Biologic Therapy and Risk of Infection

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ABSTRACT

Biologic compounds are being used more frequently to treat a multitude of systemic inflammatory conditions. These novel compounds are composed of antibodies or other peptides that act through one of three mechanisms: inhibiting inflammatory cytokine signaling (typically tumor necrosis factor or TNF), inhibiting T-cell activation, or depleting B-cells. The increase in use and ever expanding list of new immune modulating therapies make knowledge of the infectious complications associated with immune modulation even more important. Of particular concern is the risk for developing atypical and opportunistic infections including tuberculosis, herpes zoster, Legionella pneumophila, and Listeria monocytogenes.

Key words: adverse effects, anti-tumor necrosis factor-alpha, infections, monoclonal antibodies, psoriasis, risk factors, TNF-α inhibitors

Background

The availability of immune modulating drugs has revolutionized treatment for psoriasis and psoriatic arthritis, as well as a variety of other inflammatory diseases. After approximately one decade of post-marketing surveillance and experience with biologics, they are generally regarded as safe and efficacious therapy for an increasing number of diseases. However, the risk of infection is a concern with long-term immunosuppressive treatment. We review current literature regarding the risk of infection associated with the biologic therapies most commonly used by dermatologists today: tumor necrosis factor-alpha (TNF-α) inhibitors and ustekinumab.

Infliximab (a chimeric monoclonal anti-TNF antibody) (Remicade®), adalimumab (a fully human anti-TNF monoclonal antibody) (Humira®), and etanercept (a recombinant soluble decoy TNF-receptor) (Enbrel®) exert therapeutic effects via the suppression of TNF-α, a cytokine released by macrophages that is central to cell-mediated immunity.

Ustekinumab (Stelara®), an interleukin 12 and interleukin 23 antibody, targets the p40 subunit shared by the two cytokines to prevent receptor interaction, thereby inhibiting signaling and further cytokine production. Pooled data from phase 2 and 3 clinical trials suggest that there is no clear pattern of heightened infection risk compared with controls (placebo, etanercept) for up to 3 years.1 However, ustekinumab has only been US FDA approved since 2009, so knowledge of long-term risk is limited. Some associations have been reported and are outlined below.

Herpes Zoster

Available evidence regarding the risk of herpes zoster (HZ) with TNF-α therapy is conflicting. One retrospective analysis of psoriasis patients treated with anti-TNF therapy, acitretin, cyclosporine, methotrexate, corticosteroids, UVB phototherapy, or PUVA showed an elevated incidence of HZ infection in patients receiving any treatment except alefacept, efalizumab, or adalimumab when compared with controls (patients without any treatment for 1 month or without treatment for 3 months if most recent treatment was infliximab). None of the biologic drugs studied were associated with a clinically significant increased risk of HZ, however, treatment with infliximab approached clinical significance (hazard ratio [HR]: 1.77, 95% confidence interval [CI]: 0.92-3.43).2

Strangfeld et al. demonstrated a significantly higher risk of HZ in rheumatoid arthritis (RA) patients treated with etanercept, infliximab, or adalimumab compared with conventional disease-modifying antirheumatic drugs (DMARDs). The crude incidence rate per 1000 person-years of HZ was 11.1 (95% CI: 7.9-15.1) for infliximab or adalimumab, 8.9 (95% CI: 5.6-13.3) for etanercept, and 5.6 (95% CI: 3.6-8.3) for conventional RA treatments. Adjustments for age, rheumatoid arthritis severity, and glucocorticoid use demonstrated a significantly higher risk with treatment using monoclonal antibodies (HR: 1.82 [95% CI: 1.05-3.15]), but not for etanercept or the anti-TNF-α antagonists as a class.3
While ustekinumab was not included in the aforementioned studies, there is a report of two patients developing severe, mulitdermatomal herpes zoster 1 and 9 months after initiating therapy with ustekinumab. Vaccination against HZ is strongly encouraged before initiating therapy with ustekinumab.\(^4\) Currently, there are no clear recommendations regarding HZ vaccine (Zostavax\(^\circledR\)) administration during treatment with TNF-\(\alpha\) inhibitors. Interestingly, results of a recent study suggest that treatment with TNF-\(\alpha\) inhibitors may be associated with a lower incidence of postherpetic neuralgia,\(^5\) this finding is also supported by Strangfeld’s data\(^6\) as noted by Whitley in his editorial discussing the prevalence of herpes zoster during immunosuppressive therapy.\(^6\)

