Magnesium supplementation in the treatment of pseudoxanthoma elasticum: A randomized trial

To the Editor: Pseudoxanthoma elasticum (PXE) is a rare, autosomal recessive connective tissue disorder with significant systemic morbidity due to progressive elastic fiber mineralization; treatment is lacking.[1-5] Research in humans and mouse models of PXE has linked increased magnesium levels to decreased calcification. Specifically, in an animal PXE model, magnesium prevented elastic tissue calcification, and in a prior study by LaRusso et al, there was a reduction in elastic fiber calcification in the magnesium-containing placebo arm.[4,5]

We conducted a randomized, double-blind, placebo-controlled prospective trial evaluating the effect of oral magnesium oxide (MgO) versus placebo on the skin and eyes in 44 PXE patients (approved by the Institutional Review Board at the Icahn School of Medicine at Mount Sinai; Clinicaltrials.gov listing: NCT01525875). In the first year (the double-blind, placebo-controlled phase), patients were randomized 1:1 to receive twice-daily 800 mg MgO (500 mg elemental magnesium) (treatment group) or placebo (control group). In the second year (the open-label phase), all patients received 2500 mg MgO (1500 mg elemental magnesium) divided over 2 doses daily.

A baseline target lesion of representative affected skin (usually neck, axilla, or antecubital fossa) was evaluated using a 10-point numeric grading score (Table I) and 4-mm punch biopsy. Patients had to have a clinical disease severity grade of ≥1 (poorly defined, barely visible macules) at screening. These measures plus laboratory tests, electrocardiogram, bone mineral density scan, and ophthalmic examination were performed throughout the study.

The primary endpoint was calcification of skin elastic fibers. Biopsies were stained with Verrhoeff-van-Gieson and Von-Kossa stains. DensiteQuant image analyzing software quantified the area of calcification at the top and bottom of the sample. Changes in calcification were assessed with a mixed-effect model having location as a covariate. During the double-blind, placebo-controlled phase, the magnesium group had a nonsignificant decrease in calcification, whereas the placebo group was unchanged. However, during the open-label phase, both groups had increases in calcification (Fig 1, *A*).

Using a 30% decrease in elastic fiber calcification as a secondary endpoint, 36.36% of patients in the treatment group were responders compared with only 13.6% of patients in the placebo group (drop-outs are nonresponders) ($P = .17$).

Table I. Pseudoxanthoma elasticum 10-point numeric grading score investigators used for evaluating target lesions

Score	Pseudoxanthoma elasticum severity
0	No evidence of pseudoxanthoma elasticum
1.0	Poorly defined, barely visible macules
2.0	Well defined, easily identified macules
3.0	Mostly macules with <5 papules
4.0	≥5 papules
5.0	Patches consisting of confluent macules with <50% of target area covered by papules
6.0	Patches consisting of confluent macules with ≥50% of target area covered by papules
7.0	Plaques
8.0	Plaques with mild folds of skin
9.0	Plaques with redundant folds of skin

Considering only the patients completing the double-blind, placebo-controlled phase (N = 40), the response rate in the treatment group was 38.09% versus 15.79% in the placebo group ($P = .29$) (Fig 1, *C*). Although not statistically significant, this trend might be clinically significant. After 2 years of magnesium treatment, 2 of the 8 responders in year 1 kept their response level, and 5 patients who were previously nonresponders during the first year became responders in the second year.

Likewise, the treatment group had twice the reduction in target lesion score than the placebo group in the double-blind, placebo-controlled phase, albeit not statistically significant (Fig 1, *B*). In the magnesium group, the percentage of patients with a 1-point score reduction increased from 9.09% to 40.91% ($P = .0692$.) across the 2 years. The scores of the patients in the placebo group significantly decreased when treated with magnesium (change −0.336, $P < .0001$) but not placebo (change −0.046). A sharp increase in clinical improvement was observed when these patients started the open-label phase (4.54%-31.82%, $P = .125$). No significant treatment effect was observed in the ophthalmologic outcomes or bone mineral density T scores. There was no clinically significant laboratory changes (including magnesium and calcium level alterations) during the study.

