Skin Therapy Letter ©

Volume 22 • Number 1 • January-February 2017

Indexed by the US National Library of Medicine and PubMed

EDITOR: DR. RICHARD THOMAS

A Review of Brodalumab, an IL-17 Receptor Antagonist, for Moderate-to-Severe Plaque Psoriasis

Yun Tong, MD[1,2]; Andrew J. Peranteau, MD[1]; Zeena Nawas, MD[1,3]; Stephen K. Tyring, MD, PhD[1,3]

[1]Center for Clinical Studies, Houston, TX, USA

[2]Department of Dermatology, University of California San Diego, La Jolla, CA, USA

[3]Department of Dermatology, The University of Texas Health Science Center at Houston, Houston, TX, USA

Conflicts of Interest: Dr. Tyring has been an investigator for clinical trials sponsored by Abbvie, Amgen, Boehringer Ingelheim, Celgene, Coherus, Contravir, Cutanea, Dermira, Galderma, Genocea, Innovaderm, Janssen, Eli Lilly and Company, Leo Pharma, Merck, MSD, Medimmune, Novan, Novartis, Pfizer, Promius, Regeneron, Tolmar, Vitae, Watson-Actavis, and Xoma.

Drs. Tong, Peranteau, and Nawas have been sub-investigators on clinical trials sponsored by the same companies listed above.

ABSTRACT

Psoriasis is a chronic immune-mediated inflammatory disease with epidermal hyperplasia that affects 2-3% of the population. Interleukin (IL)-17 signaling has a central role in its pathogenesis. Brodalumab is a monoclonal antibody that neutralizes IL-17 receptor type A. Brodalumab is highly effective in the reversal of psoriatic phenotype and gene expression patterns.

Key words: IL-17, interleukin-17, interleukin-17A, monoclonal antibody, chronic plaque psoriasis

Introduction

An immune-mediated disease, psoriasis affects approximately 120 million people or 2% of the population.[1,2] The most common form of the disease, psoriasis vulgaris, accounts for 80% of all cases.[3] Psoriasis is increasingly recognized as more than a skin disease and may be associated with a constellation of comorbidities including psoriatic arthritis,[4] stroke, heart failure, obesity, hypertension, and diabetes. Severe psoriasis is considered an independent risk factor for cardiovascular mortality[5] and psychiatric disorders including depression, anxiety, and suicidal tendency from physical and mental distress.[6] Even patients with limited psoriatic involvement often report a substantial negative impact on their daily quality of life (QoL).

For people with moderate-to-severe plaque psoriasis (17% of all psoriasis patients[2]), topical medications usually provide unsatisfactory results.[3] Advances in the understanding of cytokines in psoriasis have led to the development of more efficacious therapeutic options including biological agents targeting tumor necrosis factor (TNF)-α, interleukin (IL)-23, and IL-17. Current pathogenic models indicate dysfunctional IL-17 signaling may play a pivotal inflammatory role in the pathophysiology of psoriasis.[3,7]

Rationale for IL-17 Inhibitors

The main physiological function of IL-17 is protection from extracellular bacteria and fungi by inducing the production of chemokines and cytokines such as TNF-α to recruit inflammatory cells to local sites of infection.[8] Additionally, IL-17 has a role in vascular dysfunction and hypertension.[5] In psoriasis, the IL-17 pathway is altered.[7] Activities of IL-17 and TNF-α are additive and synergistic drivers of inflammation upregulation that lead to a self-sustaining keratinocyte hyperproliferation of psoriasis.[3,9] Given the importance of IL-17 in inducing and mediating proinflammatory responses, it is also linked to other immune mediated diseases including rheumatoid arthritis, spondyloarthritis, uveitis, Crohn's disease, multiple sclerosis, and asthma.[10]

T-helper (Th)-17 cells and IL-17 messenger RNA (mRNA) are increased in psoriasis plaques[11] and synovial fluid of psoriatic arthritis patients.[12] Many cells are rich sources of IL-17, including gamma/delta (γδ) T-cells, which appear to have a central role in the development of psoriasis, Tc17 (a subset of CD8+, T-cells that are critical in cellular immune response), mast cells, macrophages, natural killer (NK) cells, and neutrophils.[3,7,8,11,13,14]

Current US FDA-approved IL-17 inhibitors include secukinumab and ixekizumab, and brodalumab is still under regulatory review at the time of this writing. Secukinumab and ixekizumab are directed against IL-17, whereas brodalumab is a human G2 monoclonal antibody directed against the IL-17 receptor. Under clinical investigation, brodalumab appears to benefit patients with psoriatic disease, thus further supporting the view that IL-17 and the cells that produce it play a pivotal role in disease onset and perpetuation.[14]

Several clinical psoriasis trials have confirmed that these three IL-17 inhibitors have significantly higher efficacy rates vs.

ALSO IN THIS ISSUE: **A Dermatologist's Guide to Infection Screening Prior to Initiating Immunosuppressive Therapy** *(page 8)* & **Update on Drugs** *(page 12)*

placebo and TNF-α inhibitors, which are currently first-line therapy for psoriasis.[1,3,7] More established monoclonal antibody biologics are directed against TNF-α, causing generalized immunosuppression.[15] Additionally, some patients receiving anti-TNF therapy do not achieve adequate response or experience a secondary loss in efficacy due to formation of anti-TNF-α antibodies.[16]

The IL-17 family is composed of 6 different ligand homodimers, labeled A-F, and 5 receptors subtypes A-E.[17] IL-17A is the most prevalent and prototypical isomer generally referred to as IL-17 when no distinction is made.[16] Both secukinumab and ixekizumab are monoclonal antibodies that bind to and neutralize IL-17A. Additionally, IL-17A is the most potent, with 10-30 times greater effect than IL-17F.[9] However, IL-17C, IL-17F, and IL-17A/F heterodimer are all capable of inducing the expression of psoriasis-related proinflammatory molecules in keratinocytes.[18] IL-17C has been reported as the most abundant isoform in psoriatic lesions.[7] All 3 cytokines require a heteromeric receptor for biological activity.[10]

IL-17 receptors are complexes composed of heteromeric subunits. Brodalumab targets IL-17 receptor A (IL-17RA) with high affinity and inhibits the activities of IL-17 ligands A, C, E (IL-25), F, and A/F heterodimer, all of which require subunit IL-17RA in their respective receptor complexes. IL-17A and IL-17F, which are homodimers, share a common IL-17RA/IL-17RC receptor complex.[17] IL-17C mediates further signaling by docking to an IL-17RA/IL-17RE complex. IL-17E ligand interacts with an IL-17RA/IL-17RB complex. Perhaps broader coverage through blockade of a shared receptor may allow for better effect on controlling psoriasis but may lead to increased risk.[10]

Clinical Trials

Several clinical trials have been undertaken to evaluate the efficacy and safety of brodalumab. Fairly standard inclusionary and exclusionary items were used in the study to screen for adults with moderate-to-severe plaque psoriasis.

Phase 1 Trials

Significant improvements in the major clinical parameters were seen involving 25 patients who were followed for 85 days in a phase 1[19,20] clinical study assessing the safety and clinical response of brodalumab; 20 of the 25 subjects received a single dose of brodalumab and the remaining 5 received placebo. None of the 5 placebo patients achieved Psoriasis Area and Severity Index (PASI) 50. Significant PASI improvement occurred in the brodalumab higher dosing arms (350 mg SC and 700 mg IV). Six (of the 8) administered 350 mg achieved PASI 50, and 5 also achieved PASI 75. All 8 subjects in the 700 mg arm achieved PASI 50 by day 29, and all but 1 also achieved PASI 75 or greater (3 achieved PASI 90) at week 6 (Table 1). Decreases in IL-17 A, C, and F mRNA levels and improvements in histopathological parameters of epidermal thickness, Ki-67, keratin-16 gene expression, and infiltrating leukocyte subsets were observed.

Safety and adverse event profiles of brodalumab and placebo were similar. Two subjects (1 each from 350 mg and 700 mg arms) receiving brodalumab tested positive for non-neutralizing antibodies against brodalumab at week 12.

