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Small Molecules: An Overview of Emerging Therapeutic Options in the Treatment of Psoriasis

Melinda Gooderham, MD, MSc, FRCPC

Skin Centre for Dermatology, Peterborough, ON, Canada

ABSTRACT

Psoriasis is a chronic condition which requires ongoing management with therapies that have demonstrated favorable safety and efficacy profiles in long-term use. While biologics changed the way psoriasis is treated by providing effective targeted therapy, they are not without limitations. However, small molecules are emerging therapeutic options for the treatment of psoriasis. Several oral and topical small molecules, spanning different therapeutic classes, are proving to be promising treatment options in psoriasis. While studies to date have yielded positive results, further investigation of these agents are warranted for both safety and efficacy.

Key words: apremilast, baricitinib, dimethyl fumarate, fumaric acid esters, inflammation, JAK inhibitors, Janus kinases, phosphodiesterase 4 inhibitors, ponesimod, psoriasis, ruxolitinib, small molecules, sphingosine 1-phosphate receptor agonists, tofacitinib

Introduction

Insights into the pathogenesis of psoriasis coupled with a detailed understanding of the action of cytokines and their associated transduction pathways have yielded a number of new therapeutic targets. Psoriasis is a chronic condition and, therefore, requires ongoing management with safe and effective therapy. The introduction of biological agents has changed the way we treat psoriasis, providing more efficacious and directed therapy for this complex disease. Although excellent treatment options, biological agents have limitations: side effect profile, immunogenicity, contraindication and lack or loss of efficacy in some patients. On the horizon are new therapeutic options for patients with psoriasis: small molecules including oral Janus kinase (JAK) inhibitors, tofacitinib (CP-690,550) (Pfizer), baricitinib (LY3009104) (Eli Lilly), ASP015K (Janssen), as well as a topical agent, ruxolitinib (INCB018424) (Incyte), which is also available in an oral form. Agents from other therapeutic classes are also being investigated, including two from the phosphodiesterase 4 inhibitor class, oral apremilast (CC-10004) (Celgene) and topical AN2728 (Anacor), one from the sphingosine 1-phosphate receptor agonist class, ponesimod (ACT-128800) (Actelion), and a fumaric acid ester, dimethyl fumarate (FP187) (Forward-Pharma GmbH).

JAK Inhibitors (Jakinibs)

The Janus kinases, a group of tyrosine kinases comprised of JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2), are mainly found in hematopoietic cells. These kinases reside on the cytoplasmic side of Type I and II cytokine receptors. Kinases are invoked as part of signal transmission when cytokines bind to their cognate receptors. JAKs activate the intracellular transcription factors known as signal transducers and activators of transcription (STATs). The binding of STAT to an activated JAK results in phosphorylation and subsequent dimerization and translocation to the nucleus, where it directly modulates gene transcription.[1-3]

The JAKs play an important role in immune defense as we have learned from a series of mutant cell lines, mouse knock-out models and the clinical expression of JAK3 mutations, resulting in severe combined immunodeficiency. Inhibiting this pathway has been beneficial in treating immune-mediated diseases, including rheumatoid arthritis, inflammatory bowel disease and psoriasis, as well as preventing allograft rejection.[3]

The JAK inhibitors, or so-called jakinibs, uncouple cytokine receptor signaling from downstream STAT transcription activation and, thereby, modulate immune response in these disease states (Figure 1). The potential side effects of these agents are partially predictable and are directly related to their mode of action. These effects can include neutropenia and anemia, which are likely related to JAK2 inhibition. JAK2 is associated with the erythropoietin (EPO) receptor. Such effects are possibly dose-related and, to date, have been mild and appear not to be limiting usage. Not as well understood are some reports of hyperlipidemia (total cholesterol, LDL cholesterol and HDL cholesterol) similar to that seen with the interleukin (IL)-6 inhibitor, tocilizumab.[3] This mechanism is still under investigation.

Tofacitinib

One of the first JAK inhibitors used in humans was tofacitinib (formerly called tasocitinib), a potent inhibitor of JAK3, which was also found to have activity against JAK1 and to a lesser extent JAK2.[1,3] It has been reported to be a safe and effective therapy for ulcerative colitis[4] and rheumatoid arthritis, both with and without concomitant methotrexate therapy.[5,6] Tofacitinib has

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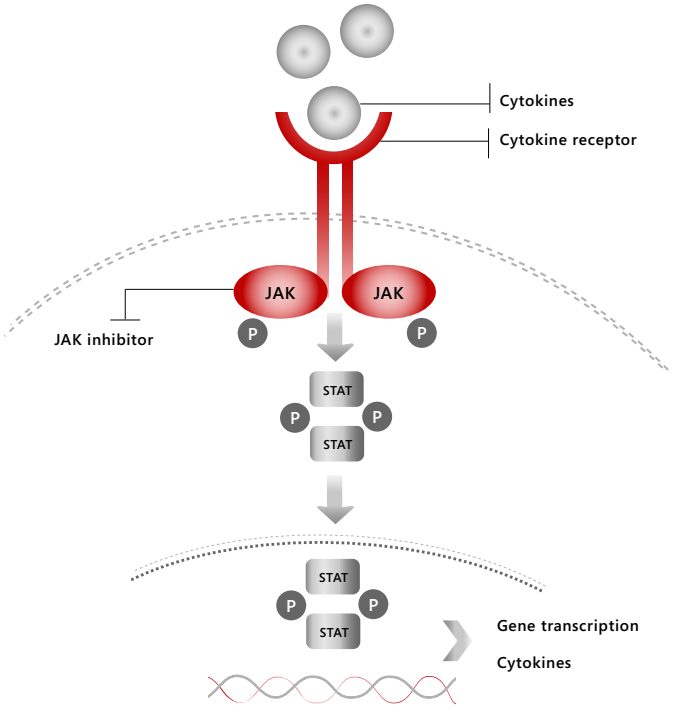

