SKIN

EDITORIALS

Should Package Insert Warnings Deter Prescribing in Psoriasis Patients with Depression?

Graham H Litchman DO, MS,[1] Quinn Thibodeaux, MD,[2] Ryan Rivera-Oyola, MS,[3] John Koo, MD,[2] Rick Fried, MD, PhD,[4] Gary Goldenberg, MD,[3,5] George Han, MD,[3] Sylvia Hsu, MD,[6] Leon Kircik, MD,[3,7] Melissa Knuckles, MD,[8] Andrea Murina, MD,[9] Jeffrey Weinberg, MD,[4] Jashin J. Wu,MD,[10] Mark Lebwohl, MD[3]

[1]St. John's Episcopal Hospital, Department of Dermatology, Far Rockaway, NY
[2]University of California San Francisco, Department of Dermatology, San Francisco, CA.
[3]Icahn School of Medicine at Mt Sinai Hospital, Department of Dermatology, New York, NY
[4]Yardley Dermatology Associates; Yardley Clinical Research Associates, Morrisville, PA
[5]Goldenberg Dermatology, New York, NY
[6]Temple University Lewis Katz School of Medicine, Department of Dermatology, Philadelphia, PA
[7]Indiana University Medical Center, Indianapolis, IN
[8]M.L.F. Knuckles Dermatology, Corbin, KY; M.L.F. Knuckles Dermatology Richmond, KY; AdventHealth Hospital, Manchester, KY
[9]Tulane University School of Medicine, Department of Dermatology, New Orleans, LA
[10]Dermatology Research and Education Foundation, Irvine, CA

ABSTRACT

Introduction: Psoriasis, an immune-mediated disease that manifests cutaneously with possible arthritic complications, affects millions of people in the United States and worldwide. Depression and suicidal ideation and behavior (SIB) are two prevalent comorbidities associated with psoriasis, due to the chronic nature of the disease, lack of a cure, as well as social stigma, all of which are detrimental to quality of life. Among the options available for management of moderate-severe psoriasis, apremilast and brodalumab represent recent additions to the therapeutic armamentarium for managing psoriasis. It has been suggested that the aforementioned drugs can lead to depression and possibly increase the risk for SIB. Furthermore, a black box warning was issued for brodalumab. This review challenges opinions that the drugs are solely responsible for exacerbating depression and SIB, when in fact it could be psoriasis itself.

Methods: An extensive search of available literature linking cytokines to suicidal behavior was performed. After filtering for relevance, 22 articles were reviewed in detail.

Results: Brodalumab and apremilast, both molecularly and clinically, do not objectively increase the risk for depression and/or suicidal ideation and behavior.

Conclusion: After careful review of the appropriate studies and relevant literature, patients with moderate-severe psoriasis, including those that experience depression resulting from their chronic condition, would likely benefit from early, rather than delayed initiation of effective medications like apremilast and brodalumab. The speed of response and high level of efficacy of brodalumab make it

INTRODUCTION

Psoriasis, an immune-mediated disease that manifests as itchy, red scaling plaques along with possible arthritic complications, affects 8 million people in the United States, and upwards of 3% of the worldwide population.[1] Depression and suicidal ideation and behavior (SIB) are two prevalent comorbidities associated with psoriasis due to the chronic nature of the disease, lack of a cure, as well as the social stigma, all of which are detrimental to quality of life. Among the options available for management of moderate-severe psoriasis, apremilast, which targets phosphodiesterase-4 (PDE4), and brodalumab, which targets interleukin-17 (IL-17) receptor A, represent recent additions to our therapeutic armamentarium for managing psoriasis. Brodalumab has a faster onset when compared to other monoclonal antibodies indicated for psoriasis.[2] This faster onset is important, in terms of more efficiently decreasing disease burden and alleviating treatment dissatisfaction, a problem that has plagued older treatment options.[3]