**Tuberculosis**

The risk of latent tuberculosis (TB) reactivation in patients treated with biologics is well-established. A Cochrane review evaluating the adverse reactions of all biologic therapies (all TNF-\(\alpha\) inhibitors, anakinra, tocilizumab, abatacept, and rituximab) for any indication found an increased risk of TB reactivation (odds ratio [OR]: 4.68, 95% CI: 1.18-18.60) in comparison with the control treatment group, and a number needed to treat to harm (NNTH) of 681.\(^7\) Several of the drugs included in this review are not commonly used by dermatologists. A recent analysis of the risks associated with TNF-\(\alpha\) inhibitors in psoriasis patients found that the lifetime risk of TB was 0-17.1% in comparison to 0.3% without the use of TNF-\(\alpha\) inhibitors. The authors point out that while there is an increased risk, the risk of tuberculosis is still far lower than the lifetime risk of America’s more common afflictions: cancer (40.4%), heart disease (36.2%), and stroke (18.4%).\(^8\)

Variation in the risk of TB reactivation in patients treated with TNF-\(\alpha\) inhibitors may be expected based on the endemic rates of TB. A recent Spanish study of psoriasis patients receiving any anti-TNF therapy found a 29% incidence of latent TB infection (LTBI), which was comparable to the incidence found in the general population.\(^9\) Conversely, a Swedish study found an increased risk of TB infection for RA patients compared with the general population. Treatment with either infliximab or etanercept was associated with a higher risk of TB in RA patients compared with RA patients not treated with TNF-\(\alpha\) inhibitors.\(^10\)

Among all TNF-\(\alpha\) inhibitors, infliximab is the agent most heavily associated with greater risk of TB. A study of the FDA Adverse Event Reporting System (AERS) between 1998-2002 concluded an increased risk of developing TB for infliximab and etanercept users (144 per 100,000 infliximab-treated patients compared with 35 per 100,000 etanercept-treated patients, p<0.001) with a rate ratio of 4.17.\(^11\) In France, a case-control analysis of newly diagnosed TB associated with anti-TNF agents found that exposure to infliximab or adalimumab versus etanercept was an independent risk factor for TB, OR: 13.3 (95% CI: 2.6-69.0) and OR: 17.1 (95% CI: 3.6-80.6), respectively.\(^12\)

**Listeria monocytogenes**

Infection with the intracellular bacterium *Listeria monocytogenes* (*L. monocytogenes*) in patients receiving biologic therapy is well-documented. An assessment of the incidence of *Listeria* infections in patients using TNF inhibitors was performed by comparing data from the Spanish Registry of Adverse Events of Biological Therapies in Rheumatic Diseases (BIOBADASER) with the Spanish Rheumatoid Arthritis Registry Cohort Study (EMECAR). RA patients treated with TNF-\(\alpha\) antagonists had an increased rate of *Listeria* infection in comparison to RA patients treated with conventional therapy, as well as the general population.\(^13\)

A recent review described the first case of *L. monocytogenes* endocarditis associated with infliximab, and identified 92 cases of *L. monocytogenes* infections related to infliximab treatment in the FDA AERS database. Meningitis was the most common type of infection reported (69 cases, 75%), followed by sepsis (20 cases, 21.7%) and listeriosis (3 cases, 3.3%). Further information was lacking on most of the cases in the AERS database, however, additional immunosuppressive therapy was being used in 22 out of 24 cases detailed in the review.\(^14\) Infectious complications with *Listeria* are seen more frequently in patient treated with infliximab versus etanercept,\(^15\) perhaps because of the more versatile binding of infliximab to both soluble and cell surface TNF-\(\alpha\) instead of predominantly soluble TNF-\(\alpha\). However, there have been several cases of *L. monocytogenes* septic arthritis in patients treated with etanercept.\(^15\)-\(^17\) Adalimumab is reported less frequently in association with *L. monocytogenes* infections, but a case of *L. monocytogenes* meningitis with this therapy has been documented.\(^18\)

**Legionella pneumophila**

*Legionella pneumophila* (*L. pneumophila*) infections account for up to 15% of cases of community-acquired pneumonia requiring hospitalization.\(^19\) Antigenic components of *L. pneumophila* are potent stimuli of TNF-\(\alpha\) production, which along with interferon-gamma, interleukin-6, and interleukin-1 drive induction of the innate immune response. Inhibiting this response with TNF-\(\alpha\) antagonists should predispose to legionellosis.