Figure 1: JAK inhibitors uncouple cytokine receptor signaling from downstream STAT transcription activation and thereby modulate immune response

STAT = signal transducers and activators of transcription; P = phosphate

been approved for use in rheumatoid arthritis in the US. For psoriasis, the initial Phase 1 trial was a randomized, double-blind, placebo-controlled, dose-escalation study examining 5 mg, 10 mg, 20 mg, 30 mg, and 50 mg twice daily (BID) and 60 mg once daily (OD) for 14 days in 59 patients.[7] Boy et al. (2009) found a significant dose-dependent decrease in erythema, induration and scaling using the Psoriatic Lesion Severity Sum (PLSS) from baseline to day 14 in all doses except 5 mg BID.[7] Results of skin biopsies showed marked histological improvement at the higher dose of 30 mg BID with decrease in lesional thickness and K16 expression (a keratinocyte growth activation marker) to normal or near normal.[7] In this initial study, adverse effects noted were an increase in total cholesterol, LDL cholesterol and triglyceride compared to placebo.

Papp et al. (2012) published results of the Phase 2b dose-ranging study in psoriasis.[8] One hundred and ninety-seven patients with severe psoriasis were randomized to receive tofacitinib 2 mg, 5 mg, 15 mg or placebo BID and a clear dose-response was observed. A significant Psoriasis Area and Severity Index (PASI) 75 response was seen as early as week 4 and lasted through week 12. They reported a PASI 75 of 25% (2 mg, $p<0.001$), 40.8% (5 mg, $p<0.0001$) and 66.7% (15 mg, $p<0.0001$) in treated patients vs. 2% of patients in the placebo group.[8] Patients treated with tofacitinib also demonstrated a significant and rapid improvement in pruritus compared to those receiving placebo.[9]

The most common adverse effect reported was infection and some dose-related changes in laboratory parameters were also observed. Mild reductions in hemoglobin and mean absolute neutrophil counts were noted starting at week 2 and were most pronounced in the 15 mg BID group; elevations in total cholesterol, HDL cholesterol and LDL cholesterol were also reported in a dose-related fashion similar to Phase 1 data.[8] Currently, Phase 3 studies are evaluating the safety and efficacy of 5 mg and 10 mg BID dosing; as well, one comparator study is being conducted with etanercept.

As of October 2013, Pfizer announced that two of the five psoriasis Phase 3 studies have reported beneficial results as expected from Phase 2 data.[10] The 12-week non-inferiority study comparing tofacitinib with high-dose etanercept and the 56-week retreatment investigation both met primary safety and efficacy endpoints, and further information should be published in the coming months.

Baricitinib

A newer JAK inhibitor under investigation is baricitinib (Eli Lilly), which preferentially inhibits JAK2 over JAK1 and JAK3. Not much has yet been published on this molecule and it has just recently completed Phase 2 trials. The Phase 2b study was a randomized, double-blind, dose-escalation study evaluating 2 mg, 4 mg, 8 mg, and 10 mg BID vs. placebo (ClinicalTrials.gov, identifier NCT01490632). Phase 1 and 2 data have not yet been published.

ASP015K

ASP015K (Janssen, previously Astellas) is another oral JAK inhibitor that has shown selectivity of JAK1/JAK3 over JAK2 in cell-based assays. A Phase 2a randomized, placebo-controlled, sequential dose-escalation study of 10 mg, 25 mg, 60 mg, 100 mg BID or 50 mg OD was carried out over 6 weeks in patients with moderate to severe psoriasis. ASP015K demonstrated efficacy with dose-dependent reductions in body surface area (BSA) and mean PASI and Psoriasis Static Global Assessment (PSGA), and was generally well-tolerated.[11] Janssen acquired ASP015K in October 2012, and there are no current plans to develop this drug in a psoriasis platform.

Topical JAK Inhibitors

In contrast to other biologics, due to their small size, these agents have also been demonstrated to be of benefit when applied topically. Topical tofacitinib has been studied (ClinicalTrials.gov, identifier NCT00678561) on 81 patients with OD or BID application of 0.02%, 0.2% and 2% ointment compared to vehicle for 28 days, although results are not yet published. A Phase 2b trial of topical tofacitinib comparing two dose strengths and two dose regimens is currently underway (ClinicalTrials.gov, identifier NCT01831466).

