

Chronic Idiopathic Urticaria: Treatment with Omalizumab

Sandra Naaman, MD, PhD¹ and Gordon Sussman, MD, FRCPC, FACP, FAAAAI²

¹Department of Internal Medicine, University of Chicago (Northshore University Health System), Evanston, IL, USA

²Division of Allergy and Clinical Immunology, St. Michael's Hospital, University of Toronto, Toronto, ON, Canada

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ABSTRACT

Chronic idiopathic urticaria (CIU) is a common autoimmune skin condition characterized by spontaneously recurring hives for 6 weeks or longer. The new terminology used for CIU in most countries including Canada is chronic spontaneous urticaria (CSU). CSU is associated with significant psychosocial morbidity with a markedly negative impact on overall quality of life. Conventional approaches with antihistamines, even at high doses, is effective in about 50% of patients suffering from CSU. A new treatment option, omalizumab, a humanized monoclonal antibody against the Fc domain of IgE, has undergone the scrutiny of randomized research studies evaluating the efficacy in CSU. This editorial reviews mechanisms of action of omalizumab, efficacy, cost and potential side effect profile. Omalizumab has emerged as a very promising treatment option for patients with CSU. Future research is necessary to establish standardized protocols related to dosing as well as monitoring possible adverse effects of long-term treatment.

Key words: angioedema, antibodies, anti-allergic agents, autoimmune skin disorder, hives, hypersensitivity, immunoglobulin E, monoclonal antibody, omalizumab, urticaria, Xolair

Introduction

Chronic idiopathic urticaria (CIU), also known as chronic spontaneous urticaria (CSU), is a common autoimmune skin disease characterized by spontaneously recurring hives or welts, which may also be accompanied by deeper cutaneous swelling termed angioedema. The primary symptom causing significant disability is itchiness or pruritus.¹ The diagnosis is defined as urticarial skin lesions occurring intermittently or continuously for more than 6 weeks. A fairly common condition, urticaria occurs across all age groups and has a lifetime prevalence of about 20% with about 1% of the population suffering from the chronic form.² CSU occurs largely in young women between 20 and 40 years of age.^{3,4} Notably, 70% of patients diagnosed with CSU report symptoms lasting more than 1 year and a significant 14% report non-remitting symptoms which have lasted for more than 5 years.⁵ This condition has been associated with significant psychosocial impairment; specifically impacting emotional and physical health-related quality of life indices; resulting in substantial disability and diminished productivity.⁶⁻⁸ Notably, the negative impact on quality of life measures reported by patients with CSU is on par with the severity reported by patients with triple vessel ischemic coronary disease. Specifically, patients in both clinical populations report similar levels of emotional distress, social isolation and lethargy.^{9,10}

Treatment of Chronic Spontaneous Urticaria

Current practice guidelines for management of CSU describe a stepwise approach with non-sedating H1 oral antihistamines as the initial agents, these can be given in up to four times the FDA recommended dose.¹¹ However, close to half of all CSU patients do not achieve adequate symptom relief with H1 antihistamines alone.¹² Second-line therapies can involve addition of H2 blockers although these are not recommended as first, second or third-line treatment because of low evidence supporting their clinical efficacy. The H2 blocking agents and anti-leukotriene medications are often tried because of their excellent safety profiles. If remission is not induced, third-line treatments may be initiated; this includes use of immune modulators. To date, cyclosporine has been the best studied agent with demonstrated efficacy based on adequately powered studies of good quality. Its significant toxicity profile, however, has limited its widespread use in many patients, especially in the older population dealing with other comorbidities.¹¹ Other immune modulators which have been used in refractory CSU include tacrolimus, mycophenolate mofetil, hydroxychloroquine, sulfasalazine and even intravenous immunoglobulin. In addition to the limited data supporting use of these agents in managing CSU, many of them are associated with substantial and often unacceptable toxicities. Systemic glucocorticoids have also been used in refractory cases and while consensus guidelines recommend their use to be limited to

exacerbations, clinical practice has often necessitated their long-term use in many patients, again posing less than desirable side effects.¹³