This study had limitations that likely contributed to the lack of statistical significance. It was a small study of a rare disease with tremendous patient variation. Individual patient changes could thus profoundly affect results. Likewise, the magnesium dose was limited because of concerns for side effects. However, magnesium was well tolerated. Also, there were not any ophthalmologic exclusion

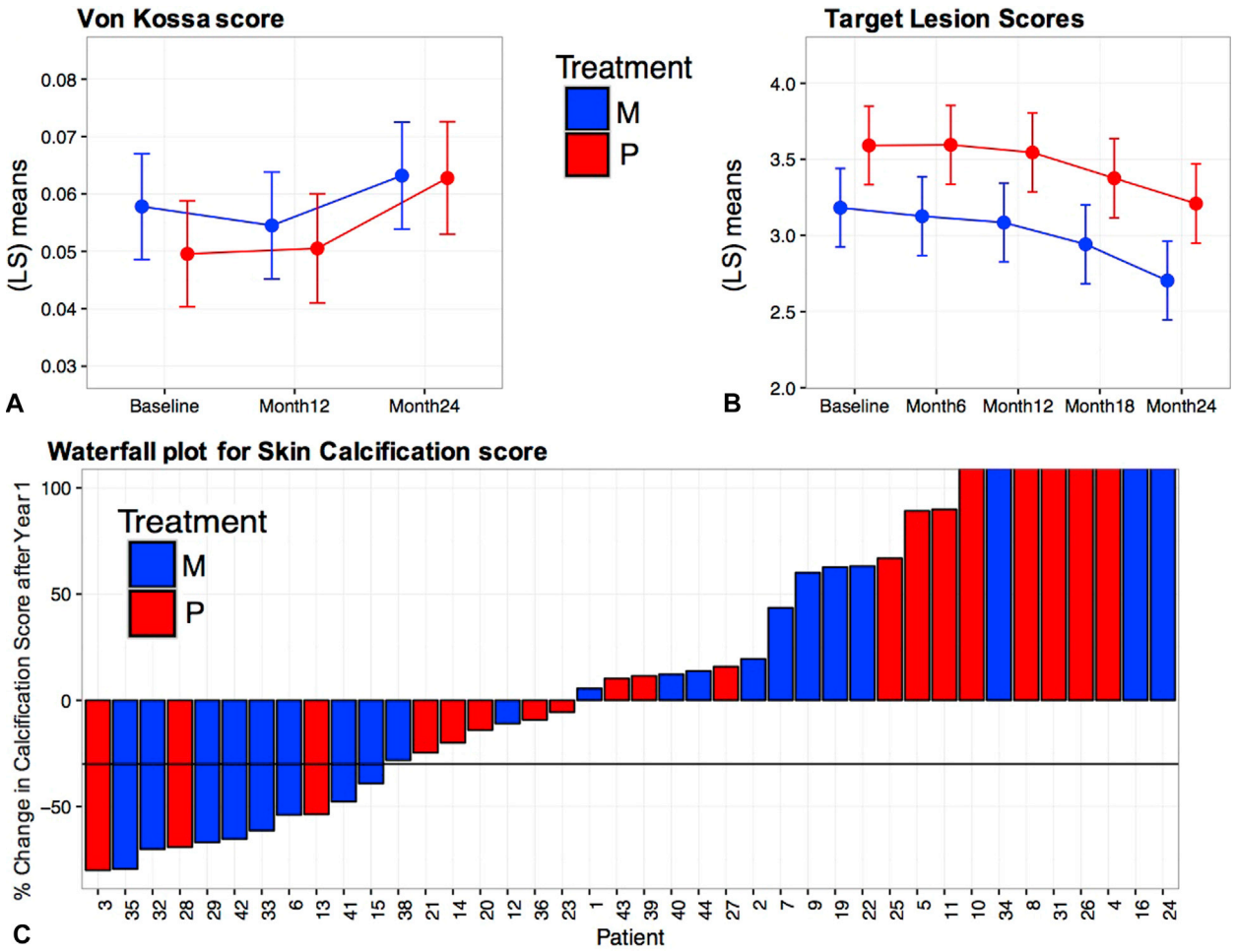

Fig 1. Pseudoxanthoma elasticum **(**PXE) calcification assessment. Least square means of the Von Kossa calcification score (**A**) and 10-point target lesion score (**B**) over time. Error bars represent the standard error of the mean. **C**, Waterfall plot for skin calcification score depicting the percentage of change with respect to baseline of the Von Kossa calcification score for the skin biopsies from each patient. Of importance, more magnesium-treated patients (*blue*) had reductions in calcification than placebo-treated patients (*red*). Patient 30 completed the first year, but his biopsy at baseline was missing. *LS*, Least squares; *M*, magnesium cohort; *P*, placebo cohort; *PXE*, pseudoxanthoma elasticum.

criteria. Many patients continued treatment with their ophthalmologists, causing their annual study visit to be merely a snapshot in their disease course.

Despite these limitations, we highlight a promising trend in the results showing calcification reduction of skin elastic fibers while on magnesium supplementation. Larger studies with higher magnesium dosage could be valuable to further elicit this beneficial trend.

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Guselkumab in the treatment of hidradenitis suppurativa: A retrospective chart review

To the Editor: Hidradenitis suppurativa (HS) is a debilitating inflammatory skin disease that leads to abscesses, fistulas, and scarring. The only Food and Drug Administration–approved medication for HS is the tumor necrosis factor antibody adalimumab. An overactive T-cell helper 17 pathway is hypothesized to contribute to the development of HS, with high numbers of interleukin (IL) 23–expressing cells found in lesional skin.[1] Although ustekinumab, an IL-12p40 antibody with activity against IL-23, has been reported to improve HS, this report is the first to evaluate the use of a pure IL-23 antibody to treat HS.[2] A literature search conducted in November 2018 combining "hidradenitis suppurativa" and each of the IL-23 antibodies approved or studied for dermatologic diseases—"guselkumab," "tildrakizumab," "risankizumab," and "mirikizumab"—yeilded no results.