Ruxolitinib, the first US FDA-approved selective JAK1/JAK2 drug used orally for myelofibrosis,[3] has also been investigated in its topical form (INCB018424, Incyte) for use in psoriasis. A Phase 2a trial comparing topical INCB018424 0.5%, 1% and 1.5% cream in a double-blind, vehicle-controlled fashion was shown to be safe and effective with improvement in total lesion score, PGA and PASI.[12,13] This study compared topical INCB018424 with currently approved topical therapies, calcipotriene 0.005% cream and betamethasone diproprionate 0.05% cream[13] (ClinicalTrials.gov, identifier NCT00820950).

Phosphodiesterase 4 (PDE4) Inhibitors

Cyclic adenosine monophosphate (cAMP) is the principal secondary messenger responsible for immune response regulation. PDE4 is the main cAMP degrading enzyme found in

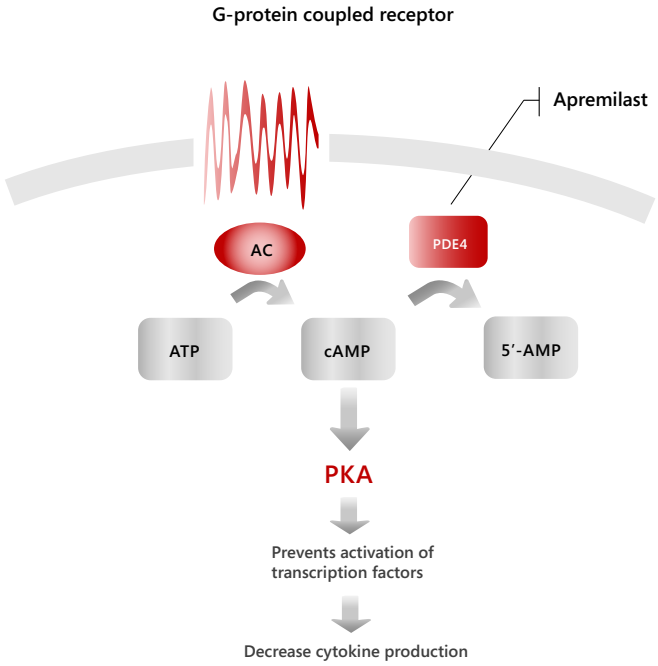

Figure 2: Action of PDE4 inhibitors can prolong or enhance effects of cAMP and result in suppression of both Th1 and Th2 immune responses

G-protein coupled receptor = integral membrane proteins that respond to extracellular stimuli in a cAMP dependent fashion; AC = adenylate cyclase; PKA = protein kinase A

cells of the immune system and keratinocytes. Inhibitors of PDE4 can prolong or enhance effects of cAMP, resulting in suppression of both Th1 and Th2 immune responses (Figure 2).[14] Due to these immune modulating effects, PDE4 inhibitors are currently under investigation for a variety of conditions including asthma, chronic obstructive pulmonary disease, atopic dermatitis, psoriasis, and psoriatic arthritis.[14,15]

Apremilast

The PDE4 inhibitor, apremilast (CC-10004, Celgene Corporation), has been shown to inhibit production of the pro-inflammatory cytokines, interferon (IFN)-gamma, tumor necrosis factor (TNF)-alpha, IL-12 and IL-23, which are major players in the pathogenesis of psoriasis. Apremilast was shown to have a range of anti-inflammatory effects on a variety of cell lines *in vitro* and reduce the psoriasiform response in a preclinical model of psoriasis *in vivo*,[15] as well as demonstrate biologic activity in a pilot study in humans[16].

A Phase 2, randomized, placebo-controlled trial demonstrated efficacy of apremilast 20 mg BID for 12 weeks in 259 patients.[17] Apremilast at 20 mg BID achieved PASI 75 in 24.4% of patients compared to only 10.3% of patients in a placebo group. A dose-response was observed with a mean percent reduction in PASI from baseline of 17.4% for placebo, 30.3% for apremilast 20 mg OD, and 52.1% for apremilast 20 mg BID.[17] Papp et al. (2012) reported results from the Phase 2b double-blind, randomized, placebo-controlled crossover trial in 352 patients, which compared apremilast 10 mg, 20 mg, 30 mg or placebo BID for 16 weeks, at which point patients receiving placebo were then randomized to 20 mg or 30 mg BID for up to 24 weeks. The primary endpoint of PASI 75 at 16 weeks was 11% for 10 mg, 29% for 20 mg, and 41% for 30 mg BID vs. 6% of patients on placebo.[18]

Patients treated with apremilast also demonstrated significant improvement on patient-reported quality of life outcomes with particular benefit noted at the 30 mg BID dose.[19] Reported adverse effects were mild to moderate and included headache, nausea, urinary tract infection and diarrhea, but no significant changes in laboratory values were observed in any of the trials.