Treating CSU is challenging, as there are often no identifiable indicators as to the responders to specific treatments. Cutaneous mast cell degranulation with release of histamine and other mediators are ascribed to urticaria, however, non-immunoglobulin E (IgE) and non-immunologic mast cell activation is responsible for ongoing urticaria.¹⁴ In up to 50% of patients with CSU, an autoimmune mechanism is thought to mediate the disease process; this either involves autoantibodies to the alpha chain of the high affinity IgE receptor or intrinsic IgE immune modulation is believed to account for the pathophysiology.^{15,16} Research-based assays have been developed to isolate an autoimmune etiology; however, at the present time, these are not readily available nor practical in a clinical setting.¹⁷

Omalizumab: Mechanism of Action

In the last few years, there has been a burgeoning interest in expanding the use of omalizumab beyond its originally approved use as adjunctive therapy for refractory asthma to CSU. Recently approved in Canada for CSU management, omalizumab is a fully humanized recombinant monoclonal antibody which binds to the fragment crystallizable (Fc) region of the IgE molecule which itself binds to FcεRI.^{18,19} In theory, this structure precludes anaphylactogenic potential since the drug does not interact directly with IgE, which is already bound to cell surfaces. Therefore, mast cell or basophil degranulation would not be possible.^{20,21} Functionally, omalizumab binds to circulating IgE, irrespective of allergen specificity. This results in circulating IgE-anti-IgE complexes, which are biologically inert and have specifically been shown not to activate the complement system.^{19,20,22} Notably, reductions in circulating IgE reaching up to 99% have been reported in studies (that is free IgE not bound to omalizumab).^{22,23} Interestingly, these serologic changes are seen within the very first administrations of the drug and are typically maintained throughout the duration of treatment; although the precise doses in CSU have not yet been established. Omalizumab has also been shown to down regulate FcεRI on basophils,²⁴ mast cells,²⁵ and dendritic cells.²⁶ A reduction in the expression of FcεRI on basophils and mast cells decreases the binding of circulating IgE, thus preventing the release of inflammatory mediators. Although most CSU patients have no identifiable allergy triggers, and there is not necessarily an increased incidence of atopy or high IgE levels, chronic urticaria may develop due to many stimuli. These include NSAIDs use, certain foods and even emotional stress. Omalizumab has also been shown to reduce the expression of FcεRI on dendritic cells; thereby attenuating the degree of allergen presentation and processing.

Evaluation of Efficacy

In addition to initial observation studies, case reports^{27,28} and one proof-of-concept study²⁹, there have been four prospective randomized clinical trials which have directly evaluated the clinical efficacy of omalizumab in treatment of refractory CSU³⁰⁻³³, in addition to one multicenter double-blinded placebo-controlled study³⁰. Omalizumab has been evaluated using a total pool of approximately 1,000 CSU patients across all studies to date.²⁷⁻³²

Results have demonstrated clinically significant efficacy of omalizumab in decreasing pruritus and Urticaria Activity Scores (UAS - a widely used patient-reported outcome measure for patients with CSU) in comparison with conventional treatments. Specifically, studies have demonstrated symptom attenuation and improvement on quality of life measures in adult patients treated with omalizumab for 6-20 months.^{27,34} In one study, which enrolled patients presenting with moderate to severe CSU who were unresponsive to antihistamines, omalizumab was associated with clinically relevant decreases in severity of hives and associated pruritus, as well as meaningful improvement on quality of life questionnaires.³² Notably, omalizumab often demonstrates an onset of action within 1 week of drug initiation, inducing complete remission; however, symptoms return when treatment is stopped, generally within 1 to 2 months. Also of relevance is the demonstrated efficacy of omalizumab in chronic inducible urticarial, such as cold and delayed pressure urticaria in small numbers of patients, for whom treatment options have generally been rather limited and outcomes unsatisfactory.³⁵

In real life studies omalizumab generally induces remissions in 50% of patients after the first dose.³⁵ Overall, more than 70% of patients achieve complete remission at some point within their treatment course. About 80% have a clinically significant response overall. The dose interval is generally between 4-8 weeks in most patients. More research is needed to more fully evaluate the dose interval and complete remission rate. The 300 mg dose was superior to the 150 mg dose in randomized clinical trials.³²

Treatment Cost

Omalizumab is substantially more expensive than mainstream therapies that have been traditionally used to treat CSU. Despite its high cost at the present time, it can be argued that using omalizumab in selected patients with refractory and chronic urticaria may in fact defray the potential long-term financial costs associated with conventional therapies; in addition to alleviating the psychosocial burden associated with loss of productivity.