In France, a registry of 486 multidisciplinary clinical departments was designed by Recherche Axiée sur la Tolérance des Biothérapies (RATIO) to prospectively collect data on severe and opportunistic infections in people receiving TNF-\(\alpha\) antagonists over a 1-year period. There were 10 cases of *L. pneumophila* infections; 6 of the patients were treated with adalimumab, 2 with etanercept, and 2 with infliximab. The median duration of therapy when infection occurred was 38.5 weeks. The relative risk of *L. pneumophila* infection in people receiving anti-TNF therapy was reported as 16.7-21.0 in comparison with the general population. However, this may be an overestimate as 9 out of 10 patients were receiving concomitant immunosuppressive therapy (prednisone, methotrexate, azothioprine, or sulfasalazine), except for one, who was receiving infliximab alone.\(^20\) A recent case review of the incidence of legionellosis in patients receiving infliximab included 10 cases\(^20\) in addition to those reported by the French registry;\(^20\) concomitant immunosuppressive therapy was being used in at least 8 out of 10 of those cases.\(^20\) A British study comparing rates of infection in rheumatoid arthritis patients receiving DMARDs therapy versus TNF inhibitors (etanercept, infliximab, adalimumab, and anakinra) found that the rate of serious infection was equal in both cohorts, but a higher rate of infection with intracellular microbes (*Legionella, Listeria*, and *Salmonella*) occurred in those using TNF inhibitors.\(^21\)
While the exact relative risk of developing *L. pneumophila* during treatment with TNF inhibitors is difficult to predict, there seems to be a clear association in the literature. It is important for clinicians to be mindful of this association and to consider adding fluoroquinolone or macrolide antibiotics for coverage of *Legionella* (and other agents of atypical pneumonia) in patients on anti-TNF-α therapy who present with pulmonary symptoms.

**Fungal Infections**

In 2008, the FDA issued a 'black box warning' to alert clinicians of the risk of endemic mycoses in patients receiving anti-TNF-α therapy. The report included 240 cases of histoplasmosis in patients treated with infliximab, etanercept, or adalimumab. Most cases occurred in areas where the fungus is most prevalent. The most concerning point raised by this report was that in 21 patients, the signs of infection were unrecognized and antifungal therapy was delayed; 12 of those patients died. A recent review addressed challenges of diagnosing fungal infections in patients receiving TNF-α antagonists: atypical presentation and symptoms of infection mimicking the underlying disease. The higher incidence of *Histoplasmosis capsulatum* (*H. capsulatum*) compared to *Blastomyces dermatitidis* or *Coccidioides spp.* in patients taking TNF-α inhibitors is attributed to the wide geographic area of *H. capsulatum*, as well as the fact that infection with *H. capsulatum* is contained almost exclusively by cell-mediated immunity. Multiple cases of aspergillosis have also been associated with TNF-α antagonists.

In patients who are starting treatment with TNF-α antagonists, there is no reliable method to predict the risk for acquiring fungal infections. However, patients should be counseled to avoid high-risk activities that may predispose them to exposure to the endemic mycosis in their geographic areas. Patients who develop endemic fungal infection while receiving TNF-α inhibitors should immediately discontinue the biologic and initiate therapy with antifungal agents in concordance with the Infectious Diseases Society of America guidelines for treatment of these infections in immunocompromised hosts.

**Conclusion**

The risk of infection is always a concern with any immunosuppressive treatment, and such infections are documented with all biologic therapies. Of the TNF inhibitors, infliximab seems to carry the highest risk of infection. In comparison to infliximab, use of etanercept (HR: 0.64, 95% CI: 0.49-0.84), abatacept (HR: 0.68, 95% CI: 0.48-0.96), rituximab (HR: 0.81, 95% CI: 0.55-1.20), and adalimumab (HR: 0.52, 95% CI: 0.39-0.72) was associated with lower rates of hospitalized infections, although the authors attributed variability in patients' risk of infection to factors other than treatment with biologics. Additionally, a 3-year national French registry (RATIO) study comparing incidence of non-tuberculosis opportunistic infections (45 cases in 43 patients) between TNF-α inhibitors found that risk factors were infliximab (OR: 17.6 [95% CI: 4.3-72.9]; p<0.0001) or adalimumab (OR: 10.0 [95% CI: 2.3 to 44.4]; p=0.002) versus etanercept.