Phase 3 studies investigating the long-term safety and efficacy of the 30 mg BID dose are currently ongoing. The preliminary findings from ESTEEM-1, a Phase 3 trial including 844 patients receiving oral apremilast 30 mg BID, reported a PASI 75 response of 33% at week 16 compared to the placebo response of 5.3%.[20]

Topical PDE4 Inhibitors

The development of oral PDE4 inhibitors has been limited in some instances by systemic side effects, which prompted development of topical therapeutic options. This led to discovery of a novel boron-containing topical PDE4 inhibitor, AN2728 (Anacor Pharmaceuticals Inc.).[21] Phase 1 and 2 trials on AN2728 have already been completed for psoriasis and Phase 2 trials are ongoing for use in atopic dermatitis. AN2728 was found to be both efficacious and well-tolerated in psoriasis.[22] In a previously reported Phase 2b randomized, double-blind, vehicle-controlled 12-week bilateral comparison study on 145 adults who acted as their own controls, subjects were randomized to 2% or 0.5% ointment vs. vehicle ointment OD or BID. In patients with mild to moderate plaque psoriasis, AN2728 2% ointment BID provided most benefit and was well-tolerated with no safety concerns.[23] Phase 3 trials in psoriasis have received clearance by the FDA, but have not yet been registered as Anacor is currently focusing the development of AN2728 in atopic dermatitis (http://www.anacor.com/an2728.php accessed October 7, 2013).

Sphingosine 1-Phosphate Receptor Agonists

Sphingosine 1-phosphate (S1P) is a sphingolipid required by lymphocytes to exit the lymphoid tissue and enter the bloodstream via a chemotactic gradient.[24] Agonists of the S1P receptor cause a blockade of lymphocyte migration out of the lymph tissue through internalization of the receptor, resulting in a sequestration of lymphocytes. Recent development of S1P agonists involve utilizing these agents in the treatment of lymphocyte-mediated autoimmune conditions such as multiple sclerosis. Most recently, a drug from this class, fingolimod, was approved for the treatment of multiple sclerosis.[25]

Ponesimod

The $S1P_1$ agonist, ponesimod, has been studied in psoriasis vulgaris in a Phase 2, randomized, placebo-controlled trial (ClinicalTrials.gov, identifier NCT01208090) involving 326 patients who were randomized to receive ponesimod 20 mg, 40 mg or placebo for a 16-week induction period, followed by re-randomization to a 12-week maintenance period.[26] At 16 weeks, 46% of the 20 mg group and 48.1% of the 40 mg group reached the primary endpoint of PASI 75 compared to 13% of patients receiving placebo. At week 28, the end of the maintenance period, the PASI 75 score further improved to 71% and 77% for the 20 mg and 40 mg groups, respectively, compared to 42% and 40% of patients who were re-randomized from ponesimod

to placebo.[26] Safety analysis revealed an expected decrease in lymphocyte counts, which returned to baseline values 2 weeks after discontinuation of therapy and was not associated with an increased risk of infection. Other notable effects include dyspnea, transaminitis, nasopharyngitis, headache and dizziness.[26]

Fumaric Acid Esters

Fumaric acid esters (FAEs) are a group of small molecules that have been used for many years in Germany to treat psoriasis. Initial use for psoriasis can be traced to 1959 by the German biochemist Schweckendiek who himself suffered from psoriasis. More recently, FAEs have gained attention as an immunomodulatory therapy for multiple sclerosis.[27] Since 1994, FAEs have been available as a mix of dimethyl fumarate (DMF) and three salts of ethylhydrogenfumarate under the trade name Fumaderm® (Fumapharm/Biogen Idec) and widely used in some European countries.[27,28] The mechanism of action is not completely understood, but one theory suggests that FAEs increase glutathione level in the cell, resulting in inhibition of nuclear factor-kappa B (NFκB) translocation into the nucleus and, thereby, a reduction of inflammatory cytokine production.[27] Other immunologic effects are discussed in more detail elsewhere.[28] The use of Fumaderm® has been limited by its gastrointestinal side effects in up to 30% of patients, thus, a newer formulation of DMF is being investigated.

Dimethyl Fumarate (FP187)

FP187 is a patented controlled-release erosion matrix tablet of DMF produced by Forward-Pharma GmbH. A pivotal Phase 2 study has been completed (ClinicalTrials.gov, identifier NCT01230138) which examined the safety and efficacy of different doses of FP187, but the results have not yet been reported. A Phase 3 study is registered to compare 500 mg of FP187 (250 mg BID) to the commercially available Fumaderm® at a dose of 720 mg (240 mg three times daily) over 20 weeks (ClinicalTrials.gov, NCT01815723) and is likely to start in the fourth quarter of 2013.

Conclusion

Psoriasis vulgaris is a chronic condition in which effective and safe therapies are needed for long-term use. To date, there have been promising results with small molecules for psoriasis including JAK inhibitors, PDE4 inhibitors, an S1P agonist, and DMF. The advantages of the small molecules are that they are amenable to both oral and topical use, do not require subcutaneous or parental administration, and avoid risk for immunogenicity. The mechanism of action of JAK inhibitors, PDE4 inhibitors and DMF provide downstream inhibition of the inflammatory cascade, resulting in blockade of multiple cytokines, which target cell types that are key players in psoriasis. The S1P agonists result in immunomodulation via sequestration of lymphocytes in lymphoid tissue. Time will tell whether any further new therapeutic targets are developed, such as TYK2, the final Janus kinase in the JAK family involved in cytokine signaling, which has not yet been investigated for psoriasis. TYK2 also appears to be a promising target as it associates with the receptors for IL-12/23 and IL-6, the major players in psoriasis pathogenesis. Another oral molecule to look out for is apilimod (STA-5326) (Synta Pharmaceuticals), which blocks the IL-12/23 pathway and has been studied in Phase 2 trials. Further investigations of these small molecules are warranted for both safety and efficacy, but we look forward to the possibility of new therapies as treatment options for our patients in the future.