This review challenges opinions that the drugs are solely responsible for exacerbating depression and SIB, when in fact it could be psoriasis itself, whether untreated or unresponsive to prior treatment, that may contribute to diminished quality of life and depression. In fact, it is successful and, more importantly, *timely* control of psoriatic symptoms that often improves psychological comorbidity outcomes. Furthermore, package insert warnings may discourage clinicians from prescribing needed medication and introduce unnecessary additional psychological burden to patients, which is counterproductive to maintaining long-term wellbeing. These concerns may be further accentuated for medications that are issued black box warnings (such as Brodalumab).[4] Instead, thorough screening and referral of patients who display signs of depression or SIB eschews the need for black box warnings. Such warnings indicate an enhanced level of danger while using the drug which is, in this case, unnecessary.

RESULTS

Cytokines and Depressive/Suicidal Behavior

A search of available literature linking cytokines to suicidal behavior implicate elevated IL-6 levels likely having an association with increases in suicidal ideation.[5] For IL-17 specific studies, all point to elevated levels of IL-17A as contributing to higher depressive symptoms;[6-8] both apremilast and brodalumab contribute to decreasing IL-17 expression, or inhibition of IL-17 binding to its receptor, respectively, and consequently would be expected to reverse depression and SIB. Similarly, other reports suggest that specifically targeting pro-inflammatory cytokines will likely decrease and treat depressive symptoms.[9]

Apremilast

Apremilast, an orally administered phthalimide-based small molecule, is a PDE4 inhibitor that prevents the hydrolysis of cyclic adenosine monophosphate (cAMP).This inhibition causes several pro-inflammatory cytokines, such as IL-17, IL-23, and tumor necrosis factor alpha (TNFa) to be down-regulated, while at the same time upregulating IL-10, an anti-inflammatory factor.[10] It was approved in 2014 to treat psoriatic arthritis and plaque psoriasis.

Due to its low molecular weight (460 Da), it could theoretically cross the blood-brain barrier (BBB) and potentially affect brain chemistry and patient mood. However, tissue distribution studies using ^{14}C-labeled drug consistently showed low concentrations of apremilast within the CNS, indicating poor penetration of the blood-brain barrier.[11] The highest levels of radioactivity were observed in organs involved with metabolism and subsequent clearance (liver, kidneys).[11]

Two phase III trials(ESTEEM 1 – 2; PALACE 1 – 3) were carried out to study long-term efficacy and tolerability of apremilast (≥ 3 years for ESTEEM, up to five years for PALACE). For the populations of both ESTEEM trials[12] (n = 1250), 178 (14.2%) patients reported a history of depression, while 156 (12.4%) were taking an antidepressant. There was one suicide attempt in the treatment arm (0 to ≤ 52 weeks), and one completed suicide in the placebo arm during ESTEEM 1. The incidence of depression did not increase with extended apremilast use and there were no other reports of suicide. More importantly, the rate of depression in the ESTEEM trials were lower than the background rate in the psoriasis population (≥10%), when compared to reported values.[13,14]

Across PALACE 1 – 3 (n = 1493),[15] reports of depression remained low, with a slightly higher incidence in the treatment arm (1.2%) compared to the placebo arm (0.8%). There were no completed suicides in the experimental arm during the study, and two reported attempts: one during the 0 to ≤ 52 weeks exposure period to apremilast, and one during the > 52 to ≤ 104 weeks of exposure. Both attempts were attributable to external risk factors (serious family altercation in the former case, and a history of depression, affective disorder, and physical/emotional abuse in the latter). There were, however, two completed suicides in the placebo arm.