Still, it is difficult to predict the true risk to patients commonly seen in the dermatologist's clinic when: 1) Most reviews of biologics-associated opportunistic infections are comprised of patients being treated for conditions other than psoriasis and 2) Most cases of opportunistic infections associated with biologic therapy occur when additional systemic immunosuppressive therapy is being utilized. Variation in dates of approval for these medications also translates to variation in experience.

The overwhelming majority of evidence supports the idea that biologics are safe for the treatment of psoriasis. Grijalva et al. recently published the results of a US multi-institutional collaboration examining whether or not TNF-α antagonists are associated with an increased risk of serious infections requiring hospitalization in comparison to non-biologic therapy. The cohorts studied included 10,484 RA, 2,323 inflammatory bowel disease, and 3,215 psoriasis and spondyloarthropathies. In total, 1,172 serious infections were identified, the majority of which (53%) included pneumonia and skin and soft tissue infections. The conclusion was that TNF-α inhibitors are in fact, not associated with an increased risk for hospitalization for serious infection. These findings contradict a general, replicated pattern seen in previous studies evaluating the safety of TNF-α antagonists, i.e. that there is a higher rate of serious infection in patients taking anti-TNF-α therapy compared to patients using non-biologic therapy that decreases with time. Dixon and Felson's editorial addressed the question of why the time-dependent risk of serious infection was not seen in Grijalva's report. The authors attribute this finding to the unique design of Grijalva's study, i.e., comparing the risk of serious infections between new user cohorts, not between patients initiating treatment with anti-TNF-α therapy versus those receiving treatment with non-biologic agents. In other words, the time-dependent risk may disappear when both cohorts are examined at the same point in their course of treatment. Of course, this finding has yet to be replicated, but it does warrant a re-evaluation of the safety of anti-TNF-α therapy. Most would agree that the benefits of biologics outweigh the risks and that clinical practice measures such as screening, prevention, and vigilance are effective in limiting the risk of potential opportunistic infections associated with immunotherapy.

**References**


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The Role of Imiquimod 3.75% Cream in the Treatment of External Genital Warts

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ABSTRACT
Imiquimod 3.75% cream has recently been approved by both the U.S. Federal Drug Administration and Health Canada for the treatment of external genital warts. Herein, we provide an overview of external genital warts, review the phase 3 clinical trials leading to the approval of imiquimod 3.75% cream, and compare its efficacy and clinical use with imiquimod 5% cream. Moreover, therapeutic options have further expanded with the relatively recent introduction of sinecatechins 15% ointment, an extract of green tea leaves.

Key words: condylomata acuminata, external genital warts, human papilloma virus, HPV, imiquimod, sinecatechins, sexually transmitted infection, STI, topical immunotherapy

External Genital Warts
External genital warts (EGW) have been reported to affect approximately 1.4 million people in the US.1 More than a half a million new cases develop annually and 10% of all adults will have EGW in their lifetime.1 The etiology of EGW has been clearly linked to infection with non-oncogenic strains (types 6 and 11) of the human papilloma virus (HPV) transmitted through sexual contact.1

EGW commonly manifest on fully or partially keratinized skin, such as the penis, vulva, groin, perineum, and perianal areas.2 While EGW can be asymptomatic, patients can experience pruritus, dyspareunia, and burning in the anogenital region. EGW can obstruct the urethral orifice and vagina, and impede normal activity. Additionally, large warts can cause obstruction of the anus and rectum.3