A Japanese phase 1 study[21] evaluating the safety, tolerability, pharmacokinetics (PK) and pharmacodynamics in 8 healthy and 13 psoriatic patients, who received a single dose of brodalumab, added evidence that IL-17RA is a viable option against psoriasis. Three of the 6 patients who received a single dose of 140 mg SC achieved PASI 75 or greater. All 7 patients in the 350 mg SC arm achieved PASI 50, with 6 achieving PASI ≥75 (Table 1). In both healthy and psoriatic patients, brodalumab was well tolerated at the studied doses with respect to adverse events (AE), and safety profiles were similar to western trials. No anti-brodalumab antibodies were detected. Mean serum brodalumab concentration and PK parameters were comparable between psoriasis patients and healthy volunteers during the study. PK and occupancy data showed brodalumab is at maximum with a serum brodalumab concentration of approximately 1 ug/ml at 2 weeks after dosing 140 mg, implying 2-week interval SC dosing could maintain maximal IL-17RA occupancy.

Phase 2 Trials

A phase 2, randomized, double-blind, placebo-controlled, dose-ranging study assessing short-term efficacy and safety of brodalumab was significant for PASI reductions at week 12 (primary endpoint).[22] Secondary endpoints of PASI 75, 90, and static physician global assessment (sPGA) at week 12 were also met. Statistically significant PASI improvement was seen as early as week 2. Dose response effect was seen in the study involving 198 patients who received either placebo, brodalumab at 70 mg, 140 mg, or 210 mg at weeks 0, 1, 2, and then every 2 weeks or monthly dosing of brodalumab 280 mg at weeks 0, 4, and 8; 188 patients completed through week 16. Primary endpoint was PASI improvement at week 12; 16% of patients in the placebo arm achieved significant ($p<0.001$) PASI improvement, whereas mean PASI improvements at week 12 for each brodalumab arm were as follows: bimonthly 70 mg (45%), 140 mg (85.9%), 210 mg (86.3%), and monthly 280 mg (76%). Seventy-two percent and 75% of the 140 mg and 210 mg recipients achieved PASI 75 or greater with 38% of the 140 mg arm and 62% of the 210 mg arm achieving PASI 100 (Table 1). At week 12, significant decreases of body surface area (BSA), sPGA, and Dermatology Quality of Life Index (DLQI) were also seen.

More AEs were reported in patients receiving brodalumab than placebo. Nasopharyngitis, upper respiratory infection, and arthralgia were the most common. Four serious adverse events (SAE) were reported during the trial including 2 cases of grade 3 asymptomatic neutropenia that normalized after withdrawal of brodalumab. Non-neutralizing antibodies were identified in all brodalumab arms (5-9.8%), which is similar to phase 1 observations.

A subanalysis of the data demonstrated patients with moderate-to-severe plaque psoriasis received similar levels of benefit whether they had a history of prior biologic use or psoriatic arthritis.[23]

Of the original 198 patients, 181 (33 placebo and 148 brodalumab) enrolled in a 5-year (264 weeks) open-label extension (OLE) study and were initially administered brodalumab 210 mg every 2 weeks.[24] At week 52, a protocol modification switched patients <100 kg to 140 mg dosing every 2 weeks, while patients >100 kg were maintained at 210 mg every 2 weeks. During the OLE, 72%

of patients maintained a sPGA of 0 or 1 (clear or almost clear) in comparison to 90% at week 12. Interim analysis at week 120 showed sustained clinical response and acceptable safety profiles through week 120. Non-neutralizing anti-brodalumab antibodies were discovered in 19 patients (11%) during the OLE, but only 2 of the 19 continued to show antibodies at final specimen collection. At interim analysis, 95% of patients reported an AE at some point during weeks 0-120 with nasopharyngitis being the most commonly reported AE at 26.5%. Fifteen SAEs were reported and 5 patients reported depression during the OLE.

A Japanese phase 2 study[25] was conducted with dosing regimens of 70 mg, 140 mg, 210 mg, or placebo SC at weeks 0, 1, 2, 4, 6, 8, and 10. Efficacy was similar to the western phase 2 study[22] (Table 1). At week 12, the primary endpoint of mean percentage improvements in the PASI scores were 37.7%, 82.2%, 96.8%, and 9.4% in the 70 mg, 140 mg, 210 mg, and placebo groups, respectively ($p<0.001$). Similarly, more patients in the brodalumab arms achieved sPGA of 0 or 1 than in the placebo group at week 12. PASI 90 response rates in the 140 mg and 210 mg brodalumab groups were 64.9% and 91.9%, respectively.

Phase 3 Trials

Three phase 3 trials were conducted: AMAGINE-1 evaluated the efficacy, safety, and withdrawal and retreatment effect of brodalumab compared with placebo. AMAGINE-2 and AMAGINE-3, 12-week induction trials followed by re-randomization at week 12, evaluated the efficacy and safety of induction and maintenance of brodalumab compared with both ustekinumab and placebo.

AMAGINE-1

AMAGINE-1 was a phase 3, randomized, double-blind, placebo-controlled trial composed of a 12-week induction phase followed by a withdrawal/retreatment phase from weeks 12 through 52.[26,27] Using a 1:1:1 randomization, 661 patients were randomized to biweekly injections of 210 mg (n=222), 140 mg (n=219), and placebo (n=220) for 12 weeks. Re-randomization occurred at week 12 for patients with sPGA of 0/1 in the 210 mg and 140 mg arms to either continue their current dose or switch to placebo. Those re-randomized to placebo and subsequently lost disease control were restarted on their original dose. Subjects originally in the placebo arm and any patient with sPGA greater than 2 received brodalumab 210 mg every 2 weeks at week 12.

Co-primary endpoints of PASI 75 and sPGA 0/1 at week 12 were statistically significant for either dosage groups compared with placebo. At week 12, PASI 75 for placebo, brodalumab 140 mg, and brodalumab 210 mg were 2.7%, 60.3%, and 83.3%, respectively (Table 1), indicating a majority of brodalumab patients achieved 75% improvement of their psoriasis while only 2.7% of patients on placebo did so. Similarly, only 1.4% of patients on placebo compared to 53.9% on brodalumab 140 mg and 75.7% on brodalumab 210 mg had a treatment response of sPGA 0/1. Following withdrawal, most subjects were able to recover treatment sPGA response with retreatment.

No meaningful or dose effect on AE rates were observed through 52 weeks. Most reported AEs included nasopharyngitis, upper respiratory tract infection, and headache. Three SAEs were reported: cellulitis (n=2) and diverticulitis (n=1). Hospital Anxiety and Depression Scale was analyzed at week 12. Statistically significant decreases ($p<0.001$) in mean depression were observed for 210 mg (5.5% to 3.4%) and 140 mg (5.2% to 3.5%) doses at week 12. The placebo arm was unchanged (5.3% at baseline and 5.5% at week 12).

AMAGINE-2 and AMAGINE-3

Most recently, AMAGINE-2 and AMAGINE-3, two large, parallel-group, double-blind, placebo-controlled, active comparator-controlled, multinational phase 3 trials were conducted involving a 12-week induction phase and 40-week maintenance phase.[28] During the 12-week induction phase, patients were randomized utilizing a 2:2:1:1 ratio to receive brodalumab 210 mg or 140 mg every 2 weeks, ustekinumab (45 mg for subjects <100 kg in weight and 90 mg for subjects >100 kg) every 4 weeks, or placebo.

All primary endpoints for all brodalumab doses against placebo and ustekinumab were met. Multiple endpoints were evaluated including primary endpoints of PASI 75 and sPGA 0/1 at week 12 of brodalumab compared to placebo. Another primary endpoint compared brodalumab to ustekinumab for PASI 100. Brodalumab 210 mg was superior ($p<0.001$) to ustekinumab at week 12 (AMAGINE-2: 44% vs 22%; AMAGINE-3 37% vs 19%). Brodalumab 210 mg was superior for maintenance of clinical responses.

