Psoriasis Improvement in Patients Using Glutathione-enhancing, Nondenatured Whey Protein Isolate

A Pilot Study

[a,b]RONALD PRUSSICK, MD; [a]LISA PRUSSICK, BSc; [c,d]JIMMY GUTMAN, MD

[a]Washington Dermatology Center, North Bethesda, Maryland; [b]Assistant Clinical Professor, George Washington University, Washington, DC; [c]McGill University, Montreal, Canada; [d]Immunotec Research, Vaudreuil-Dorion, Quebec, Canada

ABSTRACT

Background: Psoriasis is a common autoimmune disease with enhanced systemic inflammation and heightened levels of oxidative stress. Glutathione is the major antioxidant in human cells. **Objectives:** To determine if a nondenatured bioactive whey protein isolate previously demonstrated to increase glutathione levels can clinically improve patients with psoriasis vulgaris. **Methods:** A single site, prospective, non-blinded trial. Seven patients with psoriasis were recruited to take a nondenatured bioactive whey protein isolate, 20g orally per day, in addition to their current treatments, if any. Psoriasis Area and Severity Index scores and photographs were taken at baseline and monthly for three months. **Results:** Patients with psoriasis were found to have a beneficial clinical improvement, whether they were on existing topical therapy, narrowband ultraviolet B, or no other treatment. **Conclusion:** The positive preliminary outcomes from this pilot study suggest a randomized, double-blind, clinical trial would be worthwhile in evaluating whether this protein isolate would result in statistically significant improvement for patients with psoriasis.
(*J Clin Aesthet Dermatol.* 2013;6(10):23–26.)

Psoriasis vulgaris (PV) is a prevalent chronic autoimmune disease for which there is no curative treatment. It is found equally in men and women, and although seen in children, it most commonly presents in early adulthood. It is often activated by an infection or stress, but the antigen that triggers the disease is still unknown. Patients are at increased risk for other comorbidities, such as psoriatic arthritis (PsA), cardiovascular disease, obesity, diabetes, metabolic syndrome, and sleep disturbances.[1] Although many susceptibility genes have recently been identified, the actual etiology is incompletely understood. Recent advances in immunological research have led to the development of new treatments that can control symptoms, but not cure the disease.

An increase in oxidative stress and decrease in glutathione (GSH) levels have been demonstrated to be associated with psoriasis[2,3] both locally[4] and systemically.[5] Obese patients with psoriasis have been shown to have decreased plasma adiponectin and elevated oxidized GSH levels associated with enhanced systemic inflammation and oxidative stress.[6]

Oral GSH supplementation has generally been found to have a negligible effect on cellular GSH levels when ingested by humans.[7,8] Total body GSH levels are best raised by ingestion of GSH precursors.[9] N-acetylcysteine (NAC) is a well-studied drug that is an effective GSH precursor and in common use in clinical settings, such as acetaminophen overdose[10] and chemoprophylaxis against radiological intravenous dyes.[11] Its use as a daily

DISCLOSURE: Dr. Prussick has served as consultant, speaker, trainer, or investigator for AbbVie, Allergan, Amgen, Janssen, Leo, L'Oreal, PharmaDerm, Medicis/Valeant, and Medimetriks. Ms. Prussick reports no relevant conflicts of interest. Dr. Gutman is a consultant for Immunotec on medical and scientific issues.
ADDRESS CORRESPONDENCE TO: Ronald Prussick, MD; E-mail: drprussick@aol.com

TABLE 1. Monthly Psoriasis Area and Severity Scores on protein isolate with or without other therapy

PATIENT	BASELINE	MONTH 1	MONTH 2	MONTH 3	MAINTENANCE TOPICALS	MAINTENANCE NBUVB
1	4.9	1.5	1.5	0.8	No	No
2	14.9	11.5	12.0	9.6	Taclonex ointment qday	Twice per week
3*	10.6	12.5	*	*	No	No
4	11.0	7.8	9.0	6.2	Taclonex ointment qday	Twice per week
5	27.5	10.9	8.0	6.0	No	No
6**	13.6	9.8	8.8	**	Taclonex ointment qday	Once per week
7	28.8	14.0	12.0	8.4	No	Twice per week

*Patient 3 dropped out of study due to nonadherence; **Patient 6 moved out of the area and did not complete the study.

supplement is limited by its side effect profile, generally gastrointestinal symptoms.[12]

