, the goal of treatment is to prevent disease progression to more advanced stages and to preserve the patient's quality of life for as long as possible.

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Drug Class	Generic/Trade/ Company Names	Indication	Approving Regulatory Agency
Acne	Adapalene 0.1% lotion <i>Differin</i> [®] Galderma Laboratories	A novel lotion formulation of the retinoid adapalene was approved for the treatment of acne vulgaris in patients ≥12 years of age. This new formulation has been designed to improve tolerable efficacy and spreads easily. It is available in an easy-to-use pump dispenser and is indicated for application on the face and other areas of the body affected by acne.	US FDA
	Clindamycin phosphate 1.2% + tretinoin 0.025% gel <i>Veltin</i> [™] Stiefel Laboratories, Inc./GSK	This topical combination of an antibiotic with a retinoid in an aqueous gel vehicle was approved for the treatment of acne vulgaris in patients ≥12 years of age.	US FDA
	Drospirenone / ethinyl estradiol / levomefolate calcium + levomefolate calcium tablets <i>Beyaz</i> [™] Bayer HealthCare Pharmaceuticals Inc.	Approval was granted to a new oral contraceptive (OC) to raise folate levels in women who choose an OC for birth control. The addition of levomefolate calcium raises folate levels for the purpose of reducing the risk of a neural tube defect in a pregnancy conceived while taking Beyaz [™] or shortly after discontinuation. The approval of Beyaz [™] is based on Yaz [®] , which contains the same doses of estrogen and progestin, and is approved for three indications: prevention of pregnancy; treatment of symptoms of premenstrual dysphoric disorder in women who choose an OC for contraception; and treatment of moderate acne vulgaris in women ≥14 years of age, but only if the patient prefers an OC for birth control.	US FDA
Actinic Keratoses	Imiquimod cream 3.75% <i>Zyclara</i> [™] Graceway Pharmaceuticals	A new formulation of this immune response modifier was approved for the treatment of clinically typical, visible, or palpable actinic keratoses. It offers a convenient 6-week dosing cycle and is indicated for application over larger areas of skin (as compared with imiquimod 5%), including the full face and balding scalp in adults.	Health Canada US FDA
Antibacterial Agents	Ceftaroline fosamil <i>Teflaro</i> [™] Forest Laboratories, Inc.	This novel broad-spectrum injectable cephalosporin antibiotic was approved for the treatment of community acquired bacterial pneumonia and complicated skin and skin structure infections. Ceftaroline has activity against both gram-positive bacteria, including methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) and <i>Streptococcus pneumoniae</i> , and common gram-negative pathogens.	US FDA
	Daptomycin for injection <i>Cubicin</i> [®] Cubist Pharmaceuticals, Inc.	This antibiotic received an additional indication as the only approved 2-minute IV injection for the treatment of MRSA-complicated skin infections and bacteremia.	US FDA
Cancer	CD56-binding monoclonal antibody (huN901) + maytansinoid cytotoxic agent (DM1) <i>IMGN901</i> ImmunoGen, Inc.	Orphan drug designation was granted to the IMGN901 compound (an antibody-drug conjugate) for the treatment of Merkel cell carcinoma. IMGN901 binds with high affinity to CD56 expressed on the surface of tumor cells. Once bound, the conjugate is internalized and the antimitotic agent (DM1) is released.	European Medicines Agency (EMA) US FDA
Dermal Fillers and Injectables	Hyaluronic acid dermal filler + 0.3% lidocaine <i>JUVÉDERM</i> [®] XC Allergan, Inc.	A new formulation of this hyaluronic acid dermal filler was approved for the reduction of pain during treatment of moderate to severe facial wrinkles and folds (i.e., nasolabial folds). The addition of 0.3% preservative-free lidocaine may also shorten the treatment time by eliminating the need for an additional anesthetic.	US FDA
	Hyaluronic acid dermal filler + 0.3% lidocaine <i>RESTYLANE</i> [®] -L <i>PERLANE</i> [®] -L Medicis Aesthetics	Additional formulations of these dermal fillers were approved for the reduction of pain associated with the injectable correction of moderate to severe nasolabial folds. These products provide patients with the option of a single syringe containing a wrinkle filler with a local anesthetic. RESTYLANE [®] -L is approved for injection into the mid to deep dermis and PERLANE [®] -L is approved for implantation into the deep dermis to superficial subcutis.	US FDA