Regarding secondary endpoints, both doses of brodalumab were superior to placebo at all secondary endpoints including PASI 100 and sPGA 0. While brodalumab 210 mg was superior to ustekinumab in both studies for PASI 100; brodalumab 140 mg was superior to ustekinumab in the AMAGINE-3 study ($p<0.007$) but not in the AMAGINE-2 trial ($p=0.08$); however, the nominal p-value was significant ($p<0.001$). The median time to PASI 75 of brodalumab 210 mg was 4 weeks vs. approximately 2 months for ustekinumab.

At week 12, patients on brodalumab were re-randomized to receive brodalumab 210 mg every 2 weeks, 140 mg every 2 weeks, 140 mg every 4 weeks, or 140 mg every 8 weeks. Placebo patients were switched to brodalumab 210 mg every 2 weeks. Patients on ustekinumab continued to receive ustekinumab; 55 (18%) and 69 (22%) subjects assigned to ustekinumab received rescue therapy with brodalumab at week 16. Patients on 210 mg or 140 mg of brodalumab every 2 weeks maintained or achieved a sPGA 0/1 at a higher rate than 140 mg every 4 weeks or 8 weeks ($p<0.001$). The majority of placebo patients who switched to brodalumab achieved PASI 100 at week 52; 40% of patients on ustekinumab who received brodalumab rescue therapy were able to achieve PASI 100.

Anti-brodalumab antibodies that were non-neutralizing and did not cause a loss in efficacy or AE, were detected in 1.8% and 2.3% in patients in AMAGINE-2 and AMAGINE-3, respectively. Four patients had antibodies detected at baseline. Six patients were positive for non-neutralizing anti-brodalumab antibodies after initiating ustekinumab.

Higher percentages of patients on brodalumab or ustekinumab reported an AE during the first 12 weeks than placebo patients. Most common AEs were nasopharyngitis, upper respiratory tract infection, headache, and arthralgia. Non-serious and reversible neutropenia events were more frequent among brodalumab and

	Study Phase	Dosing Arm	Dosing	PASI 50	PASI 75	PASI 90	PASI 100	SPGA 0 or 1	SPGA 0
Phase 1 Studies	Papp, et al.[19,20] • Assessment at Day 43 (6 weeks) • 25 patients	Placebo (n=5)	Single dose	0%	-	-	-	-	-
		140 mg SC (n=4)		50% (2)	-	-	-	-	-
		350 mg SC (n=8)		75% (6)	62.5% (5)	25% (2)	-	-	-
		700 mg IV (n=8)		100% (8)	88% (7)	38% (3)	-	-	-
	Osamu, et al.[21] • Assessment up to Day 64 (9 weeks) • 13 patients	140 mg SC (n=6)	Single dose	50% (3)	50% (3)	-	-	-	-
		350 mg SC (n=7)		100% (7)	85.7% (6)	28.6% (2)	-	-	-
Phase 2 Studies	Papp, et al.[22] • Assessment at Week 12 • 198 patients	Placebo (n=38)	Weeks 0, 1, 2, 4, 6, 8, 10	15.8% (6)	0%	0%	0%	-	-
		70 mg (n=39)	Weeks 0, 1, 2, 4, 6, 8, 10	51.3% (20)	33.3% (13)	17.9% (7)	10.3% (4)	-	-
		140 mg (n=39)	Weeks 0, 1, 2, 4, 6, 8, 10	89.7% (35)	76.9% (30)	71.8% (28)	38.5% (18)	-	-
		210 mg (n=40)	Weeks 0, 1, 2, 4, 6, 8, 10	90% (36)	82.5% (30)	62.5% (25)	80% (32)	-	-
		280 mg (n=42)	Weeks 0, 4, 8	81% (34)	66.7% (28)	57.1% (24)	28.6% (12)	-	-
	Nakagawa, et al.[25] • Assessment at Week 12 • 151 patients	Placebo (n=38)	Weeks 0, 1, 2, 4, 6, 8, 10	-	7.9% (3)	2.6% (1)	-	5.3% (2)	-
		70 mg (n=39)	Weeks 0, 1, 2, 4, 6, 8, 10	-	25.6% (10)	15.4% (6)	2.6% (1)	25.6% (10)	-
		140 mg (n=37)	Weeks 0, 1, 2, 4, 6, 8, 10	-	78.4% (29)	64.9% (24)	35.1% (13)	78.4% (29)	-
		210 mg (n=37)	Weeks 0, 1, 2, 4, 6, 8, 10	-	94.6% (35)	91.9% (34)	59.5% (22)	94.6% (35)	-
Phase 3 Studies	AMAGINE-1[26,27,29] • Assessment at Week 12 • 661 patients	Placebo (n=220)	Weeks 0, 1, 2, 4, 6, 8, 10	-	2.7% (6)	0.9% (2)	0.5% (1)	1.4% (3)	0.5% (1)
		140 mg (n=219)	Weeks 0, 1, 2, 4, 6, 8, 10	-	60.3% (132)	42.5% (93)	23.3% (51)	53.9% (118)	23.3% (51)
		210 mg (n=222)	Weeks 0, 1, 2, 4, 6, 8, 10	-	83.3% (185)	70.3% (156)	41.9% (93)	75.7% (168)	41.9% (93)
	AMAGINE-2[28] • Assessment at Week 12 • 1831 patients	Placebo (n=309)	Weeks 0, 1, 2, 4, 6, 8, 10	-	8.1% (25)	3%	0.6% (2)	3.9% (12)	0.6% (2)
		140 mg (n=610)	Weeks 0, 1, 2, 4, 6, 8, 10	-	66.6% (406)	49%	25.7% (157)	58% (354)	25.7% (157)
		210 mg (n=612)	Weeks 0, 1, 2, 4, 6, 8, 10	-	86.3% (612)	70%	44.4% (272)	78.6% (481)	44.8% (274)
		Ustekinumab (n=300)	Weeks 0, 4, 8	-	70% (210)	3%	21.7% (65)	61% (183)	21.7% (65)
	AMAGINE-3[28] • Assessment at Week 12 • 1881 patients	Placebo (n=315)	Weeks 0, 1, 2, 4, 6, 8, 10	-	6% (19)	2%	0.3% (1)	4.1% (13)	0.3% (1)
		140 mg (n=629)	Weeks 0, 1, 2, 4, 6, 8, 10	-	69.2% (435)	52%	27% (170)	59.9% (377)	27% (170)
		210 mg (n=624)	Weeks 0, 1, 2, 4, 6, 8, 10	-	85.1% (531)	69%	36.7% (229)	79.6% (497)	36.7% (229)
		Ustekinumab (n=313)	Weeks 0, 4, 8	-	69.3% (217)	48%	18.5% (58)	57.2% (179)	18.5% (58)

Table 1: Summary of clinical investigations on brodalumab

ustekinumab. No clinically apparent differences were noticed among all study groups throughout the study. One patient (placebo followed by 210 mg of brodalumab) in AMAGINE-2 committed suicide 27 days after the last dose. An additional patient from AMAGINE-2 in the OLE receiving 210 mg of brodalumab every 2 weeks committed suicide 19 days after the last dose.

Discussion

IL-17 cytokine pathway plays an important role in psoriasis. Clinical trials validate the role of brodalumab for treating moderate-to-severe plaque psoriasis. By targeting IL-17RA, brodalumab has proven to be exceptionally efficacious with improvement of PASI 75 in over 80%, and approximately 70% of those patients achieved PASI 90 on brodalumab 210 mg by week 12 in 3 large phase 3 clinical trials. Patients with psoriasis experience impairment of their QoL. A PASI 90 response is necessary to achieve a DLQI of 0 or 1. Indeed, the new class of IL-17 antagonists has eminently shifted the expectation of treatment response, such that PASI 90 may be regarded as the new standard.[30] Based on efficacy alone, brodalumab and other IL-17 class biologics could become first-line therapy for moderate-to-severe plaque psoriasis. Safety considerations of depression and suicidality, however, could hamper the use of brodalumab in favor of the other IL-17 biologics secukinumab and ixekizumab.