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Chronic Urticaria and Autoimmunity

Kathleen Fraser BHSc[1] and Lynne Robertson MD, FRCPC[2]

[1]College of Medicine, University of Saskatchewan, Saskatoon, SK, Canada

[2]Section of Dermatology, Department of Medicine, University of Calgary, Calgary, AB, Canada

ABSTRACT

Chronic urticaria is defined as hives, typically occurring daily, for greater than 6 weeks duration. Chronic idiopathic urticaria, which has no discernable external cause, comprises the majority of cases of chronic urticaria. Over half of all cases of chronic idiopathic urticaria are thought to occur by an autoimmune mechanism, primarily autoantibodies against the high affinity immunoglobulin E (IgE) receptor (FcεRI). Chronic urticaria is hypothesized to occur because of a predilection in the patient to develop reactions to self. Supporting this hypothesis, a strong association has been found between chronic urticaria and additional autoimmune diseases, such as thyroid disease, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, celiac disease and type 1 diabetes, among others. Herein, we review the associations between chronic urticaria, thyroid disease, and other autoimmune disorders, as well as the implications that these correlations hold for therapeutic intervention in chronic urticaria.

Key words: angioedema, antibodies, autoimmune disease, chronic disease, comorbidities, complications, hives, hypersensitivity, inflammation, thyroid disease, urticaria

Introduction

It is estimated that urticaria will affect 25% of the population at some point in their lifetime.[1] Chronic urticaria (CU) involves hives, typically occurring daily, for greater than 6 weeks duration. CU generally lasts 1 to 5 years, but can have a prolonged course beyond 5 years in roughly 14% of patients.[2] Individuals affected by CU have reported emotional distress, feelings of isolation and fatigue in response to their condition, similar to findings in patients with ischemic heart disease.[3] This underscores the importance of managing CU appropriately to minimize both physical and psychological impacts of this disease.

CU can occur in response to drugs, physical stimuli, as part of inflammatory or inherited diseases, or can be idiopathic in nature. Acetylsalicylic acid (ASA) or nonsteroidal anti-inflammatory drug (NSAID) intolerant CU is hypothesized to occur due to inhibition of the cyclooxygenase pathway, which causes enhanced production of leukotrienes.[4] The physical urticarias (classically divided into heat, cold, solar, vibration, delayed-pressure, dermatographism, aquagenic and cholinergic induced urticaria) occur in response to external stimuli.[5] Urticarial vasculitis involves the appearance of urticarial lesions lasting greater than 24 hours in the hisopathological setting of vasculitis.[6] Inherited syndromes with CU include the spectrum of cryopyrinopathies, such as Familial Cold Autoinflammatory syndrome, Muckle-Wells syndrome, and Neonatal-Onset Multisystem Inflammatory Disease/Chronic Infantile Neurologic Cutaneous Articular syndrome (NOMID/CINCA).[7] Urticaria presents as a feature of many inflammatory disorders, such Schnitzler syndrome,[8] Still's disease,[9] and Gleich's syndrome[10]. Chronic idiopathic urticaria, unlike the physical urticarias and ASA or NSAID intolerant variants, has no discernable external cause.[11]

Chronic idiopathic urticaria is the most common type of CU, comprising up to 90% of all cases of CU.[1] It has been estimated that chronic idiopathic urticaria will affect between 0.6%[12] to 5%[13] of the population during their lifetime. Over half of all cases of chronic idiopathic urticaria are thought to be caused by an autoimmune mechanism.[14] This is supported by the observation that 60% of patients with chronic idiopathic urticaria will have a wheal and flare reaction to intradermal autologous serum injections in the autologous serum skin test (ASST).[15] Approximately 50% of patients with chronic idiopathic urticaria have IgG antibodies that are specific for the high affinity IgE receptor (FcεRI).[14,16] These autoantibodies activate mast cells in the skin, circulating basophils, and the complement system.[14] Additional immunological abnormalities described to play a causative role in CU include IgG antibodies directed against IgE antibodies and the low affinity IgE receptor (FcεRII),[17] anti-endothelial antibodies,[18] and complement C8 alpha-gamma (C8α-γ) deficiency[19].

In patients with chronic idiopathic urticaria, approximately 35% will experience episodes of angioedema and 25% are positive for dermatographism.[20] Like many autoimmune diseases, chronic idiopathic urticaria has a higher incidence in women than men, with the reported ratio of females to males ranging from 2:1[21,22] to 4:1[23]. Numerous autoimmune conditions have been associated with chronic idiopathic urticaria, including thyroid disease, celiac disease, and rheumatoid arthritis (RA).