Besides physical pain and discomfort, EGW can cause complicated psychological morbidity. Since the disease targets areas of the genitalia and carries the psychosocial stigma of being a sexually transmitted infection, patients can experience a range of emotions, including anger, shame, depression, and low self-worth as potential partners.3-6 Additionally, the disease can impact the sexual activity of affected individuals, either through actual physiologic pain (in cases of dyspareunia) or through abstinence due to either fear of transmitting to partners or embarrassment of the lesions.3 Finally, EGW induces anxiety over treatment efficacy7-8 and/or recurrences,9 as well as the lesion’s potential to develop into a malignancy.4 The health and economic burden of EGW is significant, e.g., average number of care days per episode was approximately 96 in 2004.9 From 1999 to 2008 the average yearly number of initial physician office visits increased from 240,000 to 385,000.10

Although EGW spontaneously regresses 30%-3-5 of the time without treatment, there is no way to determine whether a specific lesion will regress, remain unchanged, or increase in size. Treatment should be offered to all patients with EGW resulting from unprotected sexual contact or ineffective prophylactic measures (e.g., condoms, abstinence, or HPV vaccine). Treatment options are available including surgical excision, destructive modalities (e.g., cryosurgery and laser ablation), and topically applied preparations. It is not uncommon for multiple modalities to be used (e.g., excision/destruction with imiquimod). It is outside the scope of this paper to present a cogent review of all therapies, the discussion will instead focus on topically applied imiquimod 3.75%, which received recent regulatory clearance for the treatment of EGW.

Topical Immunotherapy for EGW
Imiquimod 3.75% cream (Zyclara®) is US FDA approved for the treatment of external genital (EGW) and perianal warts - it is marketed in Canada under the trade name Vyloma™ for EGW and Zyclara® for actinic keratoses. Imiquimod, an imidazoquinoline heterocyclic amine, demonstrates antiviral and antitumor properties that are thought to stem, at least in part, from its ability to induce interferon-α as shown in animal studies.11 Specifically, it is an agonist of Toll-like receptor-7 (TLR-7), a member of a pathogen-recognition receptor family.12 Activation of TLR-7 ultimately enhances antigen-presenting cell activity, migration of Langerhans cells, and cytokine (IFN-α, TNF-α, and IL-1, 6, 8, 10, and 12) release.13 Upregulation of IFN-α, β, and γ and TNF-α has a strong association with EGW regression, as well as with a reduction in human papilloma virus DNA and mRNA.13,14

Elicitation of these immunobiologic changes by imiquimod is not just theoretical. Imiquimod 3.75% was challenged in a clinical study against a vehicle control.12 Study inclusion criteria required patients to be >12 years of age with 2 to 48 visually diagnosed lesions. The wart size was at least a 6 mm cluster of warts considered as 1 lesion. At each visit, the number of warts was tallied with no differentiation as to whether the
lesion was a new growth or an older lesion that had decreased in size. The study was conducted for a maximum of 8 weeks or until complete clearance occurred. The primary endpoint of the study was complete clearance by the end of the study. Secondly, the researchers observed the sustained complete clearance for a 12-week period. This latter parameter demanded the sustained complete clearance in all areas. Of notable mention, it is very possible that new warts arising very close to the end of the study may not have received any treatment. Resultantly, such patients would have failed to meet the primary endpoint of the study.12 Overall, the imiquimod 3.75% cream achieved 27% and 29% significant complete clearance in two different studies, compared with 10% and 9% complete clearance in the respective controls. Females, who for the most part exhibited better response over males, showed a significant complete clearance of 37% in the active treatment group compared to females in the vehicle control group, who demonstrated 14% complete clearance. In treated males, 19% achieved complete clearance as opposed to 4% of males in the control group. After a 12-week observation period of patients who had achieved complete clearance, 85% treated with imiquimod 3.75% cream remained clear.12 A recent study comparing imiquimod 3.75% with placebo in female EGW patients found similar results.13 The study group had a mean wart count of 8.7 with the total mean area of 166.3 mm². Patients receiving imiquimod treatment demonstrated superior clearance over placebo; the median time to clearance was 57 days for imiquimod 3.75% compared with 71 days for placebo. Some other interesting variables that may have contributed to a higher complete clearance rate for imiquimod therapy over placebo include non-white patients, ≤7 warts, total wart area ≤150 mm², diagnosis at ≤6 months, and first episode vs. recurrence. The researchers also looked at the ≥75% clearance and found that again imiquimod 3.75% exhibited greater efficacy compared with placebo. However, the sustained clearance during a 12-week follow up was only 60.4% in imiquimod-treated patients vs. 100% in placebo.