Immunocal (Immunotec Inc.) is a nonprescription, oral, whey protein supplement indicated as a GSH precursor.[13,14] It serves to deliver nondenatured proteins high in cysteine and cysteine residues. These are the two limiting amino acids for GSH production by the cell.[15] The disulphide cysteine-cysteine linkages between protein strands are highly thermolabile and susceptible to denaturization through pasteurization and other manufacturing processes involved in whey production. Immunocal is prepared in an environment that limits its denaturization.[16]

Despite the availability of new symptomatic therapies, there are still patients who do not achieve adequate response or develop side effects requiring discontinuation of the medicine. Therefore, a preliminary study was performed on a small group of patients with moderate-to-severe PV, using a nondenatured bioactive whey protein isolate, clinically proven in previous trials[17–21] to increase GSH levels.

METHODS

Patients with moderate-to-severe PV in a single dermatology center were recruited to take a bioactive whey protein isolate powder (Immunocal, Immunotec, Dorion-Vaudreuil, Canada), 20g per day for 12 weeks. After written consent, Psoriasis Area and Severity Scores (PASI) were recorded and photographs taken during screening, then monthly. Patients were instructed to continue their usual treatments, including topical steroids or narrowband ultraviolet B (NBUVB) therapy. Patients were able to maintain a constant, but not increased, dose or frequency of phototherapy. They were also allowed to continue their topical therapy without increasing frequency or dose. All patients were already on the topical or NBUVB for at least two months prior to entry into the study. No other changes in therapy were allowed during the study. All patients were recruited late summer and early fall of the same year.

The results of the pilot study are shown in Table 1 and Figures 1 and 2. No side-effects were reported during the study.

DISCUSSION

Psoriasis is a complex autoimmune disease resulting in significant morbidity and early mortality compared to the general population.[1] Psoriasis patients are known to have abnormal GSH enzyme activities and high levels of free radicals.[3,4,22] This increase in oxidative stress can be measured systemically[2,23] and affect other tissues. For example, the degree of severity of psoriasis has been correlated with red blood cell fragility and subsequent changes in hemogram.[5] Obese patients with PV were found to have reduced levels of adiponectin, but elevated interleukin (IL)-6 and oxidized GSH levels, suggesting enhanced systemic inflammation and oxidative stress.[6] Levels of GSH antioxidant activity can also be associated with potential response to treatment. This was demonstrated in a study looking at responders versus nonresponders to the biologic agent, efalizumab. Nonresponders had increased GSH peroxidase (GPx) and GSHS-transferase and decreased catalase activity in granulocytes. Clinical response correlated with GPx activity