The purpose of this review is to discuss the association of CU with thyroid disease and other autoimmune diseases, as well as the implications that these associations hold for therapeutic intervention in CU.

Thyroid Disease and Chronic Urticaria

Thyroid disease is the most commonly reported autoimmune condition in patients with CU. In the literature, the frequency of thyroid autoimmunity in patients with CU encompasses a vast range of values, varying from 6.5%[24] to 57%[25]. Patients with coexistent thyroid autoimmunity and CU have a more severe and prolonged course of urticaria than those without thyroid autoimmunity.[26]

In patients affected by both CU and thyroid autoimmunity, there is an increased risk of developing angioedema. Leznoff and Sussman reported that the triad of thyroid autoimmunity, CU, and angioedema occurred in 15% of patients with CU.[27] The risk

of developing angioedema in patients with thyroid autoimmunity and CU is estimated to be 16.2 times greater than those with CU without thyroid autoimmunity.[28]

In a recent large study of 12,778 CU patients by Cofino-Cohen et al., it was found that 9.8% of patients had hypothyroidism, compared with 0.6% in the control group.[21] Hypothyroidism was the most commonly detected thyroid disease in patients with CU. Females were more likely to be affected by the combination of hypothyroidism and CU than their male counterparts. Patients with hyperthyroidism and CU comprised 2.7% of the study population, compared to 0.09% in the control group. In most patients, the thyroid disease was identified in the 10 years following the diagnosis of CU. This implies that thyroid autoimmunity developed subsequent to the initial presentation of CU. In the same study, anti-thyroid antibodies were significantly more common in CU patients than controls. Of the patients with CU who were clinically euthyroid, anti-thyroperoxidase antibodies were found in approximately 2.7% and anti-thyroglobulin antibodies were found in 0.6%. Aamir et al. also noted the association between anti-thyroid antibodies and CU, as anti-thyroglobulin and anti-microsomal antibody levels were significantly increased in patients with CU and hypothyroidism.[25]

The development of thyroid disease is often considered to be a marker of autoimmunity. Thyroid disease has been connected to a variety of autoimmune diseases, including pernicious anemia, celiac disease, type 1 diabetes and systemic lupus erythematosus (SLE), in addition to CU.[29] Although a specific mechanism linking the development of thyroid disease and CU has yet to be firmly elucidated, it is widely thought that both diseases occur because of a propensity within the patient to develop reactions to self. It has been hypothesized that thyroid disease may worsen urticaria and angioedema through activation of the complement system. Blanchin et al. demonstrated the thyroperoxidase enzyme contains a domain that binds to complement protein C4, cleaving it to C4a and activating the classical pathway of the complement cascade.[30] Kirpatrick noted that C4a levels decrease when thyroid disease is treated, resulting in remission of CU.[31] Therefore, while it is hypothesized that thyroid disease and CU may coexist due to a patient's predilection for autoimmunity, thyroid disease may additionally exacerbate urticaria and angioedema through direct mechanisms that result in complement activation.

Other Autoimmune Diseases and Chronic Urticaria

Beyond thyroid disease, a variety of additional autoimmune diseases have been examined for associations with CU. Confino-Cohen et al. found that 12.5% of patients had one additional autoimmune disease, 2.1% had two diseases, 0.1% had three diseases, and single patients each had an additional four or five diseases. Of patients with CU and hypothyroidism, RA was the most frequently identified additional autoimmune disease. The odds of having RA were 13.25 times higher in those with CU than in the control group.[21] The major laboratory marker of RA, rheumatoid factor, was reported by Ryhal et al. to be significantly increased in patients with CU.[32]

The risk of developing type 1 diabetes is increased in CU patients of both genders. In women with CU, the development of Sjögren's syndrome, celiac disease, or SLE was significantly higher than controls. Most patients received their diagnosis of an additional autoimmune disease in the 10 years following the CU diagnosis,[21] which emphasizes that these diseases developed subsequently and were not incidentally picked up at the time of CU diagnosis. The association of celiac disease and CU has previously been highlighted in the pediatric population.[33,34] Raynaud's phenomenon with positive anti-centromere antibodies was described with CU by Asero et al.[35] Additional autoimmune diseases such as vitiligo and pernicious anemia have also been associated with CU.[36]

CU has been shown to have a genetic association to the human leukocyte antigen (HLA)-DR4 and HLA-DQ8 alleles.[37] Interestingly, HLA-DR4 is strongly associated with RA,[38] and HLA-DQ8 holds associations with celiac disease[39] and type 1 diabetes[40]. Complement deficiencies have been associated with autoimmune diseases, such as Sjögren's syndrome,[41] RA,[42] and SLE,[43] and Park et al. have reported the development of CU, anti-nuclear antibodies and spondyloarthropathy in a 9 year old boy with C8α-γ deficiency[19]. CU was described in a 10 year old boy with a strong autoimmune phenotype.[44] The full inventory of diseases experienced by this patient included alopecia totalis, vitiligo, psoriasis, Graves' disease, CU, an autoimmune form of Lambert-Eaton myasthenic syndrome, and IgA deficiency. This patient had HLA genes that are found within the extended haplotype 8.1 AH (ancestral haplotype), which has been associated with the development of many autoimmune conditions.[45] These cases highlight that CU may occur as part of a larger constellation of autoimmune diseases in affected patients.