How does Zyclara® differ from Aldara®?

Imiquimod 5% cream (Aldara®) has been FDA approved for the treatment of EGW since 1997. While imiquimod 5% is efficacious for EGW treatment, it is associated with localized adverse effects, including erythema, pruritus, burning, and pain. The standard treatment course requires dosing at 3 times weekly for up to 16 weeks, which may discourage adherence to the regimen.16 Tolerance of burning and itching for close to 4 months in the anogenital areas can be challenging for patients to endure. A compounding complication is the cumbersome number of treatment days per week, potentially contributing to unintentional noncompliance due to forgetfulness, missed dosing, and confusion as to how to proceed when therapy deviates from the prescribed regimen. Treatment complexity can frustrate patients and contribute to premature termination of therapy. This thought process is confirmed by Murphy and Coster, who have noted that long treatment duration and adverse affects have been associated with decreased compliance.17 In addition, they suggest linking treatment times with daily habits as one of the strategies to increase compliance,17 which can be quite difficult if the regimen is 3 times per week.

Development of imiquimod 3.75% focused in part on increasing tolerability and simplifying the treatment regime. Investigation of the 3.75% formulation was undertaken with the intention of reducing the incidence and severity of local skin reactions commonly associated with imiquimod 5%. The total treatment period for imiquimod 3.75% is 8 weeks14 as opposed to 16 weeks for imiquimod 5% cream.16 The significantly reduced treatment duration and simplified once-daily application offers a more intuitive dosing regimen that can enhance patient adherence.

Another favorable aspect of imiquimod 3.75% that may encourage treatment compliance is its improved tolerability profile as compared with the 5% formulation. In the phase 3 trials, pruritus only occurred in 3% of all imiquimod 3.75% treated patients and irritation was experienced by 6%.12 Burning was not listed as an independent parameter.12 Similarly, Baker et al. reported pruritus in 7.8% of treatment patients and irritation in 5.5%.15 To put these findings into perspective, in patients treated with imiquimod 5%, pruritus was reported by 32% of female patients and 22% of males; burning was experienced by 26% of female subjects and 9% of males.14 Therefore, imiquimod 3.75% not only shortens a course of therapy by half, but it also demonstrates increased tolerability and dosing simplicity, thereby encouraging treatment follow-through and optimizing outcomes.

Sinecatechins (Green Tea Extract)

It is appropriate to briefly mention sinecatechins 15% ointment (Veregen®), the first botanical drug product approved by the FDA for the treatment of external genital and perianal warts. It contains sinecatechins, including epigallocatechin gallate, derived from green tea leaves. Sinecatechins 15% ointment is applied 3 times a day for up to 16 weeks.18 Two randomized, double-blind, vehicle controlled studies of both men and women with EGW reported an overall clearance rate of 54.9%; after 6 weeks of therapy, statistically significant differences in clearance rates were observed in patients receiving active treatment.18 The 12-week sustained clearance was 93.5% of fully cleared patients. Interestingly, the comparator vehicle group showed a complete clearance rate of 35.4% and a sustained clearance rate of 94.2%.

Insights into the possible mechanism(s) of action of sinecatechins in treating EGW were recently presented.19 In vitro experiments indicated inhibition of matrix metalloproteinase 1, 2, 7, and 9, as well as 20S proteasome activity. In addition, significant suppression of human epidermal growth factor receptor (EGFR) kinase and partial inhibition of extracellular signal-regulated kinases ERK-1 and ERK-2 were also implicated. Furthermore, suppression of inflammatory mediators COX-1 and COX-2 and the lipoxygenase (LO) 12 and 15 proteins were detected. These pathways are involved in the pathogenesis of HPV infection and epidermal proliferation, thereby leading the author to reasonably conclude that these inhibitory activities confer immunostimulant, antiviral, and antitumor properties to sinecatechins that contribute to EGW clearance.19

Conclusion

In our opinion, imiquimod 3.75% (Zyclara®/Vyloma™) offers a more tolerable and simplified therapeutic option for EGW patients to adhere to therapy. In addition, the recent US regulatory
approval of this agent in a pump dispenser further widens the
dosing options (established forms consist of individual packets
of Aldara® and generic 5% imiquimod cream), such a vehicle
advance can facilitate ease of use, improve patient acceptability,
and enhance compliance. A study determining the combined
effectiveness of sequential cryotherapy followed by a course
of imiquimod 3.75% is warranted, as in clinical practice many
patients, if not most, are treated with both modalities.