Il-17 blockade compared to TNF-α or Il-12/23 may be associated with lower potential for broad immune system adverse effects.[9] Il-17RA deficient patients, however, have higher associated recurrent mucocutaneous infections caused by *Candida albicans*. Two studies reported increased rates of candida infections with brodalumab vs. ustekinumab (5.2 and 5.7 per 100 patient-years vs. 4.1 and 1.6 per 100 patient-years, AMAGINE-2 and AMAGINE-3, respectively). Meta-analysis of several phase 2 trials for IL-17 agents, brodalumab, ixekizumab, and secukinumab, demonstrated no significant difference between biotherapy groups and placebo for adverse events including infections, upper respiratory tract infections, and headaches, excluding nasopharyngitis.[2] Overall, IL-17 agents appear tolerable and are promising therapies with possibly less side effects than current biologics.

While the majority of clinical data points to brodalumab's improvement of depression and QoL, OLE studies of AMAGINE-1, AMAGINE-2, and AMAGINE-3 were terminated in May 2015. Amgen, one of the co-developers with AstraZeneca, withdrew due to fears of black box labeling requirements that would preclude universal first-line adoption in an increasingly competitive market for psoriasis, which already includes the anti-IL-17 antibodies secukinumab and ixekizumab without restrictive labeling. Valeant Pharmaceuticals, in September 2015, entered into an agreement with AstraZeneca to develop and commercialize brodalumab.[31] Four instances of suicidal ideation among 3180 pooled patients on brodalumab (0.13%) were reported against 1 report out of 613 patients (0.16%) on ustekinumab.[32] Lebwohl[28] reported 2 suicides were completed in the 210 mg treatment arm of AMAGINE-2, with 1 during the study and 1 in the OLE compared to none in patients on ustekinumab or placebo. During its own long-term treatment trials, however, 2 suicides (0.06%) in 3117 subjects on ustekinumab were reported.[33] Comparatively, no suicides were reported during the treatment periods of secukinumab phase 3 trials.[34] Ixekizumab phase 3 trials UNCOVER-2 and UNCOVER-3 reported no deaths with 2 (0.14%) out of 1469 subjects on ixekizumab attempting suicide.[35] No subjects on placebo (n=361) or etanercept comparator (n=740) attempted suicide.

Theoretically, brodalumab does not cross the intact blood-brain barrier due to its inherent size. The anti-TNF pathway has been associated with central demyelination,[11] of which IL-17 may be significantly involved. Indirect action by brodalumab on the brain may be possible as there is evidence of peripheral cytokine modulation. Alternatively, Danesh and Kimball[36] suggest the suicides may be considered within the context of broader suicide trends and attributable to the economic recession. They argue that participants were predominantly middle-aged white males who represent the demographic most at risk for suicide, which as a group has climbed from 20.7 suicides in 2007 to 23.4 per 100,000 in 2013. Before the recession from 1999-2007, suicide mortality increased 0.12 per 100,000 per year whereas an additional 0.51 deaths per 100,000 per year were experienced between 2008-2010 (translating to an additional 1580 suicides annually).[36,37] With the lack of a comparator or placebo during OLE, and more details out of public domain, it remains to be seen what effect IL-17RA inhibition has on suicidality. The key difference in brodalumab's IL-17 inhibition is the receptor target as compared to the IL-17A ligand for secukinumab and ixekizumab. Perhaps this difference has unknown effects on suicidal behavior. Given the substantial improvement in QoL and depression for the majority of subjects in all brodalumab trials, more investigations are warranted.

References

1. Kivelevitch DN, Menter A. Use of brodalumab for the treatment of psoriasis and psoriatic arthritis. *Immunotherapy.* 2015;7(4):323-33.
2. Chen Y, Qian T, Zhang D, et al. Clinical efficacy and safety of anti-IL-17 agents for the treatment of patients with psoriasis. *Immunotherapy.* 2015;7(9):1023-37.
3. Yamauchi PS, Bagel J. Next-generation biologics in the management of plaque psoriasis: a literature review of IL-17 inhibition. *J Drugs Dermatol.* 2015 Mar;14(3):244-53.
4. El Malki K, Karbach SH, Huppert J, et al. An alternative pathway of imiquimod-induced psoriasis-like skin inflammation in the absence of interleukin-17 receptor a signaling. *J Invest Dermatol.* 2013 Feb;133(2):441-51.
5. Karbach S, Croxford AL, Oelze M, et al. Interleukin 17 drives vascular inflammation, endothelial dysfunction, and arterial hypertension in psoriasis-like skin disease. *Arterioscler Thromb Vasc Biol.* 2014 Dec;34(12):2658-68.
6. Cohen BE, Martires KJ, Ho RS. Psoriasis and the Risk of Depression in the US Population: National Health and Nutrition Examination Survey 2009-2012. *JAMA Dermatol.* 2016 Jan;152(1):73-9.
7. Gooderham M, Posso-De Los Rios CJ, Rubio-Gomez GA, et al. Interleukin-17 (IL-17) inhibitors in the treatment of plaque psoriasis: a review. *Skin Therapy Lett.* 2015 Jan-Feb;20(1):1-5.
8. Isailovic N, Daigo K, Mantovani A, et al. Interleukin-17 and innate immunity in infections and chronic inflammation. *J Autoimmun.* 2015 Jun;60:1-11.
9. Girolomoni G, Mrowietz U, Paul C. Psoriasis: rationale for targeting interleukin-17. *Br J Dermatol.* 2012 Oct;167(4):717-24.
10. Lonnberg AS, Zachariae C, Skov L. Targeting of interleukin-17 in the treatment of psoriasis. *Clin Cosmet Investig Dermatol.* 2014 Sep 15;7:251-9.
11. Yiu ZZ, Griffiths CE. Interleukin 17-A inhibition in the treatment of psoriasis. *Expert Rev Clin Immunol.* 2016;12(1):1-4.
12. Mease PJ, Genovese MC, Greenwald MW, et al. Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. *N Engl J Med.* 2014 Jun 12; 370(24):2295-306.
13. Schon MP. The plot thickens while the scope broadens: a holistic view on IL-17 in psoriasis and other inflammatory disorders. *Exp Dermatol.* 2014 Nov; 23(11):804-6.