Side Effect Profile

Use of omalizumab in the asthmatic population is more extensive compared to CSU. In asthma there are reports of anaphylactic reactions in about 1 in 50,000 injections. It should be noted, however, that omalizumab is designed to interact with the Fc region of the IgE molecule, making its anaphylactogenic potential very low and clinical experience confirms that it is safe.^{20,21} There is still a recommendation for all patients to be observed for 2 hours after the first injection as well as carry epinephrine auto-injectors as some anaphylactic reactions have been reported as being delayed. Recently, the malignancy warning has been removed from the product monograph as patients with undiagnosed cancer were enrolled in one early trial.³⁴ The most common adverse side effects reported by patients include viral infections, headaches, sinus inflammation; however, these did not reach statistical significance when compared to patients enrolled in the placebo group. Notably, omalizumab is approved for children >12 years of age. The data available on its safety in children showed that that after 1 year of use, there was a slight increase in frequency of headaches and upper respiratory tract infections in the omalizumab group compared to placebo.³⁶

Future Directions

Omalizumab has emerged in recent years as a very effective treatment for refractory CSU. Future research should aim at investigating its mechanism of action and optimal dose schedule and treatment duration required for long-term remission. To date, the longest trial duration has been 24 months.³⁷

Conclusion

Chronic spontaneous urticaria (CSU) or CIU is a common autoimmune skin condition characterized by spontaneously recurring hives, occurring either intermittently or continuously for 6 weeks or longer. A significant association is a deeper localized swelling called angioedema, which is observed in about one-third of patients.¹ This is associated with significant psychosocial morbidity in the form of depression, social isolation and lethargy.^{9,10} The impact of CSU on quality of life is notably substantial. There are recently developed standardized tools to assess the quality of life in CSU.³² A simple general test to assess disease severity is the Urticaria Activity Score (UAS7) that assesses pruritus and urticaria severity weekly, which should be used in clinical practice.³⁸ Conventional treatment guidelines prescribe a stepwise approach with non-sedating non-impairing antihistamines as first-line agents followed by increasing to four times the licensed doses as second-line treatment.² Third-line treatments include cyclosporin, which is associated with toxicity and requires frequent monitoring.^{11,12} Omalizumab, a fully humanized monoclonal antibody against the Fc domain of IgE, has gained widespread use as a new third-line treatment in CSU. A solid body of research including double-blinded, randomized clinical trials investigating its clinical utility in inducing remission in CSU has demonstrated robust efficacy.²⁷⁻³³ Specifically, patients treated with omalizumab experienced clinically relevant decrements in severity of hives and associated pruritus, as well as meaningful improvement on quality of life measures.³² Omalizumab often demonstrated onset of action within 1 week of drug initiation, although the treatment generally appears to be given every 4 to 6 weeks. Two doses of 150 mg and 300 mg have been shown to be effective. As such, omalizumab has emerged as a very promising treatment option for patients with CSU. Future research will need to establish standardized protocols related to dosing and duration, as well as monitor possible long-term side effects, particularly in vulnerable clinical populations.

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5% Minoxidil: Treatment for Female Pattern Hair Loss

Aditya K. Gupta, MD, PhD, FRCPC^{1,2} and Kelly A. Foley, PhD²

¹Division of Dermatology, Department of Medicine, University of Toronto, Toronto, ON, Canada

²Mediprobe Research Inc., London, ON, Canada

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ABSTRACT

Minoxidil is a Health Canada and US FDA-approved medication for hair loss in men and women. While 5% minoxidil foam has been approved for men since 2006, Health Canada and the FDA only approved 5% minoxidil foam for female pattern hair loss (FPHL) in 2014. Recent Phase III clinical trials demonstrated the efficacy of once daily 5% minoxidil foam for treatment of FPHL, where a significant change from baseline in the target area hair count was observed compared to placebo. Similar changes in hair count for 5% foam and twice daily 2% minoxidil solution established noninferiority of the 5% foam formulation. Five percent minoxidil foam provides an additional option for women with FPHL and will soon be available in Canada.