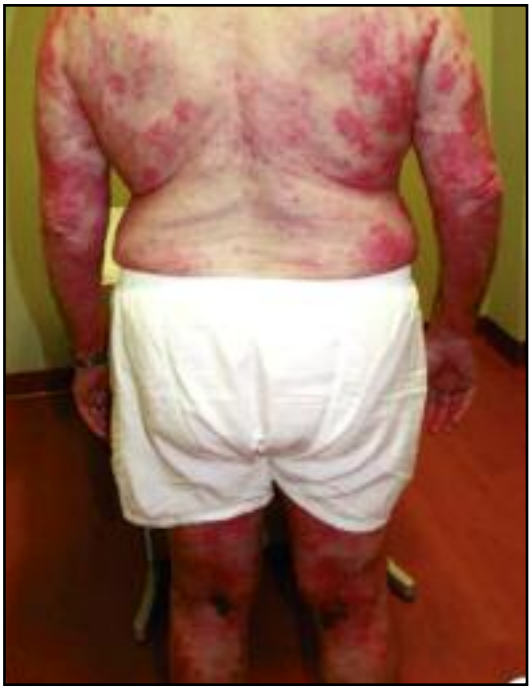

Figure 1. Patient 5 at baseline

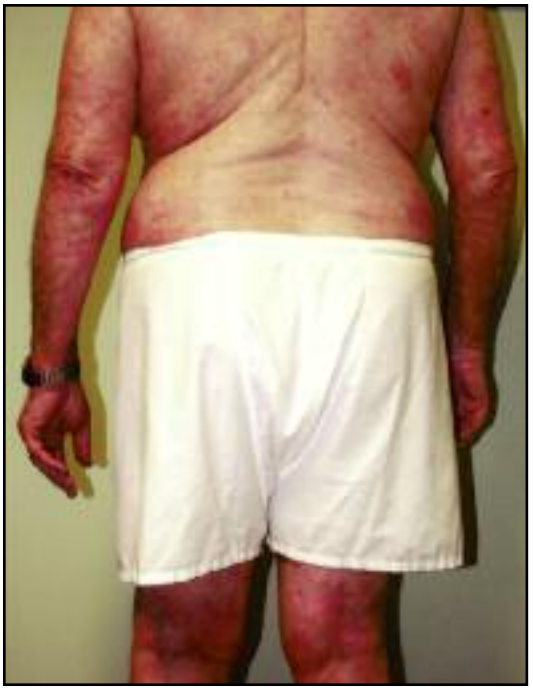

Figure 2. Patient 5 after three months on protein isolate

in blood cells, suggesting high oxidative stress levels is involved in psoriasis persistence.[24]

GSH or GSH sulfhydryl is a tripeptide consisting of three amino acids, glycine, glutamate, and cysteine. Cysteine is a sulfur-containing amino acid that contributes to the sulfhydryl group, where most redox reactions take place. Cysteine is also the rate-limiting amino acid in GSH production, given its relative scarcity in our diet.[25] Cysteine can become easily depleted in many diets or when cells are exposed to prolonged oxidative stress as seen in autoimmune diseases.[26,27]

GSH is the major endogenous antioxidant ubiquitous throughout the body.[28,29] Other antioxidants including vitamin C, vitamin E, and selenium require GSH in order to return to their reduced (nonoxidized) state.[30] In this sense, the majority of antioxidants depend on GSH for their normal functioning.[31] In addition, GSH is the only antioxidant that does not become a free radical itself after donating a free electron.[32]

The GSH precursor, Immunocal, has been demonstrated to have positive effects in other conditions of oxidative stress and heightened inflammatory response, such as cystic fibrosis,[19] acquired immunodeficiency syndrome/human immunodeficiency virus,[16] anaerobic muscle performance,[9] and cancer.[20] Based on these previous clinical trials, it prompted the authors to explore whether similar beneficial outcomes could be witnessed in patients with psoriasis vulgaris.

The authors' psoriasis patients showed improved PASI scores over the three-month study (Table 1). Although it is possible the PASI scores could have improved over time with maintenance topical or NBUVB therapy, the authors believe the bioactive whey contributed to the improvement since some patients were on no treatments other than the bioactive whey. In addition, the authors did not increase the NBUVB dosages or alter maintenance topical therapies over the three-month study period and the improvements documented were subsequent to the addition of whey protein isolate.

CONCLUSION

This small single-center prospective, unblinded pilot study showed a positive clinical response in patients using a bioactive whey protein isolate powder. During the trial period, the authors purposely continued the patients' maintenance treatments to determine if they can augment their patients' response with a purified nondenatured bioactive whey protein isolate. These positive preliminary findings have led the authors to believe a prospective, double-blind, randomized trial would be worthwhile in evaluating statistically significant efficacy in this population group.

REFERENCES

1. Prussick R, Prussick L. Biologic therapies for psoriasis in 2013: do we use them enough? *Practical Dermatol.* 2013;10(2):32–34.
2. Wozniak A, Drewa G, Krzyzynska-Maliniowska E, et al. Oxidant-antioxidant balance in patients with psoriasis. *Med Sci Monit.* 2007;13(1):CR30–CR33.
3. Yildirim M, Inaloz HS, Baysal V, Delibas N. The role of oxidants and antioxidants in psoriasis. *J Eur Acad Dermatol*