Drug Class	Generic/Trade/ Company Names	Indication	Approving Regulatory Agency
<i>Lysosomal Storage Diseases</i>	Agalsidase alfa <i>REPLAGAL</i> ® Shire plc	Fast Track designation was granted to this human-cell-line-derived enzyme replacement therapy for the long-term treatment of Fabry disease. Therapy is administered every other week by intravenous infusion.	US FDA
	Velaglucerase alfa <i>VPRIV</i> ™ Shire plc	Approval was granted to this hydrolytic lysosomal glucocerebrosidase-specific enzyme for long-term enzyme replacement therapy in pediatric and adult patients with Type 1 Gaucher disease. Therapy is administered every other week by intravenous infusion.	European Medicines Agency (EMA) US FDA
<i>Psoriasis</i>	Adalimumab <i>Humira</i> ® Abbott Japan Co./Eisai Co.	This fully-human monoclonal anti-TNF- antibody was approved for the additional indications of plaque psoriasis and psoriatic arthritis.	MHLW (Japan)
	Calcipotriene/Calcipotriol 0.005% foam <i>Sorilux</i> ™ Stiefel, a GSK Company	A novel foam formulation of calcipotriene 0.005% was approved for the topical treatment of mild to moderate plaque psoriasis in patients ≥18 years of age. Calcipotriene has been formulated using the VersaFoam® vehicle, a proprietary delivery technology.	US FDA
	Calcitriol ointment <i>Silkis</i> ™ Galderma Canada	Approval was granted to this topical vitamin D3 agent for the treatment of mild-to-moderate plaque psoriasis in adults. This product was US FDA approved in 2009 under the trade name of Vectical™	Health Canada
<i>Psoriatic Arthritis</i>	Adalimumab <i>Humira</i> ® Eisai Co., Ltd.	This fully-human monoclonal anti-TNF- antibody was approved for the additional indications of plaque psoriasis and psoriatic arthritis.	MHLW (Japan)
<i>Vaccines</i>	Human papillomavirus quadrivalent (Types 6, 11, 16, and 18) recombinant vaccine <i>Gardasil</i> ® Merck & Co., Inc.	An additional indication was granted to this human papillomavirus (HPV) vaccine for the prevention of infection caused by HPV types 6, 11, 16 and 18 and genital warts caused by HPV types 6 and 11 in boys and men 9-26 years of age.	Health Canada
		This HPV recombinant vaccine received an additional approved indication for the prevention of anal cancer caused by HPV types 16 and 18 and for the prevention of anal intraepithelial neoplasia (AIN) grades 1, 2 and 3 (anal dysplasias and precancerous lesions) caused by HPV types 6, 11, 16 and 18, in males and females 9-26 years of age.	US FDA
<i>Wound Care</i>	Small molecule oxychlorine compound <i>Microcyn</i> ® Skin and Wound <i>HydroGel</i> Oculus Innovative Sciences	New dermatology indications were granted to Microcyn® Skin and Wound HydroGel. This prescription product is intended for use, under the supervision of a healthcare professional, in the management of wounds, including itch and pain relief associated with skin irritation, sores, injuries, and ulcers of dermal tissue.	US FDA
<i>Other</i>	Collagenase clostridium histolyticum <i>XIAFLEX</i> ™ Auxilium Pharmaceuticals	This novel first-in-class, orphan-designated biologic was approved for the treatment of Dupuytren's contracture in adults with a palpable cord. The injected enzymes dissolve and weaken the contracted collagen cord. This new treatment represents the only nonsurgical option for Dupuytren's disease.	US FDA
	Polidocanol injection <i>Asclera</i> ® BioForm Medical Inc./ Chemische Fabrik Kreussler & Co.	Regulatory approval was granted to this sclerotherapy agent to improve the appearance of varicose veins. The injection treatment is used to close spider veins (<1 millimeter in diameter) and reticular veins (1-3 millimeters in diameter). The agent acts by damaging the cell lining of blood vessels, causing the vessels to close, and leading to subsequent replacement by other types of tissue.	US FDA

Update on Drugs

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Name/Company	Approval Dates/Comments
Human papillomavirus quadrivalent (Types 6, 11, 16, and 18) recombinant vaccine Gardasil® Merck & Co., Inc.	The US FDA granted an additional indication to this human papillomavirus (HPV) recombinant vaccine in December 2010 for the prevention of anal cancer caused by HPV types 16 and 18 and for the prevention of anal intraepithelial neoplasia (AIN) grades 1, 2 and 3 (anal dysplasias and precancerous lesions) caused by HPV types 6, 11, 16 and 18, in males and females 9 to 26 years of age.
Daptomycin for injection Cubicin® Cubist Pharmaceuticals, Inc.	The US FDA approved this currently-marketed antibiotic for once-a-day dosing as a 2-minute intravenous (IV) injection in December 2010 for the treatment of methicillin-resistant <i>Staphylococcus aureus</i> (MRSA) complicated skin infections and bacteremia. In addition to 2-minute IV injection, several other changes to the drug's label were incorporated. These include changes and reformatting of the Warnings and Precautions in the label, updates to the Post Marketing Experience section of the label, and re-formatting of the label to be compliant with the FDA's Physician Labeling Rule (PLR).

Drug News

The American Academy of Dermatology and AAD Association recently released their updated position statement on isotretinoin, which continues to support physician-monitored use of the drug for the treatment of severe acne. The AAD's stance affirms patient safety is the primary concern and its commitment to the safe and responsible use of isotretinoin, generally considered by dermatologists to be the most effective treatment for severe recalcitrant nodular acne. This most recent amendment dated November 13, 2010 includes the following revisions:

- The AAD advocates compliance with the manufacturer-sponsored and US FDA-approved risk management program for prescribing isotretinoin (iPLEDGE®). The Association opposes on-line Internet dispensing, sharing, or use without physician supervision, because these activities do not provide for sufficient patient education about isotretinoin risks and do not require participation in the iPLEDGE® program.
- A correlation between isotretinoin use and depression/anxiety symptoms has been suggested, but an evidence-based causal relationship has not been established. Other studies give evidence that treatment of acne with isotretinoin was accompanied by improvement of both depressive and anxiety symptoms, as well as improved quality of life of patients with acne.
- Current evidence is insufficient to prove either an association or a causal relationship between isotretinoin use and inflammatory bowel disease (IBD) in the general population. While some recent studies have suggested such a relationship, further studies are required to conclusively determine if an association or causal relationship exists and/or whether IBD risk may be linked to the presence of severe acne itself.

The position statement concludes that the prescription of isotretinoin for severe nodular acne continues to be appropriate as long as prescribing physicians are aware of the risks and concerns related to isotretinoin use and that their patients are monitored for any signs of IBD and psychiatric disturbances. Education by treating physicians to encourage patient vigilance in recognizing and reporting signs of IBD and depressive symptoms is also endorsed.

The complete AAD position statement on isotretinoin is available at: <http://www.aad.org/forms/policies/Uploads/PS/PS-Isotretinoin.pdf>

*Information on the iPLEDGE program is available at: <https://www.ipledgeprogram.com/>