Brodalumab

Brodalumab is a humanized monoclonal antibody, approved in 2017 to treat severe plaque psoriasis, in particular for patients who have not responded to or have low tolerability for other systemic therapy.[16] It binds directly to the IL-17 receptor A, preventing activation by IL-17A, IL-17F, IL17A/F, IL-17C, and IL-17E (IL-25); this is in contrast to other monoclonal antibodies such as ixekizumab, which only binds to IL-17A.[17]

Brodalumab, being a whole antibody (144 kDa), is too large, and too hydrophilic, for successful penetration of the BBB; by comparison, the largest known protein able to cross the blood-brain barrier via transmembrane diffusion is cytokine-induced neutrophil chemoattractant (CINC-1), at 7.8 kDa.[18] Saturable transport systems, whether efflux or influx, primarily have small molecule substrates, such as glucose, amino acids, and signaling molecules such as epinephrine.[19]

There were three phase III trials for brodalumab (AMAGINE 1 – 3; n = 4373) to assess efficacy and safety, monitored at up to 52 weeks. Several clinical assessments were used to ascertain patient response, including Hospital Anxiety and Depression Scale (HADS), Psoriasis Area and Severity Index (PASI), Psoriasis Symptom Inventory (PSI), and static Physician's Global Assessment (sPGA).

In AMAGINE-1,[20] pooled population data (n = 220 for placebo, n = 441 for treatment) indicated substantial improvement of psoriasis symptoms at 12 weeks exposure: 317 patients had achieved at least PASI 75,

compared to 6 in placebo. Of those 317, 249 had PASI 90, and 144 had PASI 100. Improvement was also seen in their HADS scores: baseline mean scores for the 140 mg treatment arm saw a reduction in depression scores from 5.2 ± 4.1 to 3.6 ± 0.3 after 12 weeks, while the 210 mg treatment arm saw a similar reduction from 5.5 ± 4.2 at baseline, to 3.5 ± 0.2 after 12 weeks. Through week 52 in AMAGINE-1, there was one completed suicide by hanging. In AMAGINE 2-3, there were two additional completed suicides.[4]

In addition to the three completed suicides mentioned above, one (secondary to a drug overdose with opiates and alcohol) was subsequently ruled indeterminate by the Columbia Classification Algorithm for Suicide Assessment (C-CASA). For the remaining three, all had received 210 mg doses of brodalumab, and had PASI scores of 73, 100, and 100; however, none of the suicides occurred within three months of treatment initiation (140, 329, and 845 days after first dose, respectively). In addition, similar to the suicide observed in the PALACE trials for apremilast, the three patients had external factors unrelated to brodalumab treatment, including financial stressors, the possibility of incarceration due to legal difficulties, and ongoing treatment for depression and anxiety.[4]

DISCUSSION

From a molecular perspective, both apremilast and brodalumab are unable to effectively penetrate the blood-brain barrier. The inhibition of IL-17 receptors or IL-17 and related isoforms, based on previous studies, would imply that reducing the effects of IL-17 would help in *decreasing* depression and suicidal ideation and behavior. Clinically, the instances of suicide attempts and completed suicides reported in phase III trials for apremilast (ESTEEM and PALACE) and brodalumab (AMAGINE) are confounded by external factors that are unrelated to drug or biologic administration. As previously stated, none of the three completed suicides in the brodalumab psoriasis trials occurred within three months of treatment initiation, the period in which the majority of patients showed substantial improvement in controlling psoriasis symptoms, as shown by statistically significant improvement in HADS and PASI scores after 12 weeks. Reports of depression for the duration of each clinical trial are also below population averages of psoriasis patients when previous data and meta-analyses are considered. Many factors should be considered when selecting the optimal therapy for patients with psoriasis.[21,22]

CONCLUSION

After careful review of the appropriate studies and relevant literature, patients with moderate-severe psoriasis, including those that experience depression resulting from their chronic condition, would likely benefit from early, rather than delayed initiation of effective medications like apremilast and brodalumab. The speed of response and high level of efficacy of brodalumab make it an ideal intervention for patients suffering depression caused by their psoriasis.