Key words: androgenetic alopecia, AGA, female pattern hair loss, FPHL, 5% minoxidil foam, hair loss, treatment, clinical efficacy

Introduction

Female pattern hair loss (FPHL), also known as androgenetic alopecia (AGA), is one of the most common forms of alopecia in women. Onset of hair loss can occur as early as one's 20s and affect as many as 40% of Caucasian women over the age of 70 years.^{1,2} FPHL can be a source of social distress and greatly impair quality of life.³ There are a variety of treatments for FPHL including anti-androgen medications, topical treatments, laser/light devices, and hair transplantation,⁴ with choice of treatment depending on the extent of hair loss, patient health, cost, and preference. The goal of treatment is to slow hair loss and potentially increase hair growth; however, treatment is not always successful.

Until recently, the only US FDA-approved medication for women was 2% minoxidil solution, while both the 2% and 5% solutions are available for men. Minoxidil may stimulate hair growth by increasing the anagen phase of the hair cycle, but the exact mechanisms are currently unknown.⁵ In 2006, the FDA approved 5% minoxidil foam for the treatment of androgenetic alopecia in men after clinical testing showed that it increased hair growth after 48 weeks of twice daily use.^{6,7} Additionally, the incidence of pruritus in men was lower with the 5% foam than the 5% solution, likely due to propylene glycol in the solution formulation.^{6,7} Because of its efficacy in treating male hair loss, 5% minoxidil became a viable option for women suffering from FPHL. Clinical trial results in women suggest that 5% minoxidil foam is an effective treatment for FPHL, leading to its Health Canada and FDA approvals for this indication in 2014.⁸

Past Clinical Evidence

In Phase III clinical trials, both the 5% and 2% minoxidil formulations have demonstrated similar efficacy in promoting hair growth in women with hair thinning over the frontoparietal scalp. Lucky et al. conducted a 48-week randomized, double-blind, placebo controlled trial that assessed target area hair count (TAHC) following twice daily application of 5% minoxidil

solution, 2% minoxidil solution, or 5% solution vehicle in women with frontoparietal hair loss that could be accompanied with, or without, frontal hairline recession.⁹ Patient and investigator assessments of hair growth and scalp coverage were performed in addition to TAHC. Both the 5% and 2% minoxidil solutions showed significantly higher TAHCs compared to placebo ($P < 0.001$, Table 1). The investigator assessments followed the same pattern as the TAHC results; however, patient-reported assessment of hair growth was significantly greater in the 5% minoxidil solution group than the 2% minoxidil solution or vehicle groups.⁹

The efficacy of once daily application of 5% minoxidil foam against 2% minoxidil solution in the treatment of frontoparietal hair loss in women was investigated in a randomized, single-blind Phase III trial.¹⁰ Change in non-vellus hair count and width, blind evaluator and patient review of photographs, and patient assessment of product aesthetics and benefits were assessed after 24 weeks of use. Five percent minoxidil foam applied once daily was shown to be noninferior to twice daily 2% minoxidil solution, as measured by change in non-vellus hair count (Table 2) and hair width. Women in the 5% foam group agreed more strongly that treatment did not interfere with grooming routines than did women in the 2% solution group ($P = 0.002$).¹⁰ In separate studies, both the twice daily use of 5% minoxidil solution and once daily use of 5% minoxidil foam were shown to be non-inferior compared to twice daily use of 2% minoxidil solution.

Recent Clinical Trials

Two randomized, double-blind, parallel, international multi-center Phase III trials of 5% minoxidil foam were recently completed. Both trials assessed the efficacy of once daily use of 5% minoxidil foam in female participants aged 18 years and older.^{11,12} In the first trial, participants were assigned to once a day treatment with 5% minoxidil foam or vehicle foam for 24 weeks (minoxidil: $n=203$, vehicle: $n=201$).¹¹ Efficacy was assessed at weeks 12 and 24 and safety and adverse events were

monitored every 6 weeks. At weeks 12 and 24, changes in TAHC from baseline were significantly higher in the minoxidil-treated group than the vehicle-treated group ($P < 0.0001$, Table 2). Also at 24 weeks, patient-reported assessment of scalp coverage was determined to be significantly higher with minoxidil treatment compared to vehicle ($P < 0.0001$).¹¹

