

Use of Isoquercetin in the Treatment of Prurigo Nodularis

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ABSTRACT

Atopic dermatitis and prurigo nodularis result from complex interactions between the skin, the immune system, and the external environment. The pruritus associated with these conditions greatly impacts patients' quality of life and lacks uniformly effective treatment. A 57-year-old patient presented with severe atopic dermatitis and subsequent prurigo nodularis refractory to numerous standard therapies. The supplement isoquercetin was initiated and he noted significant, sustained reduction in his pruritus after only four weeks. Isoquercetin is a glycoside derivative with antihistamine properties of quercetin, a natural polyphenol flavonoid found in many plants. It may offer itch relief in patients who have failed more conventional therapies.

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CASE

A 57-year-old man with past medical history significant for hypertension and atopy presented with a flare of atopic dermatitis. Although a lifelong problem, his eczema had recently worsened with widespread pruritic, erythematous, scaly, excoriated patches on his trunk, antecubital and popliteal fossae, arms, and lower legs. He had no recent medication changes and had been taking hydrochlorothiazide, lisinopril, amlodipine, ranitidine, and hyoscyamine for several years. The rash did clear with a 6-day course of prednisone prescribed by his primary care physician; unfortunately, it rebounded upon tapering. Allergy evaluation revealed an eosinophilia of 11%, elevated IgE level of 2880 IU/ml, and numerous environmental allergies. He was diagnosed with adult atopic dermatitis (AD) and started on a soak-and-smear routine with triamcinolone ointment (0.1%).

Although initially responsive to this conservative therapy regimen, he experienced frequent exacerbations over the next few years and eventually developed prurigo nodularis (PN) on his arms, legs, and upper back (Figure 1). Although the background AD improved, the prurigo nodules were refractory to clobetasol (0.05% ointment), topical tacrolimus (0.1%), diphenhydramine (25-50 mg), cetirizine (10-20 mg), doxepin (25 mg), gabapentin (300 mg TID), wet dressings with triamcinalone (0.1%), intralesional triamcinolone injections (10 mg/ml), oral prednisone courses (10-80 mg), doxycycline (100 mg BID), cryotherapy, and narrow-band ultraviolet B light therapy. Ultimately, an integrative medicine specialist (author JN) was consulted and the patient was offered treatment with the natural anti-pruritogen quercetin (1000 mg BID). After three months with no improvement on quercetin, he was switched to isoquercetin (500 mg BID). After four weeks of isoquercetin treatment, the patient noted significant reduction in his pruritus with improved sleep and considerable skin healing. He maintained this improvement with isoquercetin and topical steroids for the next two years of follow-up in our clinic (Figure 2).

DISCUSSION

Atopic dermatitis (AD) and prurigo nodularis (PN) result from a complex interaction between immunologic dysregulation, epidermal barrier dysfunction, decreased epidermal defenses, environmental allergens, and patient response to lesions (eg, scratching or rubbing). The mediators of itch in AD and PN have not been clearly defined and neural mechanisms of itch are not well understood. Galli and colleagues suggest that the pruritus and erythema present in atopic dermatitis following allergen exposure might be related to substances released by mast cells with allergen-specific IgE.[1] However, studies of plasma histamine levels in AD patients have been inconsistent and typical antihistamines are only mildly helpful in alleviating pruritus, which suggests that histamines cannot be the only pruritogen.[2-5]

Quercetin, a natural polyphenol flavonoid consisting of three rings and five hydroxyl groups, is found in various fruits and vegetables including yellow onions, curly kale, leeks, cherry tomatoes, broccoli, apples, green and black tea, black grapes, blueberries, cauliflower, and cabbage.[4] It has antioxidant properties that include free radical scavenging, interfering with inducible nitric oxide synthase activity, inhibiting xanthine oxidase activity, and inhibiting TNF-alpha release. Its potential therapeutic utility has been studied in cardiovascular disease, ischemia-reperfusion injury, ocular disease, allergic disease, arthritis, diabetes, gastrointestinal disease, and cancer. There are several mechanisms by which it could minimize pruritus in atopic patients. In vitro research has shown that quercetin inhibits histamine release from human basophils as well as rat, mouse,

FIGURE 1. Pre-Isoquercetin Prurigo Nodularis. Prominent lichenified discrete nodules can be seen on the patient's left arm, consistent with prurigo nodularis. Atopic dermatitis is relatively well-controlled at this point.