Therapeutic Interventions

Guidelines for the treatment of CU have been established using the Grading of Recommendations, Assessment, Development and Evaluations (GRADE) system.[46,47] Second generation nonsedating H1 antihistamines are the first-line treatment for patients with CU.[48,49] If the patient fails first-line therapy after 2 weeks, second-line therapy involves increasing the dose of antihistamines used, up to four times the standard dose.[50] Patients should be advised that symptoms of sedation and drug interactions may occur with the increased dose of antihistamines. Cetirizine, desloratadine, fexofenadine, and bilastine (the latter is not licensed for use in Canada) were determined to be the safest antihistamines to up dose.[51] In an estimated 50% of patients, symptoms persist following the use of antihistamines alone.[52,53] Third-line treatment involves changing the antihistamine used or adding a leukotriene antagonist. Leukotriene antagonists have been shown to improve patients with ASA or NSAID intolerant CU, ASST positive CU, and food-additive hypersensitivity induced CU, but not chronic idiopathic urticaria.[54] A short 3 to 7 day course of systemic steroids may be used in conjunction with the third-line treatment options.[55] If third-line therapy fails, fourth-line therapeutic options include adding cyclosporine A, H2 blockers, dapsone or omalizumab.[56]

The most effective fourth-line treatment in CU is thought to be omalizumab,[56] a humanized monoclonal antibody against IgE, approved for treatment of severe asthma. Maurer et al. published a randomized, double-blind study assessing the efficacy of omalizumab in patients with CU that had failed first-line treatment and found it significantly reduced CU symptoms.[57] Omalizumab reduces free IgE and the levels of the high affinity

IgE receptor present on mast cells and basophils,[58] thereby resulting in decreased activation of mast cells and basophils, the cells hypothesized to be responsible for the development of hives in CU.

Additional treatment options reported in the literature for patients that fail fourth-line treatment include mycophenolate mofetil,[59] hydroxychloroquine,[60] methotrexate,[61] tacrolimus,[62] sulfasalazine[63] and intravenous immunoglobulin (IVIG)[64].

Treatment of concomitant thyroid disease was reported to induce remission of CU.[65] Kirkpatrick performed a study on CU patients with evidence of clinical or serological thyroid autoimmunity.[66] These patients had previously failed first-line treatment with antihistamines. It was demonstrated that in patients with thyroid autoimmunity and CU levothyroxine induced remission of angioedema and urticaria in all six subjects. Rumbryt reported that seven out of ten euthyroid patients with anti-thyroid antibodies experienced clinical remission of CU following treatment with thyroxine, but relapsed once therapy was stopped.[67] These studies suggest that in patients with CU the clinical identification and management of thyroid autoimmunity with levothyroxine may play a role in inducing remission of CU. However, Magen et al. recently reviewed patients with CU and thyroid disease treated with levothyroxine and compared them to untreated euthyroid controls.[68] The patients treated with levothyroxine experienced a clinical improvement in urticaria; however, the same improvement in symptoms was also noted in the euthyroid controls. This led to the conclusion that improvement of clinical symptoms in CU occurred spontaneously, independent of thyroid treatment. The conflicting literature regarding the impact of treatment of thyroid autoimmunity on the clinical course of CU indicates the need for larger studies to establish the role of levothyroxine in patients with CU.

NSAID use has been shown to aggravate CU symptoms in approximately 20% of patients with a prior CU diagnosis.[69] NSAIDs are commonly used to manage the pain and inflammation associated with RA, inflammatory spondyloarthropathies, and lupus arthritis. Autoimmune inflammatory arthropathies, especially RA, have been shown to occur more frequently in patients with CU than the general population.[21] Therefore, exacerbation of symptoms due to NSAID use should be monitored in patients with CU and autoimmune inflammatory arthropathies. Zembowicz et al. demonstrated that selective COX-2 inhibitors do not induce urticaria in patients with CU that is aggravated by NSAIDs.[70] This suggests that selective COX-2 inhibitors may be preferred over general NSAIDs to prevent exacerbation of CU symptoms.

Helicobacter pylori (*H. pylori*) infection has been previously hypothesized to be an etiological factor in CU. This was based on reports demonstrating a high prevalence of *H. pylori* infection amongst CU patients,[71] and improvement of clinical symptoms following *H. pylori* eradication[72,73]. However, this hypothesis was brought into question by the fact that other authors have found no difference in the prevalence of *H. pylori* between those with CU and controls,[74] and no difference in autoantibody production,[24] as well as the additional finding that *H. pylori* eradication did not affect clinical outcomes[75]. This divergence in the literature has been speculated to occur because of different detection methods, resistance to therapy, and the possibility of recurrences of *H. pylori* shortly after therapy.[76] To further complicate the issue, recent evidence suggests that *H. pylori* eradication may trigger CU.[77] Shakouri et al. completed a review of the literature regarding *H. pylori* eradication and CU using the GRADE system, and concluded that the evidence for treatment was weak and larger studies are needed to establish if *H. pylori* eradication is beneficial to CU patients.[78]