Conflict of Interest Disclosures:
GHL, QT, RRO have no relevant conflicts of interest. **JK** is a speaker and advisor for Abbvie, Amgen, Celgene, Janssen, Eli-Lilly, Leo Pharma, Novartis, Pfizer, Strata Skin Science, SUN Pharma, and OrthoDermatologic. **RF** has no relevant conflicts of interest. **GG** is a consultant and speaker for Abbvie, AMLA, Bayer, Celgene, Dermira, Leo, Novartis, Pharmaderm, Pfizer, and Regeneron/Sanofi. He is a consultant for Allergan, Amgen, Almirall, Castle, Eclipse, Galderma, Genentech, GSK/Stiefel, Intraderm, ISDIN, Janssen, Menlo, Ranbaxy, Scibase, Suneva, TEVA, Valeant/Ortho

Dermatologic, and Verrica. He is a speaker for Merz and on the board of directors of Verrica.
GH is an advisor, speaker and consultant for Janssen, OrthoDermatologic, Regeneron/Sanofi, Eli Lily, UCB, Abbvie, SUN Pharma, and Pfizer. He is an investigator for Pfizer, Novartis, Eli Lily, Janssen, MC2 Therapeutics, Bond Avillion, Celgene, and Athenex. **SH** has been an investigator for Celgene and Novartis and an advisor for Janssen, Ortho Dermatologics, and Menlo Therapeutics.
LK is a speaker for Abbott Laboratories, Allergan, Amgen, Assos Pharma, Astellas Pharma US, Inc., Cipher, CollaGenex, Connetics Corporation, Dermik Laboratories, Embil Pharmaceuticals, Exeltis, Genentech, Innocutis, Innovail, Johnson & Johnson, Leo, L'Oreal, 3M, Onset, OrthoNeutrogena, PediaPharm, PharmaDerm, Serono, SkinMedica, Stiefel Laboratories, SUN Pharma, Taro, Triax, UCB, Valeant Pharmaceuticals, and Warner-Chilcott. He has participated in advisory boards for Aclaris, Allergan, Almirall, Anacor, Biogen-Idec, Colbar, Celgene, Cipher, Connetics, EOS, Exeltis, Ferndale Laboratories, Genentech, Intendis, Innocutis, Isdin, Johnson & Johnson, Merz, OrthoNeutrogena, Promius, Quinnova, SkinMedica, Stiefel Laboratories, SUN Pharma, Valeant, and Warner-Chilcott. He is an investigator for Acambis, Allergan, Amgen, Anacor, Astellas, Asubio, Berlex, Biolife, Biopelle, Boehringer-Ingleheim, Breckinridge Pharma, Celgene, Centocor, Cellceutix, Coherus, CollaGenex, Combinatrix, Connetics Corporation, Coria, Dermavant, Dermira, Dow Pharmaceutical Sciences, Dusa, Eli Lilly, Exeltis, Ferdale Laboratories, Foamix, Genentech, GlaxoSmithKline, Health Point, Idera, Intendis, Johnson & Johnson, Leo, L'Oreal, 3M, Maruho, Merck, Medicis, Merz, Novartis, Noven, Nucryst, Obagi, Onset, OrthoNeutrogena, Promius, QLT, PharmaDerm, Pfizer, Quinnova, Quatrix, SkinMedica, Stiefel, SUN Pharma, TolerRx, UCB, Valeant, Warner-Chilcott, and XenoPort. He is a consultant for Allergan, Almirall, Amgen, Anacor, Colbar, Cipher, CollaGenex, Connetics, Exeltis, Genentech, Intendis, Isdin, Johnson & Johnson, Laboratory Skin Care, Leo, Medical International Technologies, Merck, Merz, Novartis, OrthoNeutrogena, Promius, PuraCap, SkinMedica, Stiefel, SUN Pharma, Taro, UCB, Valeant, and ZAGE. **MK** is a speaker for Siliq, Cosentyx, Otezla, Eucrisa, Ilumya, Cimzia, SunPharma, Novartis, Celgene, Abbvie, Amgen, Duobrii, Bryhali, Dupixent, Enbrel, Amgen, Abbvie, Humira, Skyrizi. She is on advisory boards for Promius, Siliq, Ortho Dermatologics, Corrona Investigator, Castle Bioscience, Novartis, Sanofi-Regeneron, and Ilumya. **AM** is a speaker for Abbvie, Amgen, Eli Lilly and Company, Janssen, and Novartis. She has participated in advisory boards for Ortho Dermatologics and Janssen. **JW** is a speaker and investigator for Celgene and a speaker for OrthoDermatologic. **JJW** is or has been an investigator, consultant, or speaker for AbbVie, Almirall, Amgen, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermavant, Dermira, Dr. Reddy's Laboratories, Eli Lilly, Janssen, LEO Pharma, Novartis, Regeneron, Sanofi Genzyme, Sun Pharmaceutical, UCB, Valeant Pharmaceuticals North America LLC. **ML** is an employee of Mount Sinai and receives research funds from: Abbvie, Amgen, Arcutis, AstraZeneca, Boehringer Ingelheim, Celgene, Clinuvel, Eli Lilly, Incyte, Janssen Research & Development, LLC, Kadmon Corp., LLC, Leo Pharmaceutucals, Medimmune, Novartis, Ortho Dermatologics, Pfizer, Sciderm, UCB, Inc., and ViDac, and is also a consultant for Allergan, Almirall, Arcutis, Inc., Avotres Therapeutics, BirchBioMed Inc., Boehringer-Ingelheim, Bristol-Myers Squibb, Cara Therapeutics, Castle Biosciences, Corrona, Dermavant Sciences, Evelo, Foundation for Research and Education in Dermatology, Inozyme Pharma, LEO Pharma, Meiji Seika Pharma, Menlo, Mitsubishi, Neuroderm, Pfizer, Promius/Dr. Reddy's Laboratories, Theravance, and Verrica.