Participants in the second trial were assigned to once a day treatment with 5% minoxidil foam or 2% minoxidil solution twice daily for 52 weeks ($n=161$ in each group).¹² TAHC was assessed at weeks 12, 24, and 52 and safety and adverse events were monitored regularly. The change in TAHC from baseline in the 5% minoxidil group was shown to be similar to that of the 2% topical minoxidil solution group at weeks 12 ($P < 0.4158$) and 24 ($P = 0.9170$, Table 2), as well as at week 52 ($P = 0.5980$).¹²

Adverse Events

Five percent minoxidil foam was well tolerated in each of the recent clinical trials. The number of participants reporting adverse events after using 5% minoxidil foam was similar to that of participants who used 2% minoxidil solution or vehicle. The most common adverse events reported in at least 2% of participants included weight gain, headache, pruritus, and nasal and upper respiratory tract infections.^{11,12} These are similar to the adverse events reported previously by Lucky et al. and Blume-Peytavi et al., who also reported dermatitis, dandruff, erythema, and burning/stinging in both 5% and 2% minoxidil treatment groups.^{9,10} Additionally, 5% foam may encourage greater compliance, as Blume-Peytavi et al. reported that pruritus and dandruff occurred significantly less with application of 5% foam than with the 2% solution.¹⁰

Hypertrichosis is a well-known concern among women using hair growth products. While hypertrichosis has been reported with the use of 5% minoxidil,^{9,10,13} unwanted growth in sideburn areas was significantly less with 5% foam than with the 2% solution.¹⁰ Advice to women to further limit hypertrichosis

includes application of the medication 2-4 hours prior to bedtime and hand washing immediately after application;⁸ however, the presence of hirsutism or hypersensitivity may increase susceptibility to unwanted hair growth that is beyond physician and patient control.^{13,14}

Six participants in the 5% minoxidil group reported serious adverse events (SAEs) in the placebo controlled trial (1 incidence each of cardiac disorder, gastritis, dehydration, osteoarthritis, ovarian neoplasm, uterine leiomyoma, renal failure, and hypertensive crisis) in comparison to 4 participants in the vehicle group (1 incidence each of fatigue, ovarian cancer, memory impairment, mental status changes, and PTSD; 2 incidences each of cardiac disorder and asthenia).¹¹ In the comparative trial, 2 participants treated with 5% minoxidil reported SAEs (wrist fracture and anxiety) in comparison to 8 participants in the 2% minoxidil group (1 incidence each of angina pectoris, abdominal pain, bile duct stone, anal abscess, influenza, metastatic neoplasm, menometrorrhagia, and asthma).¹² The SAEs are not considered to be clinically relevant to the drug.

Discussion

Recent clinical trials of 5% minoxidil foam for the treatment of FPHL have demonstrated it to be safe and effective, with hair growth outcomes similar to that of the traditional 2% minoxidil solution.^{11,12} Phase III clinical trials demonstrated that hair growth with once daily use of 5% minoxidil foam is noninferior to twice daily use of 2% minoxidil solution in women with frontoparietal hair loss.^{10,12} Patient-reported improvement in hair volume and coverage appears to be greater with 5% minoxidil foam and once daily application does not substantially interfere with grooming routines.¹⁰ Adverse events may occur with both 5% foam and 2% solution, but these rarely lead to discontinued use. Susceptibility to hypertrichosis may be individual-specific, and should be discussed with patients as a possible side-effect of minoxidil use.

Study	Regimen	Treatment	n	TAHC†
Lucky et al. ⁹	2x day/48 weeks	5% solution	101	24.5 ± 21.9*
		2% solution	108	20.7 ± 17.6*
		Placebo solution	51	9.4 ± 14.6
Blume-Peytavi et al. ^{10,15}	1x day/24 weeks	5% foam	56	31.9 ± 19.40
	2x day/24 weeks	2% solution	57	28.4 ± 18.90

Table 1: Change from baseline in target area hair count of previous Phase III trials of 5% minoxidil

† TAHC = target area hair count (hairs per cm²). Values represent mean ± standard deviation (SD) change in TAHC from baseline.