Conclusion

CU is defined as hives lasting longer than 6 weeks. Currently, it is thought that up to 50% of CU is caused by autoimmune mechanisms.[14] Autoantibodies to the high affinity IgE receptor are the most commonly identified offender, activating mast cells, basophils, and the complement system, resulting in the wheal and flare reaction.[14,16] CU is hypothesized to occur because of a predisposition in the patient to develop autoimmune diseases. In concordance with this hypothesis, additional autoimmune diseases are observed in patients with CU. Thyroid disease, particularly hypothyroidism, is the most common additional autoimmune disease diagnosed.[21] Furthermore, thyroid disease may directly exacerbate CU severity by activating the complement system.[30,31] Other autoimmune diseases that occur more frequently in patients with CU include RA, SLE, vitiligo, pernicious anemia, celiac disease, and Sjörgen's syndrome.[21,36] In case reports, CU has been identified as part of a larger autoimmune phenotype.[19,45] These associations support the theory that patients who develop CU do so because of an innate propensity to mount autoimmune reactions. Treatment of thyroid disease has been reported in the literature to have varying effects on CU, as it has been demonstrated to induce remission[65-67] and alternatively to have no effect on the clinical symptoms of CU[68]. Autoimmune diseases occurring in patients with CU, especially thyroid disease, may be an important therapeutic target, but further studies are needed to establish the role of treatment on the clinical course of CU.

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Update on Drugs

Name/Company	Approval Dates/Comments
Brimonidine tartrate 0.33% topical gel *Mirvaso®* Galderma Laboratories	The US FDA approved this alpha-2 adrenergic receptor agonist in August 2013 for the topical treatment of the facial erythema (redness) of rosacea in adults ≥18 years of age. It is not indicated for the treatment of inflammatory lesions (papules and pustules). Brimonidine is thought to work by constricting dilated facial blood vessels to reduce the redness of rosacea. The drug has a rapid onset of action, with effects occurring as quickly as 30 minutes after application and lasting up to 12 hours.
Mechlorethamine gel *Valchlor™* Ceptaris Therapeutics	The FDA granted marketing approval to the orphan drug Valchlor™ gel in August 2013 for the once-daily topical treatment of stage IA and IB mycosis fungoides-type cutaneous T-cell lymphoma (CTCL) in patients who have received prior skin-directed therapy. Mechlorethamine (nitrogen mustard) is a chemotherapeutic agent that was previously approved for the intravenous treatment of mycosis fungoides, the most common type of CTCL.
OnabotulinumtoxinA for injection *Botox® Cosmetic* Allergan, Inc.	The FDA approved an additional indication to this neuromuscular paralytic agent in September 2013 for the temporary improvement of moderate to severe lateral canthal lines (crow's feet). With this most recent approval, onabotulinumtoxinA is the only pharmaceutical indicated to treat both lateral canthal and glabellar lines.
Ustekinumab *Stelara®* Janssen Biotech, Inc.	In September 2013, the FDA approved an additional indication for this fully human anti-interleukin (IL)-12 and anti-IL-23 monoclonal antibody (mAb) to be used alone or in combination with methotrexate for the treatment of adult patients aged ≥18 years with active psoriatic arthritis.
Certolizumab pegol *Cimzia®* UCB, Inc.	The FDA approved certolizumab pegol in September 2013 for the treatment of adult patients with active psoriatic arthritis, which represents the third US approved indication for this humanized tumor necrosis factor-alpha inhibitor mAb.
Infliximab *Inflectra™* Hospira, Inc.	In September 2013, the European Commission (EC) approved Inflectra™ (infliximab; innovator product Remicade®, Janssen), Europe's first biosimilar mAb therapy for the treatment of inflammatory diseases including psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis. Inflectra™ is the first mAb to be approved through the European Medicines Agency (EMA) biosimilars regulatory pathway.
Efinaconazole 10% topical solution *Jublia®* Valeant Canada LP	Health Canada approved efinaconazole 10% topical solution in October 2013 for the treatment of mild to moderate onychomycosis. Efinaconazole is the first topical triazole antifungal agent developed for distal lateral subungual onychomycosis (DLSO). This is the first regulatory approval world-wide for the drug.

Drug News

Launched in Canada in September 2013 was the new fixed-dose Clindoxyl® ADV gel (GlaxoSmithKline Inc.) consisting of clindamycin phosphate 1% with a lower strength benzoyl peroxide (BP) component of 3% (vs. 5% in the parent product) for the topical treatment of moderate acne vulgaris. The lower BP concentration and preservative-free formulation improves tolerability with efficacy similar to the original product.

In August 2013, Biocon Limited announced the launch in India of its first-in-class novel biologic itolizumab (Alzumab™), the first anti-CD6 humanized monoclonal antibody to be introduced for treating patients with moderate to severe chronic plaque psoriasis. Marketing authorization for this indication was granted to itolizumab in January 2013 by the Drugs Controller General of India (DCGI).