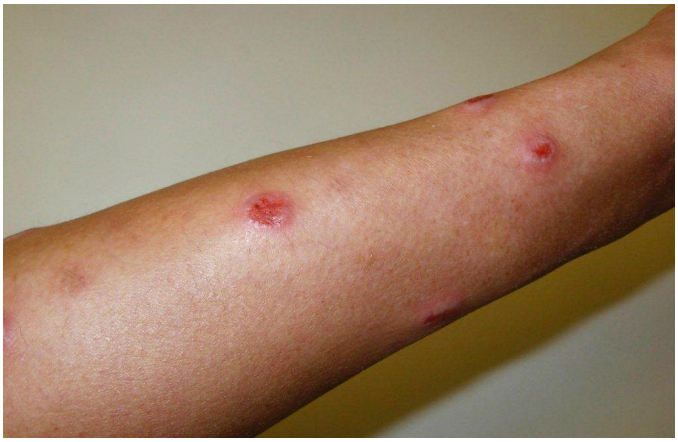
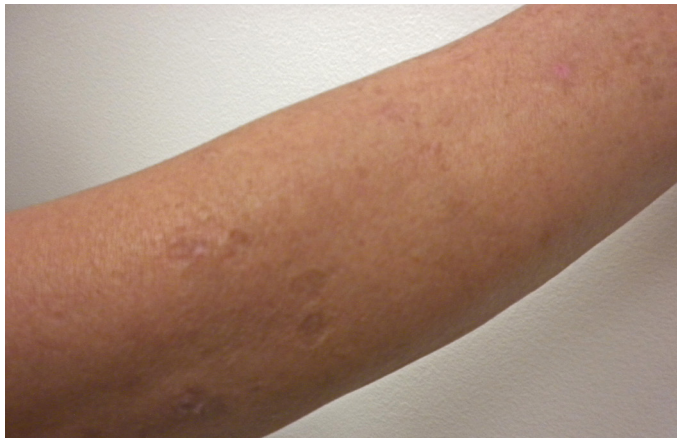


FIGURE 2. Post-Isoquercetin healed skin with scarring. Significantly improved appearance of the skin on the left arm two years after starting isoquercetin. The prurigo nodules have resolved with scarring and the atopic dermatitis remains well-controlled with topical steroids.



and hamster peritoneal and mucosal mast cells.[4,6,7] It decreases release of tryptase and IL-6 and inhibits mast cell degranulation in human mast cell (HMC)-1 cells by down-regulating histidine decarboxylase mRNA. Moreover, it has direct gram-positive and gram-negative antibacterial properties.[8]

Isoquercetin is the glycoside derivative of quercetin and has a different pharmacokinetic profile. Quercetin's oral bioavailability is highly affected by dietary fat content, with greater fat content leading to greater quercetin absorption and delayed elimination.[6] Peak plasma levels occur 0.7-to-7 hours following ingestion and the half-life is approximately twenty-five hours. Quercetin is subject to first pass metabolism and strongly binds to plasma albumin, further decreasing the effective available compound. While the majority of pharmacokinetic research has been done on the parent compound, quercetin, several studies investigating isoquercetin pharmacokinetics in animals show that it is roughly three times more bioavailable than quercetin and is absorbed up to twice as quickly.[4,6,9] Diet composition, specifically dietary fat content, has less impact on its absorption. Additional pharmacokinetic information, including absorption and bioavailability in humans, is lacking.

Quercetin and isoquercetin are generally well tolerated. The most common side effect is gastrointestinal upset and, rarely, patients will complain of headaches or mild peripheral paresthesias.[7] The potential mutagenicity of quercetin is less clear. Early toxicity data derived from in vitro studies and a report by the Federation of American Societies for Experimental Biology indicated carcinogenicity in laboratory animals with long-term exposure to high-dose quercetin.[4,7] It is unclear if isoquercetin differs from quercetin in its toxicity. However, other long-term studies and large clinical human trials have reported inverse relationships between isoquercetin consumption and the incidence of cancer and actually support antimutagenic and genoprotective properties in vivo. Much of the data indicating quercetin's mutagenicity is derived from in vitro and animal studies, whereas its protective properties have been shown in human trials. More recent reviews of quercetin safety concluded that orally administered quercetin is unlikely to cause significant adverse effects.[4,7]

The average diet supplies between 15 and 40 mg of quercetin per day from fruits and vegetables. Therapeutic quercetin doses are much higher and can be obtained from dietary supplements in the form of capsules (250 mg, 300 mg, and 500 mg) and tablets (50 mg, 250 mg, and 500 mg). While recommended doses for isoquercetin have not been determined, recommended adult quercetin doses for treatment of allergies and chronic hives range from 250 to 600 mg three times per day.[4]

The complex factors underpinning pruritus make a universally effective treatment difficult to attain.[10] However, our patient with AD and PN experienced a clinically significant improvement in pruritus after the addition of isoquercetin. Despite isoquercetin's anti-allergic and antihistamine properties, additional mechanisms of action are probable and remain to be elucidated. Importantly, pharmacokinetic, dosing, and safety data on isoquercetin are limited and need further study. Although future experimental trials are needed, isoquercetin may be another tool in the arsenal against pruritus.

DISCLOSURES

The authors have no conflicts of interest or financial disclosures to declare.

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