14. Marinoni B, Ceribelli A, Massarotti MS, et al. The Th17 axis in psoriatic disease: pathogenetic and therapeutic implications. *Auto Immun Highlights.* 2014 Jun;5(1):9-19.
15. Tausend W, Downing C, Tyring S. Systematic review of interleukin-12, interleukin-17, and interleukin-23 pathway inhibitors for the treatment of moderate-to-severe chronic plaque psoriasis: ustekinumab, briakinumab, tildrakizumab, guselkumab, secukinumab, ixekizumab, and brodalumab. *J Cutan Med Surg.* 2014 May-Jun;18(3):156-69.
16. Waisman A. To be 17 again--anti-interleukin-17 treatment for psoriasis. *N Engl J Med.* 2012 Mar 29;366(13):1251-2.
17. Johansen C, Usher PA, Kjellerup RB, et al. Characterization of the interleukin-17 isoforms and receptors in lesional psoriatic skin. *Br J Dermatol.* 2009 Feb;160(2):319-24.
18. Martin DA, Towne JE, Kricorian G, et al. The emerging role of IL-17 in the pathogenesis of psoriasis: preclinical and clinical findings. *J Invest Dermatol.* 2013 Jan;133(1):17-26.
19. Papp KA, Reid C, Foley P, et al. Anti-IL-17 receptor antibody AMG 827 leads to rapid clinical response in subjects with moderate to severe psoriasis: results from a phase I, randomized, placebo-controlled trial. *J Invest Dermatol.* 2012 Oct;132(10):2466-9.
20. Russell CB, Rand H, Bigler J, et al. Gene expression profiles normalized in psoriatic skin by treatment with brodalumab, a human anti-IL-17 receptor monoclonal antibody. *J Immunol.* 2014 Apr 15;192(8):3828-36.
21. Osamu N, Hirotaka N, Koji S, et al. Clinical pharmacology of the anti-IL-17 receptor antibody brodalumab (KHK4827) in Japanese normal healthy volunteers and Japanese subjects with moderate to severe psoriasis: a randomized, dose-escalation, placebo-controlled study. *J Dermatol Sci.* 2014 Sep;75(3):201-4.
22. Papp KA, Leonardi C, Menter A, et al. Brodalumab, an anti-interleukin-17-receptor antibody for psoriasis. *N Engl J Med.* 2012 Mar 29;366(13):1181-9.
23. Papp K, Menter A, Strober B, et al. Efficacy and safety of brodalumab in subpopulations of patients with difficult-to-treat moderate-to-severe plaque psoriasis. *J Am Acad Dermatol.* 2015 Mar;72(3):436-9 e1.
24. Papp K, Leonardi C, Menter A, et al. Safety and efficacy of brodalumab for psoriasis after 120 weeks of treatment. *J Am Acad Dermatol.* 2014 Dec;71(6):1183-90 e3.
25. Nakagawa H, Niiro H, Ootaki K, Japanese brodalumab study group. Brodalumab, a human anti-interleukin-17-receptor antibody in the treatment of Japanese patients with moderate-to-severe plaque psoriasis: Efficacy and safety results from a phase II randomized controlled study. *J Dermatol Sci.* 2016 Jan; 81(1):44-52.
26. Papp K, Reich K, Leonardi C, et al. AMAGINE-1: a phase 3, randomized, double-blind, placebo-controlled study of brodalumab in subjects with psoriasis. *Br J Dermatol.* 2014 Dec;171(6):e119–e120.
27. Papp K, Reich K, Leonardi C, et al. Efficacy and safety of brodalumab in patients with moderate to severe plaque psoriasis: Results of AMAGINE-1, a phase 3, randomized, double-blind, placebo-controlled study through week 12. *J Am Acad Dermatol.* 2015 May;72(5 Suppl 1):AB233.
28. Lebwohl M, Strober B, Menter A, et al. Phase 3 Studies Comparing Brodalumab with Ustekinumab in Psoriasis. *N Engl J Med.* 2015 Oct;373(14):1318-28.
29. Papp KA, Reich K, Paul C, et al. A prospective phase III, randomized, double-blind, placebo-controlled study of brodalumab in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol.* 2016 Aug;175(2):273-86.
30. Puig L. PASI90 response: the new standard in therapeutic efficacy for psoriasis. *J Eur Acad Dermatol Venereol.* 2015 Apr;29(4):645-8.
31. AstraZeneca and Valeant Pharmaceuticals to partner on brodalumab [Internet]. Published: September 1, 2015. AstraZeneca, 2015 press releases. Available at: https://www.astrazeneca.com/media-centre/press-releases/2015/astrazeneca-valeant-pharmaceuticals-brodalumab-dermatology-psoriasis-01092015.html. Accessed November 20, 2016.
32. Powers M. Valeant fills Amgen gap as Astrazeneca hands off brodalumab; $100M up front [Internet]. BioWorld. Available at: http://www.bioworld.com/content/valeant-fills-amgen-gap-astrazeneca-hands-brodalumab-100m-front-0. Accessed November 20, 2016.
33. Papp KA, Griffiths CE, Gordon K, et al. Long-term safety of ustekinumab in patients with moderate-to-severe psoriasis: final results from 5 years of follow-up. Br *J Dermatol.* 2013 Apr;168(4):844-54.
34. Langley RG, Elewski BE, Lebwohl M, et al. Secukinumab in plaque psoriasis--results of two phase 3 trials. *N Engl J Med.* 2014 Jul 24;371(4):326-38.
35. Griffiths CE, Reich K, Lebwohl M, et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet.* 2015 Aug 8;386(9993):541-51.
36. Danesh MJ, Kimball AB. Brodalumab and suicidal ideation in the context of a recent economic crisis in the United States. *J Am Acad Dermatol.* 2016 Jan;74(1):190-2.
37. Reeves A, Stuckler D, McKee M, et al. Increase in state suicide rates in the USA during economic recession. *Lancet.* 2012 Nov 24;380(9856):1813-4.

2016 Peer Reviewers

During 2016, the reviewers listed below gave generously of their time and talents and completed manuscript reviews for *Skin Therapy Letter*. On behalf of our Editorial Advisory Board and our readers, we wish to thank them for their efforts and valuable contributions.

Michael Abrouk
Benjamin Barankin
Danny Barlev
Vince Bertucci
Gillian de Gannes
Steven Feldman
Barbara Gilchrest
Melinda Gooderham
Lyn Guenther
Vincent Ho
Joanna Hooten
Shannon Humphrey
John Koo
Rod Kunynetz
Charles Lynde
Howard Maibach
Kevin McElwee
Barbara Melosky
Eileen Murray
Jaggi Rao
Jason Rivers
Jerry Tan
Stephen Tyring
Ronald Vender
Marni Wiseman

Skin Therapy Letter©

Available for iPad, iPhone and iPod touch

Content & instructions can be found at:

http://www.skintherapyletter.com/ipad/about.html http://www.skintherapyletter.com/ipad/support.html

skininformation.com

To get more information, medical professionals and consumers can access all of our sites from www.SkinInformation.com or go directly to:

Patient sites:

AcneGuide.ca	ActinicKeratosis.ca	BotoxFacts.ca	ColdSores.ca
CosmeticProcedureGuide.ca	DermatologyCare.ca	EczemaGuide.ca	FungalGuide.ca
GenitalWarts.ca	HandEczema.ca	HerpesGuide.ca	Lice.ca
MildCleanser.ca	MohsSurgery.ca	PsoriasisGuide.ca	PsoriaticArthritisGuide.ca
RosaceaGuide.ca	SkinCancerGuide.ca	SkinCoverup.com	Sweating.ca
UnwantedFacialHair.ca			

Medical professional sites:

Dermatologists.ca	PASItraining.com	SkinCareGuide.ca	SkinInformation.com
SkinPharmacies.ca	SkinTherapyLetter.ca	SkinTherapyLetter.com	

A Dermatologist's Guide to Infection Screening Prior to Initiating Immunosuppressive Therapy

Marisa G. Ponzo, MD, PhD[1] and Chih-Ho Hong, MD, FRCPC[1,2]

[1]Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada

[2]Division of Dermatology, St. Paul's Hospital, Vancouver, BC, Canada

Conflicts of interest: None Reported.

ABSTRACT

Dermatologists have within their armamentarium numerous immunosuppressant agents, both traditional and new, that are useful in the treatment of chronic cutaneous disorders such as autoimmune bullous diseases and psoriasis. It is imperative that users of these agents are aware of potential sequelae from therapy, particularly infections. In this review, we summarize the most common immunosuppressant medications currently used in dermatology, and provide recommendations for infection screening prior to initiating treatment.

Key words: immunosuppression, infection, TNF-α inhibitors, IL-12/23 inhibitors, IL-17 inhibitors, clinical protocol, drug therapy, skin diseases

Introduction

Psoriasis, connective tissue diseases, and autoimmune bullous diseases such as bullous pemphigoid and pemphigus are but a few examples of the dermatological indications for which immunomodulatory/immunosuppressive therapy may be indicated. Treating patients with these inflammatory cutaneous diseases often involves one or more immunosuppressive agents, either sequentially or in combination, which increases the risk of infection-related morbidity and mortality. One of the main safety concerns for the dermatologist prior to initiating therapy is the risk of infection. Risk factors for infection include age, medical comorbidities, travel history, location of residence, occupation, as well as the type, duration and extent of immunosuppression. Although pretreatment infection-testing guidelines exist for the disciplines of gastroenterology, hepatology, rheumatology, and transplant medicine, no specific guidelines have been developed for the dermatologist wishing to begin immunosuppressive therapy. This discussion is timely and of interest within the dermatology literature, as multiple publications have emerged within the last 5 years.[1-3] The dermatologist has a therapeutic armamentarium of immunosuppressive drugs including traditional therapies such as systemic corticosteroids, methotrexate, cyclosporine, azathioprine, mycophenolate mofetil as well as novel therapeutics known as biologics. Within the last decade or so there has been an emergence of novel biologic therapeutics including inhibitors of tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, CD20, p40 subunit of IL-12/23, and more recently IL-17. Herein, we discuss the current pre-treatment infection guidelines for the dermatologist prior to beginning immunosuppressive therapy.