Venereol. 2003;17:34–36.
4. Aceto A, Martini F, Dragani B, et al. Purification and characterization of glutathione transferase from psoriatic skin. *Biochem Med Metab Biol.* 1992;48:212–218.
5. Rocha-Pereira P, Santos-Silva A, Rebelo I, et al. Erythrocyte damage in mild and severe psoriasis. *Br J Dermatol.* 2004;150(2):232–244.
6. Kaur S, Zilmer K, Kairane C, et al. Clear differences in adiponectin level and glutathione redox status revealed in obese and normal-weight patients with psoriasis. *Br J Dermatol.* 2008;159(6):1364–1367.
7. Flagg EW, Coates RJ, Eley JW, et al. Dietary glutathione intake in humans and the relationship between intake and plasma total glutathione level. *Nutr Cancer.* 1994;21(1): 33–46.
8. Witschi A, Reddy S, Stofer B, Lauterburg BH. The systemic availability of oral glutathione. *Eur J Clin Pharmacol.* 1992;43(6):667–669.
9. Lands LC, Grey VL, Smountas AA. The effect of supplementation with a cysteine donor on muscular performance. *J Appl Physiol.* 1999;87(4):1381–1385
10. Hodgman MJ, Garrard AR. A review of acetaminophen poisoning. *Crit Care Clin.* 2012;28(4):499–516.
11. Ellis JH, Cohan RH. Prevention of contrast-induced nephropathy: an overview. *Radiol Clin North Am.* 2009;47(5):801–811.
12. Sandilands EA, Bateman DN. Adverse effects associated with acetylcysteine. *Clin Toxicol.* 2009;47(2):81–88.
13. PDR (Physician's Desk Reference) Vol. 67, 2013, p. 2762-2763. PDR Network LLC. Montvale N.J. USA. CPS (Compendium of Pharmaceuticals & Specialties) 2013, p. 1510.
14. CANADIAN ASSOCIATION OF PHAMACISTS, Ottawa, ON, Canada
15. Bounous G. Whey protein concentrate and glutathione modulation in cancer treatment. *Anticancer Res.* 2000;20(6C):4785–4792.
16. Baruchel S, Viau G, Olivier R, et al. Nutriceutical modulation of glutathione with a humanized native milk serum protein isolate, Immunocal: application in AIDS and cancer. In: Luc Montagnier et al. *Oxidative Stress in Cancer, AIDS and Neurodegenerative Diseases,* 1st ed. New York, NY: Marcel Dekker Inc; 1998: 447–461.
17 Kennedy RS, Konok GP, Bounous G, et al. The use of a whey protein concentrate in the treatment of patients with metastatic carcinoma: a Phase I-II clinical study. *Anticancer Res.* 1995;15:2643–2650.
18. Bounous G, Baruchel J, Gold P. Whey proteins as a food supplement in HIV-seropositive individuals. *Clin Invest Med.* 1993;16:204–209.
19. Grey V, Mohammed SR, Smountas AA, et al. Improved glutathione status in young adult patients with cystic fibrosis supplemented with whey protein. *J Cyst Fibros.* 2003;2:195–198.
20. Tozer R, Tai P, Falconer W, et al. Cysteine-rich protein reverses weight loss in lung cancer patients receiving chemotherapy or radiotherapy. *Antiox & Redox Signaling.* 2008;10:395–402.
21. Kern JK, Grannemann BD, Gutman J, Trivedi MH. Oral tolerability of cysteine-rich whey protein isolate in autism—a pilot study. *JANA.* 2008;11:36–41.
22. Seifert O, Holmberg J, Linnarsson BM. Decreased activity of neutrophil glutathione peroxidase in chronic plaque-type psoriasis. *J Am Acad Dermatol.* 2007;57(3):528–529.
23. Drewa G, Krzyzyńska-Malinowska E, Woźniak A. Activity of superoxide dismutase and catalase and the level of lipid peroxidation products reactive with TBA in patients with psoriasis. *Med Sci Monit.* 2002;8(8):BR338–BR343.
24. Pastore S, Mariani V, Gubineli E, et al. Glutathione peroxidase activity in the blood cells of psoriatic patients correlates with their responsiveness to efalizumab. *Free Radic Res.* 2011;45(5):585–599.
25. Kidd P. Glutathione: systemic protectant against oxidative and free radical damage. *Alt Med Review.* 1997;2:155–176.
26. Lang CA, Naryshkin S, Schneider DL, et al. Low blood GSH in healthy aging adults. *J Lab Clin Med.* 1992;120:720–725.
27. Nutall SL, Martin U, Sinclair AJ, Kendall MJ. Glutathione in sickness and health. *Lancet.* 1998;351:645–646.
28. Anderson M. Glutathione and glutathione delivery compounds. *Adv Pharmacol.* 2007;38:65–78.
29. Meister A. Glutathione metabolism and itsSelective modification. *J Biol Chem.* 1988;263:17205–17208.
30. Lomaestro B, Malone M. Glutathione in health and disease: Pharmacotherapeutic issues. *Ann Pharmacother.* 1995;29:1263–1273.
31. Chan TS, O'Brian PJ. Nutritional antioxidants. In: Pantopoulos K, Schipper HM. *Principles of Free Radical Biomedicine, Vol II.* 1st ed. New York; Nova Science Pub; 2012: 61–77.
32. Dickenson DA, Iles KE. Glutathione. In: Pantopoulos K, Schipper HM. *Principles of Free Radical Biomedicine, Vol II.* 1st ed. New York; Nova Science Pub; 2012:3–19.