We present a retrospective chart review of 8 patients with moderate-to-severe HS who were treated with guselkumab 100 mg administered subcutaneously at weeks 0 and 4 and then every 8 weeks thereafter. Four patients (50%) had comorbid psoriasis, with 3 starting guselkumab for psoriasis. In 1 patient, HS developed after starting an anti–IL-17 agent; all other cases of HS were primary.

Demographic information and patient outcomes are shown in Table I. Patient ages ranged 15-68 years, with an average age of 32 years, and average weight was 98 kg. Five patients (63%) were male. Four patients (50%) had Hurley stage III disease, and 4 patients (50%) had Hurley stage II disease. Seven patients (88%) were previously treated with other biologics: 5 with adalimumab, 4 with secukinumab, 2 with ixekizumab, and 1 with ustekinumab. Five patients had prior treatment with oral antibiotics and 2 patients isotretinoin. Three patients (38%) continued antibiotics while on guselkumab. There are a total of 4.8 treatment years on guselkumab.

After treatment with guselkumab, 5 patients (63%) reported improvement in their HS and 1 patient's disease remained quiescent. Three patients who ultimately improved did not show improvement at 2-4 months. The drug was well tolerated in all patients.

Guselkumab might be effective for HS after other biologic treatment failures. Patients improved even without concurrent antibiotics. Limitations of our study include its small size, retrospective nature, the absence of a wash-out period, and the absence of standardized outcome measures. We have also found that patients might not improve in the first 2-4 months after treatment initiation, suggesting that more time might be needed to reach maximum efficacy. It is worth noting that our patients were treated with psoriasis-level dosing of guselkumab. It is possible that higher or more frequent doses would lead to greater or faster improvement. Studies on adalimumab have shown that weekly dosing is more effective for HS than the twice-monthly dosing indicated for psoriasis.[3] Guselkumab and other IL-23 antibodies present a new option for a disease with limited effective treatments and warrant further study to determine efficacy and optimal dosing.

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