Non-biologic immunosuppressive therapy

The non-biologic immunosuppressive therapies that will be discussed are corticosteroids, methotrexate, azathioprine, cyclosporine and mycophenolate mofetil (Table 1). Since their introduction in the 1950s, corticosteroids have revolutionized the management of inflammatory diseases.[4] Corticosteroids are among the oldest immunosuppressants; their mechanism of action is through inhibition of gene transcription and downregulation of secreted inflammatory cytokines.[5,6] The risk of infection with corticosteroid use depends upon the patient's underlying disease state, duration, dose and route of administration.[7] A lower dose of corticosteroids as well as a shorter duration are associated with a reduction in infectious complications.[8] Corticosteroid use in combination with other immunosuppressive agents, such as methotrexate or azathioprine, increases the risk of serious infections as evidenced in inflammatory bowel disease and rheumatoid arthritis.[9] However, given the short half-life of

Agent	Mechanism of Action	Immunosuppressive Effect
Azathioprine	Purine anti-metabolite	Apoptosis of T-cells
Corticosteroids	Inhibition of transcription of genes response for secretion of inflammatory cytokines	Multiple cytokine alterations; overall effects are decreased leukocyte migration and phagocytosis; decreased T-cell function
Cyclosporine	Inhibition of cytosolic enzyme calcineurin	Suppression of cell-mediated immunity
Methotrexate	Folic acid antagonist; inhibition of purine synthesis; JAK/STAT inhibitor	Mechanism for immunosuppression not fully elucidated
Mycophenolate mofetil	Inhibitor of purine biosynthesis	Decreased migration of inflammatory cells; decreased immunoglobulin production by B-cells

Table 1: Traditional immunosuppressive agents and their mechanism of action

systemic corticosteroids (e.g., prednisone plasma half-life is 60 minutes, prednisolone plasma half-life is 115-212 minutes), it is reasonable to start these medications, if needed, while awaiting infection screening results.

Azathioprine and its derivative 6-mercatopurine are structurally similar to the endogenous purines adenine and guanine. The exact mechanism of action of this immunosuppressive agent is unknown, however it is thought that the structural similarity to endogenous purines allows it to be incorporated into DNA and RNA with subsequent inhibition of purine metabolism and cell division. Azathioprine use is associated with increased bacterial, fungal and viral infections.[10] Prior to initiating azathioprine, the dermatologist should ascertain whether the patient has been immunized or previously infected with varicella zoster virus and if not, immunization prior to commencing immunosuppression should be recommended.[10] Furthermore, azathioprine in combination with prednisolone is associated with an increased risk of infection which can be fatal in the elderly.[11]

Methotrexate is a potent competitive inhibitor of dihydrofolate reductase and a partially reversible inhibitor of thymidylate synthetase, which ultimately acts by inhibiting purine synthesis. However, the definitive mechanism of action of methotrexate is, to date, incompletely understood, as novel modes of action continue to be published; most recently its role as a Janus kinase/signal transducers and activators of transcription (JAK/STAT) pathway inhibitor has been described.[12] In patients receiving long-term treatment with methotrexate, hepatotoxicity is an important consideration and patients should be screened for hepatitis B and C infection prior to initiating treatment. In addition, untreated chronic tuberculosis and active tuberculosis infections are contraindications to treating with methotrexate.

Cyclosporine is postulated to act by inhibition of the intracellular enzyme calcineurin, resulting in reduced activity of the transcription factor nuclear factor of activated T-cells (NFAT-1). With decreased NFAT-1 activity, the transcription of a number of downstream cytokine genes, most notably IL-2, are suppressed. Furthermore, impaired production of IL-2 leads to a decline in the number of activated T-cells within the epidermis. Thus, cyclosporine results in decreased functional T-cell mediated immunity, leading to increased susceptibility to cytosolic microorganisms, including atypical *Mycobacterium*, and viruses.[13,14]

Mycophenolate mofetil (MMF) is a prodrug of mycophenolic acid that inhibits inosine monophosphate dehydrogenase (IMPDH). Inhibition of this critical enzyme, IMPDH, subsequently deprives T- and B-cells of purine metabolites necessary for growth and replication. The net effect is selective immunosuppression. MMF is associated with an increased risk of infection especially when doses in excess of 2 g daily are used.[15,16] Serious infections are most common in renal and cardiac (2%) and hepatic (5%) transplant patients at doses of 2-3 g daily. Viral (herpes zoster, herpes simplex), bacterial, atypical mycobacterial and fungal infections have been reported in the literature.[17-20]

Biologic Immunosuppressive Therapy

The biologics account for a relatively novel class of medications refered to as specialty drugs or specialty pharmaceuticals.[21] Biologics are derived from living cells and are administered by injection, infusion or oral route, and are used to treat a variety of rare conditions. Biologic immunosuppressive therapies include TNF-α inhibitors (infliximab, adalimumab, etanercept), IL-12/23 inhibitors (ustekinumab), CD20 inhibitors (rituximab) and most recently the IL-17 pathway inhibitors (secukinumab, ixekizumab, brodalumab) (Table 2). Given the relative success of TNF-α inhibitors and ustekinumab in the treatment of psoriasis, there has been an emergence of biologics targeting various other cytokines. Inhibitors of IL-17 are the latest wave of therapeutics developed for the treatment of psoriasis and psoriatic arthritis, which deplete the Th17 population of T-cells. Other types of

Biologic Class	Generic Name/ Trade Name	Monoclonal Ab vs. Receptor	Mechanism of Action
TNF-α inhibitors	Infliximab (Remicade®)	Monoclonal Ab (chimeric), IgG1κ	Binds TNF-α only, inhibits binding to soluble and transmembrane TNF receptor
	Adalimumab (Humira®)	Monoclonal Ab (fully human), IgG1	Binds TNF-α only, inhibits TNF binding to p55 and p75 transmembrane TNF receptor
	Etanercept (Enbrel®)	Receptor, dimeric fusion protein, p75 TNF receptor linked to Fc IgG1	Binds to both TNF-α and TNF-β; binding to soluble and membrane bound TNF-α
IL-12/23 inhibitor	Ustekinumab (Stelara®)	Monoclonal Ab (fully human), IgG1	Binds the common p40 subunit of IL-12 and IL-23 preventing interaction with IL-12Rβ1; decreased Th1 and Th17 signalling
IL-17 pathway inhibitors	Secukinumab (Cosentyx®)	Monoclonal Ab (fully human), IgG1κ	Neutralizes IL-17A; decreased IL-23 signalling pathway downstream of Th17 cells
	Ixekizumab (Talz®)	Monoclonal Ab (fully human), IgG4	Neutralizes IL-17A; decreased IL-23 signalling pathway downstream of Th17 cells
CD20 inhibitor	Rituximab (Rituxan®)	Monoclonal Ab (chimeric), IgG1κ	Binds CD20 surface molecule on B-cells

Table 2: Biologic immunosuppressive therapy. Ab = antibody; IgG = immunoglobulin G antibody; Th = T helper cells

IL-17 inhibitors are currently in various phases of clinical trials for psoriasis and psoriatic arthritis.[22] The clinical trials for these agents are currently ongoing and data pertaining to incidence and type of infections have not yet been published.