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- Lice.ca
- PsoriaticArthritisGuide.ca
- Sweating.ca
- StaphInfection.com
- GenitalWarts.ca
- MildCleanser.ca
- RosaceaGuide.ca

Medical professional sites:
- Dermatologists.ca
- PASItreatment.com
- SkinTherapyLetter.ca
- SkinCareGuide.ca
- SkinPharmacies.ca

Social networking sites for patients and health care professionals:
- GenitalWartsPatients.com
- PsoriasisPatients.com
Ivermectin 0.5% lotion

Sklice™
Sanofi Pasteur U.S.

The US FDA approved this broad-spectrum antiparasitic agent in February 2012 for the topical treatment of head lice in patients 26 months of age. Treatment eradicates most infestations with a single 10-minute application and without nit combing. In clinical trials, <1% of patients experienced adverse events, such as conjunctivitis, ocular hyperemia, eye irritation, dandruff, xerosis, and burning sensation of the skin.

Ipilimumab

Yervoy™
Bristol-Myers Squibb

Health Canada approved this human monoclonal antibody in February 2012 for the treatment of metastatic melanoma. Administered intravenously, the drug blocks a T-lymphocyte antigen (CTLA-4), altering the body’s ability to fight off cancerous cells and allowing the immune system to recognize, target, and attack cells in melanoma tumors.

Vemurafenib

Zelboraf®
Plexxikon Inc.

Daiichi Sankyo Group

The European Commission approved this oral, small molecule, kinase inhibitor in February 2012 for the treatment of adult patients with BRAFV600 mutation-positive unresectable or metastatic melanoma. This BRAF enzyme inhibitor was approved with a companion diagnostic (cobas® 4800 BRAF V600 Mutation Test) that determines a patient’s eligibility for treatment.

Device News

Cellulite removal laser device

Cellulaze™ Cellulite Laser Workstation

Cynosure, Inc.

The US FDA granted 510(k) clearance for commercial distribution to this novel aesthetic laser device in January 2012 for the long-term reduction of cellulite. This anti-cellulite system utilizes laser fiber and thermal technologies to reduce fat deposits, release areas of skin depression, and increase elasticity and skin thickness. The surgical procedure is minimally invasive (though insertion of a small cannula under the skin), performed under local anesthesia, and completed in one treatment session.

Drug News

Phase 2 data for a promising new non-surgical injectable treatment for the reduction of submental (under the chin) fat were presented in March 2012 at the American Academy of Dermatology’s 70th Annual Meeting in San Diego, CA. The results were from phase 2B and long-term follow-up clinical trials on ATX-101 (KYTHERA Biopharmaceuticals, Inc.), an investigational drug that causes localized adipocytolysis.1-2 ATX-101 is a proprietary, non-animal derived form of deoxycholate and is being evaluated as a pharmacologic treatment for the reduction of submental fat (SMF). The phase 2B trial was a double-blind, randomized, placebo-controlled study of 129 subjects with moderate or severe SMF. Subjects received injections of one of two ATX-101 doses (1 mg/cm² or 2 mg/cm²) or placebo, administered monthly for up to 5 months into the SMF area. ATX-101 at the 2 mg/cm² dose demonstrated a statistically significant clinical benefit compared with placebo in the reduction of SMF as assessed by three efficacy measures: a validated clinician scale, patient reported outcome scale, and MRI measuring SMF volume and thickness. Adverse events were generally mild, the most common included swelling, pain, numbness, bruising, and induration. No systemic adverse events were observed. Additionally, 2-year results from a long-term follow-up study of subjects enrolled in earlier phase 2A trials demonstrated that >90% of subjects who responded to ATX-101 treatment sustained aesthetic correction as measured by the validated clinician scale.

1. Reduction of submental fat with ATX-101: Results from a phase 2B study using investigator, subject, and magnetic resonance imaging assessments (Poster#: 4787).

2. ATX-101 treatment offers long-term durability of submental fat reduction: Preliminary follow-up study results of subjects from phase 2 studies (Poster#: 4899).