* $P < 0.001$, each minoxidil solution different from vehicle

Study	Regimen	Treatment	n	TAHC 12 weeks†	TAHC 24 weeks†
Phase III RCT ¹¹	1x day/24 weeks	5% Minoxidil foam	200	16.4 ± 21.5*	13.5 ± 22.3*
		Vehicle foam	197	5.4 ± 15.3	4.0 ± 16.2
Phase III RCT ¹²	1x day/52 weeks	5% Minoxidil foam	161	24.9 ± 26.0	23.7 ± 22.9
	2x day/52 weeks	2% Minoxidil solution	161	22.5 ± 22.8	23.8 ± 24.7

Table 2: Efficacy outcomes of recent Phase III trials of 5% minoxidil foam

† TAHC = target area hair count (hairs per cm²). Values represent mean ± SD change in TAHC from baseline.

* $P < 0.0001$, 5% minoxidil different from vehicle

RCT = randomized controlled trial

It is suggested that 5% minoxidil be applied for 3-6 months before noticeable improvement can be observed.⁸ While the results of clinical trials demonstrate a statistically significant increase in the total hair count, sometimes these results may fall short of patient expectations; therefore, patients need to be informed that individual results may vary even after 6-12 months of therapy.^{4,16} Recent evidence demonstrates that a sulfotransferase enzyme test can successfully identify non-responders to minoxidil.¹⁷ To our knowledge, this test is not commercially available. In addition, some patients may experience an increase in hair shedding, or at least continued hair loss, for the first few months and should be counselled accordingly.^{4,16} When women experience improvement in hair growth, continued treatment is required or else improvement will likely be lost and hair loss will revert back to its natural course.^{4,18}

Five percent minoxidil foam, applied only once daily, has the potential for milder side effects, improved compliance, and greater patient satisfaction with treatment. Indeed, the use of minoxidil as a treatment for FPHL has been shown to improve women's quality of life.³ Additionally, 5% minoxidil foam provides an alternative option for women who do not wish to use, or who are unable to use, oral anti-androgen or hormonal contraceptive medications as hair loss treatments. The recent approval and availability of 5% minoxidil foam in Canada provides a safe and effective treatment for women with FPHL.

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Name/Company	Approval Dates/Comments
Omalizumab <i>Xolair</i> ® Novartis Pharmaceuticals	Health Canada approved omalizumab (a recombinant humanized monoclonal antibody that blocks the high-affinity Fc receptor of immunoglobulin E) in August 2014 for the treatment of chronic idiopathic urticaria. This 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). The approved doses are 150 mg and 300 mg by subcutaneous injection every 4 weeks.
Pembrolizumab <i>Keytruda</i> ® Merck & Co., Inc.	The US FDA granted accelerated approval to pembrolizumab in September 2014 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 programmed cell death 1 (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. The recommended dose of pembrolizumab is 2 mg/kg administered as an intravenous infusion over 30 minutes every 3 weeks. This is the first PD-1 inhibitor to be marketed in the US. Several other companies, including Bristol-Myers Squibb and Roche Holding AG, also have compounds that target PD-1. Nivolumab (Opdivo®, Bristol-Myers Squibb) has already gained regulatory approval in Japan and is under review by the FDA.
Oritavancin <i>Orbactiv</i> ™ The Medicines Company	The FDA approved this novel semisynthetic glycopeptide antibiotic in September 2014 to treat adults with acute bacterial skin and skin structure infections (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> . A 1200 mg single dose is administered by intravenous infusion over 3 hours. Oritavancin is the third new antibacterial drug approved by the FDA this year to treat ABSSSI. The agency approved dalbavancin (Dalvance™) in May 2014 and tedizolid phosphate (Sivextro™) in June 2014.
Calcipotriene 0.005% + betamethasone dipropionate 0.064% topical suspension <i>Taclonex</i> ® Leo Pharma Inc.	In September 2014, the FDA approved a new indication for this topical combination treatment for plaque psoriasis of the scalp in patients 12 to 17 years – the first indication for adolescent patients aged ≥12 years with scalp plaque psoriasis on the market. This once-daily combination product is indicated for treatment of both scalp and body plaque psoriasis in adults aged ≥18 for up to 8 weeks, and now for the treatment of plaque psoriasis of the scalp in pediatric patients aged 12 to 17 years for the same duration.
Drug News	
In September 2014, Epirus Biopharmaceuticals, Inc., a Boston-based biopharmaceutical company focused on the global development and commercialization of biosimilar monoclonal antibodies, announced that it has received final marketing and manufacturing approvals for its Remicade® (infliximab) biosimilar, BOW015, from the Drug Controller General of India (DCGI). BOW015 is the first infliximab biosimilar approved in India.	