Rituximab, a biologic that targets the B-cell surface antigen CD20, can be used in several dermatologic conditions including pemphigus vulgaris. Rituximab became the first monoclonal antibody approved by the US FDA for the treatment of cancer. Since rituximab depletes CD20+ B-cells, it should not be administered to patients with active infections. Live vaccines should not be given to patients taking rituximab, and recombinant or killed vaccines should be given at least 4 weeks prior to initiating treatment. Patients should undergo screening for active and latent infections. Rituximab has been associated in particular with reactivation of hepatitis B virus (HBV).[23] The time from last rituximab dose to reactivation of HBV was 3 months, although 29% occurred >6 months after last rituximab. Patients with previous exposure to HBV should be screened prior to initiating rituximab. Carriers should be closely monitored for clinical and laboratory signs of infection as reactivation may lead to liver failure and death in the months following therapy. There is an argument for the consideration of prophylactic treatment in selected patients.[24] Reactivation of the JC virus (a type of human polyomavirus), leading to progressive multifocal leukoencephalopathy (PML) has also been associated with rituximab treatment.[25] Among human immunodeficiency virus (HIV)-negative patients, the median time to diagnosis of PML was 5.5 months following the last dose of rituximab and a 90% fatality was reported. These data warrant vigilant monitoring for new onset neurologic findings during and after the course of treatment.

Pretreatment Infection Workup

Recent publications within the dermatology literature have provided recommendations for an infection workup for the dermatologist prior to initiating immunosuppressive agents.[2,3] In general, the suggested steps apply to all immunosuppressants, whether non-biologic or biologic. Table 3 provides a summary of these and our recommendations.

Although the morbidity and mortality from infectious complications can be significant, careful patient selection and monitoring can mitigate risk and reduce potential harm. General recommendations include conducting a thorough history and physical exam, with particular focus on country of birth and residence, travel history, sexual and social risk factors and exposure to sick contacts. Vaccination records should be

1. Screen patient for risk factors of infection:

- Comorbid medical conditions (i.e., organ/hematopoietic transplant, active malignancy, renal or liver failure, diabetes mellitus etc.)
- Age
- Occupation
- History of travel to areas of endemic disease
- History of high risk sexual activity, drug abuse
- History of exposure to tuberculosis
- History of blood transfusion

2. On a case by case basis, consider laboratory screening for patients at risk:

- Hepatitis B (HBsAg, anti-HBc, IgM anti-HBc, anti-HBs)
- Hepatitis C (HCV enzyme immunoassay)
- HIV (HIV ELISA)
- *Strongyloides* (stool culture for ova and parasites; *Strongyloides* ELISA)
- Tuberculosis (PPD tests; interferon-gamma release assay; chest x-ray, for patients with a positive PPD test from previous Bacillus Calmette-Guérin vaccination)
- Systemic fungal infections, such as cryptococcosis, histoplasmosis, coccidiomycosis, blastomycosis, and paracoccidioidomycosis (serum and/or urine test; chest x-ray)
- Consider pneumocystis pneumonia prophylaxis

3. Ensure immunizations are up-to-date according to latest recommendations (www.cdc.gov/vaccines/schedules/)

- Seasonal influenza vaccination (non-live vaccine; avoid live vaccine after immunosuppressive therapies have been initiated)
- *Pneumococcus* vaccination (non-live vaccine)
- Herpes zoster vaccination (live vaccine; initiate prior to starting immunosuppressive therapy)
- Tetanus/diphtheria vaccination (non-live vaccine)

4. Patient education in regards to:

- Frequent handwashing
- Avoiding high-risk infectious exposures if possible (i.e., over-crowded areas, child care centres, nursing homes, farms, compost, travel to countries where aforementioned diseases are endemic)
- Early signs and symptoms of infection (e.g., including impetiginization, and systemic bacterial, fungal and viral infections)

Table 3: A dermatologist's checklist to infection screening prior to initiating immunosuppressive therapy (adapted from Lehman JS et al.[2])
Anti-HBc = hepatitis B virus core antibody; anti-HBs= hepatitis B virus surface antibody; ELISA = enzyme-linked immunosorbent assay; HBsAg = hepatitis B virus surface antigen; HCV = hepatitis C virus; PPD = purified protein derivative

reviewed and, if feasible, age-appropriate vaccinations should be updated prior to initiating immunosuppressive therapy. Patients should be educated on the importance of general hygiene (i.e., handwashing), signs and symptoms of early infection and when they should seek urgent medical care. Likewise, the dermatologist should be vigilant for early signs and symptoms of infection, and have a low threshold to treat bacterial, fungal and viral illness. Physicians should assess patients at each visit for impetiginization and treat appropriately.

All patients should undergo HIV, HBV, and hepatitis C virus (HCV) testing. Furthermore, testing and diagnosis of tuberculosis should be undertaken as per Centers for Disease Control and Prevention (CDC) and Health Canada recommendations (Health Canada: http://www.phac-aspc.gc.ca/tbpc-latb/pubs/tb-canada-7/tb-standards-tb-normes-ch3-eng.php and CDC: http://www.cdc.gov/tb/topic/testing/).

Testing for parasitic infections, particularly *Strongyloides stercoralis* (*S. stercoralis*) should be considered and done on an individualized basis. Infection with *S. stercoralis* is usually chronic and asymptomatic in immunocompetent patients and may persist undetected for many years. In immunosuppressed patients, strongyloidiasis can cause hyperinfection and dessimination and carries a high mortality rate. It is reasonable to screen those who have resided in an endemic area for a prolonged period even if it was in the distant past (i.e., southeastern United States and subtropical areas, Europe) and those who possess other risk factors (i.e., occupation, activities). Unexplained hypereosinophilia should also trigger the physician to screen for *Strongyloides*. Conversely, the physician should be mindful that prolonged corticosteroid use can suppress hypereosinophilia. Stool microscopy for ova and parasites is currently the gold standard for diagnosis, however, up to seven collections may be required in order to reach a sensitivity of 100%.[26] A single stool sample collection has a low sensitivity of 30-75%.[27,28] Sensitivity for the enzyme-linked immunosorbent assay (ELISA) for *S. stercoralis* serology is 83-93% with 95-97% specificity.[29]

Conclusion

We have provided an overview of some of the major immunosuppressant drugs used in dermatology and have presented a summary of recommendations prior to initiating these medications (Table 3). Regardless of the immunosuppressive agent used, the type of infections that the dermatologist needs to screen for and prevent are similar. Overall, the risk of infection is likely to be directly proportional to the dose and duration of immunosuppressant therapy.