Funding: None

Corresponding Author:
Graham H. Litchman, DO, MS
Department of Dermatology
St. John's Episcopal Hospital
Far Rockaway, NY
Phone: 203-940-0373
Email: graham.litchman@gmail.com

References:

1. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM; Identification and Management of Psoriasis and Associated ComobidiTY (IMPACT) project team. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2013 Feb;133(2):377-85.
2. Foulkes AC, Warren RB. Brodalumab in psoriasis: evidence to date and clinical potential. Drugs Context. 2019 Apr 17;8:212570.
3. Stern RS, Nijsten T, Feldman SR, Margolis DJ, Rolstad T. Psoriasis is common, carries a substantial burden even when not extensive, and is associated with widespread treatment dissatisfaction. *J. Investig. Dermatol. Sympos. Proc.* 2004 Mar;9(2):136-139.
4. Lebwohl, MG, Papp KA, Marangell LB, Koo J, Blauvelt A, Gooderham M, Wu JJ, Rastogi S,

Harris S, Pillai R, Israel RJ. Psychiatric adverse events during treatment with brodalumab: Analysis of psoriasis clinical trials. *J Am Acad Dermatol.* 2018 Jan;78(1): 81-89.
5. Ganança L, Ouquendo MA, Tyrka AR, Cisneros-Trujillo S, Mann JJ, Sublette ME. The role of cytokines in the pathophysiology of suicidal behavior. *Psychoneuroendocrinology.* 2016;63:296-310.
6. Davami MH, Baharlou R, Ahmadi Vasmehjani A, Ghanizadeh A, Keshtkar M, Dezkham J, ATashzar MR. Elevated IL-17 and TGF- serum levels: a positive correlation between T-helper 17 cell-related pro-inflammatory responses with major depressive disorder. *Basi Clin. Neurosci.* 2016 Apr;7(2):137-142.
7. Nadeem A, Ahmad SF, Al-Harbi NO, Fardan AS, EL-Sherbeeny AM, Ibrahim KE, Attia SM. IL-17A causes depression-like symptoms via NF B and p38MAPK signaling pathways in mice: implications for psoriasis associated depression. *Cytokine.* 2017 Sept;97:14-24.
8. Tsuboi H, Sakakibara H, Minamida Y, Tsujiguchi H, Matsunaga M, Hara A, Nakamura H. Elevated levels of serum IL-17A in community-dwelling women with higher depressive sumptoms. *Behav. Sci. (Basel).* 2018 Nov;8(11):102-108.
9. Raison CL, Capuron L, Miller AH. Cytokines sing the blues: inflammation and the pathogenesis of depression. *Trends Immunol.* 2006 Jan;27(1):24-31.
10. Schafer P. Apremilast mechanism of action and application to psoriasis and psoriatic arthritis. *Biochem. Pharmacol.* 2012;(83(12):1583-1590.
11. European Medicines Agency. (2014). *Assessment Report: Otezla*. Retrieved from https://www.ema.europa.eu/en/documents/assessment-report/otezla-epar-public-assessment-report_en.pdf.
12. Crowley J, Thaçi D, Joly P, Peris K. *et al*. Long-term safety and tolerability of apremilast in patients with psoriasis: Pooled safety analysis for ≥ 156 weeks from 2 phase 3, randomized, controlled trials (ESTEEM 1 and 2). *J Am Acad Dermatol*. 2017;77(2):310-317.
13. Gooderham M, Papp K. Selective phosphodiesterase inhibitors for psoriasis, focus on apremilast. *Biodrugs*. 2015;29(5):327-339.
14. Dowlayshahi EA, Wakkee M, Arends LR, Nijsten T. The prevalence and odds of depressive symptoms and clinical depression in psoriasis patients: a systematic review and meta-analysis. *J Invest Dermatol.* 2014;134(6):1542-1551.
15. Kavanaugh A, Gladman DD, Edwards CJ, Schett G, Guerette B, Delev N, Teng L, Paris M, Mease PJ. Long-term experience with apremilast in patients with psoriatic arthritis: 5-year results from a PALACE 1-3 pooled analysis. *Arthritis Res. Ther.* 2019;21(118).
16. Menter A, Strober BE, Kaplan DH, Kivelevitch D *et al*. Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with biologics. *J. Amer. Acad. Dermatol.* 2019 Apr;80(4):1029-1072.
17. European Medicines Agency. (2016). *Assessment Report: Taltz*. Retrieved from https://www.ema.europa.eu/en/documents/assessment-report/taltz-epar-public-assessment-report_en.pdf.
18. Pan W, Kastin, AJ. Changing the chemokine gradient: CINC1 crosses the blood-brain barrier. *J. Neuroimmunol.* 2011;115(1-2):64-70.
19. Banks WA. Characteristics of compounds that cross the blood-brain barrier. *BMC Neurology.* 2009;9(Suppl. 1):S3.
20. Papp KA, Reich K, Paul C, Blauvelt A, Baran W, Bolduc C, Toth D, Langley RG, Cather J, Gottlieb AB, Thaçi D, Kreuger JG, Russell CB, Milmont CE, Li J, Klekotka PA, Kricorian G, Nirula A. A prospective phase III, randomized, double-blind, placebo-controlled study brodalumab in patients with moderate-to-severe plaque psoriasis. *Br J Dermatol.* 2016 Aug;175(2):273-286.
21. Kaushik SB, Lebwohl MG. Psoriasis: Which Therapy for Which Patient:
22. Psoriasis comorbidities and preferred systemic agents. J Am Acad Dermatol. 2019;80(1):27-40.
23. Kaushik SB, Lebwohl MG. Psoriasis: Which Therapy for Which Patient. Focus on special populations and chronic infections. J Am Acad Dermatol. 2019;80(1):43-53.