References

1. Keith PJ, Wetter DA, Wilson JW, et al. Evidence-based guidelines for laboratory screening for infectious diseases before initiation of systemic immunosuppressive agents in patients with autoimmune bullous dermatoses. *Br J Dermatol.* 2014 Dec;171(6):1307-17.
2. Lehman JS, Wetter DA, Davis MD, et al. Anticipating and preventing infection in patients treated with immunosuppressive medications for dermatologic indications: a dermatologist's checklist. *J Am Acad Dermatol.* 2014 Oct; 71(4):e125-6.
3. Lehman JS, Murrell DF, Camilleri MJ, et al. Infection and infection prevention in patients treated with immunosuppressive medications for autoimmune bullous disorders. *Dermatol Clin.* 2011 Oct;29(4):591-8.
4. Hench PS, Kendall EC, Slocumb CH, et al. Effects of cortisone acetate and pituitary ACTH on rheumatoid arthritis, rheumatic fever and certain other conditions. *Arch Intern Med (Chic).* 1950 Apr;85(4):545-666.
5. Rhen T, Cidlowski JA. Antiinflammatory action of glucocorticoids--new mechanisms for old drugs. *N Engl J Med.* 2005 Oct 20;353(16):1711-23.
6. Buttgereit F, Straub RH, Wehling M, et al. Glucocorticoids in the treatment of rheumatic diseases: an update on the mechanisms of action. *Arthritis Rheum.* 2004 Nov;50(11):3408-17.
7. Cutolo M, Seriolo B, Pizzorni C, et al. Use of glucocorticoids and risk of infections. *Autoimmun Rev.* 2008 Dec;8(2):153-5.
8. Stuck AE, Minder CE, Frey FJ. Risk of infectious complications in patients taking glucocorticosteroids. *Rev Infect Dis.* 1989 Nov-Dec;11(6):954-63.
9. Stein RB, Hanauer SB. Comparative tolerability of treatments for inflammatory bowel disease. *Drug Saf.* 2000 Nov;23(5):429-48.
10. Meggitt SJ, Anstey AV, Mohd Mustapa MF, et al. British Association of Dermatologists' guidelines for the safe and effective prescribing of azathioprine 2011. *Br J Dermatol.* 2011 Oct;165(4):711-34.
11. Wojnarowska F, Kirtschig G, Highet AS, et al. British Association of Dermatologists. Guidelines for the management of bullous pemphigoid. *Br J Dermatol.* 2002 Aug;147(2):214-21.
12. Thomas S, Fisher KH, Snowden JA, et al. Methotrexate Is a JAK/STAT Pathway Inhibitor. *PLoS One.* 2015 Jul 1;10(7):e0130078.
13. Amor KT, Ryan C, Menter A. The use of cyclosporine in dermatology: part I. *J Am Acad Dermatol.* 2010 Dec;63(6):925-46; quiz 47-8.
14. Ryan C, Amor KT, Menter A. The use of cyclosporine in dermatology: part II. *J Am Acad Dermatol.* 2010 Dec;63(6):949-72; quiz 73-4.
15. Beissert S, Mimouni D, Kanwar AJ, et al. Treating pemphigus vulgaris with prednisone and mycophenolate mofetil: a multicenter, randomized, placebo-controlled trial. *J Invest Dermatol.* 2010 Aug;130(8):2041-8.
16. Powell AM, Albert S, Al Fares S, et al. An evaluation of the usefulness of mycophenolate mofetil in pemphigus. *Br J Dermatol.* 2003 Jul;149(1):138-45.
17. Murray ML, Cohen JB. Mycophenolate mofetil therapy for moderate to severe atopic dermatitis. *Clin Exp Dermatol.* 2007 Jan;32(1):23-7.
18. Benez A, Fierlbeck G. Successful long-term treatment of severe atopic dermatitis with mycophenolate mofetil. *Br J Dermatol.* 2001 Mar;144(3):638-9.
19. Rowin J, Amato AA, Deisher N, et al. Mycophenolate mofetil in dermatomyositis: is it safe? *Neurology.* 2006 Apr 25;66(8):1245-7.
20. Saha M, Black MM, Groves RW. Risk of herpes zoster infection in patients with pemphigus on mycophenolate mofetil. *Br J Dermatol.* 2008 Nov;159(5):1212-3.
21. Gleason PP, Alexander GC, Starner CI, et al. Health plan utilization and costs of specialty drugs within 4 chronic conditions. *J Manag Care Pharm.* 2013 Sep;19(7):542-8.
22. Mease PJ. Inhibition of interleukin-17, interleukin-23 and the TH17 cell pathway in the treatment of psoriatic arthritis and psoriasis. *Curr Opin Rheumatol.* 2015 Mar;27(2):127-33.
23. Evens AM, Jovanovic BD, Su YC, et al. Rituximab-associated hepatitis B virus (HBV) reactivation in lymphoproliferative diseases: meta-analysis and examination of FDA safety reports. *Ann Oncol.* 2011 May;22(5):1170-80.
24. Leung C, Tsoi E, Burns G, et al. An argument for the universal prophylaxis of hepatitis B infection in patients receiving rituximab: a 7-year institutional experience of hepatitis screening. *Oncologist.* 2011;16(5):579-84.
25. Carson KR, Evens AM, Richey EA, et al. Progressive multifocal leukoencephalopathy after rituximab therapy in HIV-negative patients: a report of 57 cases from the Research on Adverse Drug Events and Reports project. *Blood.* 2009 May 14;113(20):4834-40.
26. Sarubbi FA. Hyperinfection with Strongyloides during treatment of pemphigus vulgaris. *Arch Dermatol.* 1987 Jul;123(7):864-5.
27. Siddiqui AA, Berk SL. Diagnosis of Strongyloides stercoralis infection. *Clin Infect Dis.* 2001 Oct 1;33(7):1040-7.
28. Cartwright CP. Utility of multiple-stool-specimen ova and parasite examinations in a high-prevalence setting. *J Clin Microbiol.* 1999 Aug;37(8):2408-11.
29. Centers for Disease Control and Prevention, Infectious Disease Society of America, American Society of Blood and Marrow Transplantation. Guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *MMWR Recomm Rep.* 2000 Oct;49(RR-10):1-125, CE1-7.

Update on Drugs

Name/Company	Approval Dates/Comments
Nivolumab + ipilimumab *Opdivo® + Yervoy®* Bristol-Myers Squibb Company	In October 2016, Health Canada granted conditional approval to the nivolumab (Opdivo®) + ipilimumab (Yervoy®) regimen for the treatment of previously untreated adults with unresectable or metastatic melanoma. This new therapeutic option consists of the first-ever combination of two immuno-oncologic agents targeting distinct and complementary immune pathways at the same time, resulting in the potential to increase progression-free survival in certain patients. Health Canada also issued a notice of compliance with conditions for Opdivo® monotherapy for the treatment of unresectable or metastatic BRAF V600 mutation-positive melanoma in previously untreated adults. An improvement in survival has yet to be established for either indication.
Etanercept for SC injection *Enbrel®* Amgen Inc.	The US FDA approved the supplemental Biologics License Application (sBLA) for the expanded use of etanercept (Enbrel®) in November 2016, making it the first and only systemic therapy to treat pediatric patients aged 4-17 with chronic moderate-to-severe plaque psoriasis. The approval is based on results from a Phase III 1-year study and its 5-year open-label extension study to evaluate the safety and efficacy of Enbrel® in pediatric patients with chronic moderate-to-severe plaque psoriasis. In addition to demonstrating significant efficacy, the adverse events were similar to those seen in previous studies in adults with moderate-to-severe plaque psoriasis. Enbrel® is a tumor necrosis factor (TNF) blocker that was first approved in 1998 to treat moderate-to-severe rheumatoid arthritis. It was subsequently approved in 1999 to treat polyarticular juvenile idiopathic arthritis, in 2002 to treat psoriatic arthritis, in 2003 to treat ankylosing spondylitis, and in 2004 to treat plaque psoriasis in adults.
Crisaborole 2% ointment *Eucrisa™ (formerly AN2728)* Pfizer/Anacor	The FDA approved crisaborole ointment in December 2016 to treat mild-to-moderate eczema (atopic dermatitis) in patients ≥2 years of age. Cisaborole is a novel non-steroidal topical anti-inflammatory phosphodiesterase-4 (PDE-4) inhibitor that is applied topically twice daily. Crisaborole is a boron-based small molecule that appears to inhibit PDE-4 in target cells, thereby inhibiting the production of pro-inflammatory cytokines thought to cause the signs and symptoms of atopic dermatitis. Safety and efficacy were established in two placebo-controlled trials with a total of 1522 participants, ranging in age from 2-79 years, with mild-to-moderate atopic dermatitis. Overall, participants receiving topical cisaborole achieved greater response with clear or almost clear skin after 28 days of treatment.
Hyaluronic acid dermal fillers *Restylane® Refyne* *Restylane® Defyne* Galderma Laboratories	The FDA approved two new next generation hyaluronic acid (HA)-based dermal fillers in December 2016 for the treatment of nasolabial folds or laugh lines in patients >21 years of age. Restylane® Refyne was approved for moderate-to-severe facial wrinkles and folds and Restylane® Defyne for treating moderate-to-severe deep facial wrinkles and folds. These HA fillers have been shown to maintain efficacy for treating nasolabial folds for up to 12 months and are manufactured with XpresHAn technology, which customizes the degree of HA crosslinking in each product to allow a range of flexibly and support. According to the manufacturer, distinct from fillers already commercially available, the XpresHAn technology allows the product to move within the face as facial expressions are made, resulting in a more natural-looking outcome. Although new to the US, both Restylane® Refyne and Defyne gained approval in the EU under the name trade name of Emervel® in 2010.

Skin Therapy Letter®
EDITOR: DR. RICHARD THOMAS

Index for Volume 21 (2016)

Articles are indexed by drug names, trade names and disease terms. Bold entries refer to major references.

Skin Therapy Letter©
EDITOR: DR. RICHARD THOMAS

Index for Volume 21 (2016)

Articles are indexed by drug names, trade names and disease terms. Bold entries refer to major references.