Title: Prolidase Deficiency *GeneReview* – Partially successful or unsuccessful treatments
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Oral proline has been tried at various doses, including 1 g/day [Arata et al 1986], 4 g/day [Isemura et al 1979], 6 g/day [Ogata et al 1981], and 10 g/day [Sheffield et al 1977], all without success. Conversely, a proline-free diet was also reported to be unsuccessful [Caselli et al 2012].

Topical proline. Jemec & Moe [1996] reported significant reduction in ulcer size ($p<0.02$) after application of 5% proline ointment consisting of white Vaseline with liquid paraffin, with daily dressing changes. Dunn & Dolianitis [2008] tried topical proline 5% in white soft paraffin ointment daily and occluded beneath nonstick dressings; the ulcers reportedly improved compared to the pretreatment period, but it did not prevent new ulcers from appearing. Karthikeyan et al [2019] reported short-term improvement of a 5% proline ointment in liquid paraffin base after one week and resolution of ulcers after three weeks.

Wet proline dressings applied for six months did not prove beneficial [Ogata et al 1981]. Arata et al [1986] tried a 1% proline ointment without improved results, with the strength increased to 5% and then to 10%, still with no improvement.

Topical proline plus topical glycine. Arata et al [1986] applied a 5% proline-5% glycine ointment thickly once daily followed by covering with a dressing gauze and bandage. They reported healing of the ulcers, with no change in imidodipeptiduria. Jemec & Moe [1996] reported significant reduction in ulcer size ($p<0.02$) after application of 5% proline plus 5% glycine ointment consisting of white Vaseline with liquid paraffin, with daily dressing changes. This mixture reportedly caused a more rapid reduction in ulcer size as compared to 5% proline alone ($p<0.02$).

However, application of 5% proline and 5% glycine ointment was also used without success by other authors [Berardesca et al 1992, Caselli et al 2012, Koechel et al 2017].

Vitamin C. De Rijcke et al [1989] 4 g/day of ascorbic acid with reported healing of ulcers, but the patient decided to discontinue the treatment two years later, with the ulcers reappearing soon afterward.

However, other authors found no ulcer improvement with vitamin C treatment [Berardesca et al 1992, Monafo et al 2000], with doses as high as 3 g/day [Arata et al 1986, Bissonnette et al 1993].

Manganese. Manganese chloride has been tried without success [Berardesca et al 1992]. Pedersen et al [1983] treated a patient with $MnCl_2$ in doses of 5 and 10 mg/day, followed by addition of vitamin C (2 g/day) and later also proline (2 g/day). The skin almost normalized except for slight diffuse telangiectasia and brownish pigmented spots (but with improvement of ulcers), and reportedly there was improved IQ as well.

However, other authors reported no improvement with this therapy [Monafo et al 2000]. Leoni et al [1987] administered 1.18 mg/day of manganese, followed by 1.64 mg/day, plus vitamin C (1 g/day), with no improvement noticed in the ulcers.

Dapsone. Dapsone was administered at a dose of 75 mg/day for 2.5 months in one patient, with accelerated epithelialization of the ulcer, although with no tendency to heal earlier [Ogata et al 1981].

Steroids. Yasuda et al [1999] presented a patient whose ulcers did not respond to oral prednisolone <20 mg/day. Methylprednisolone IV at 1g/day for three days was then given, repeated three times over two years. This produced almost complete regression of the ulcers one to two months after each pulse, followed by oral prednisolone 30 mg/day. A second patient reported by the same authors showed similar results, but with a few remaining ulcers enlarging one year after stopping prednisolone.

High-dose steroids caused partial regression of manifestations in other cases [Palumbo et al 2010]. Oral steroids were reported to be unsuccessful by other authors [Dunn & Dolianitis 2008].

Skin grafting. Ogata et al [1981] performed split-thickness skin grafting for coverage of ulcers in a patient, with temporary success reported for one month before loss of the graft. In a second individual reported by the same authors, the skin grafts were lost two years after the procedure. It was also reported as unsuccessful by other authors [Palumbo et al 2010].

Blood transfusions. Endo et al [1982] transfused a patient with 800 mL of whole blood, with red blood cell prolidase activity increased to around 35% of normal values, but gradually decreasing over time with a half-life of 41 days. The patient's ulcer was slightly improved, and there was no significant change in imidodipeptiduria. Berardesca et al [1992] performed repeated transfusions of concentrated red blood cells, a total of six transfusions every two months. The ulcers of their patient decreased in size and some completely healed following the fourth transfusion, but the ulcers had recurred by follow up 18 months after the last transfusion. They showed increased red blood cell prolidase activity following the transfusion, but the imidodipeptiduria remained unaltered.

However, blood transfusions were given unsuccessfully by other authors [Ogata et al 1981, Monafo et al 2000].

Plasmapheresis. Monthly aphreresis exchanges for four months were performed in two patients, with reported improvement of skin ulceration [Lupi et al 2002].

Hematopoietic stem cell transplantation. Caselli et al [2012] performed an allogenic stem cell transplant, with successful engraftment demonstrated by full-donor chimerism. The post-transplant red blood cell prolidase activity had increased to carrier levels, and imidodipeptiduria was decreased. However, the patient died on day +92 from an invasive fungal infection.

Another patient undergoing hematopoietic stem cell transplant also showed increased RBC prolidase activity post transplant, but with no clinical improvement in the frequency or appearance of the ulcers [Authors, personal observation].

Growth hormone. Replacement therapy with recombinant human growth hormone at 15 IU/m^2/week subcutaneously was associated with considerable improvement in the ulcers after two months [Monafo et al 2000]. Topical growth hormone was then combined with the systemic treatment, consisting of 4 IU of a sterile powder of growth hormone added to 50 mL of ointment containing Vaseline and cod liver oil. After one month of this combined systemic-topical treatment, the ulcers had healed completely, but they recurred six months later despite treatment.

The authors are also aware of other cases of anecdotal healing of ulcers with topical growth hormone application [Authors, personal observation].

Low molecular weight heparin. In a recent report [Süßmuth et al 2020], low molecular weight heparin improved ischemia, increased wound healing, and reduced pain in one affected individual.

Hyperbaric oxygen therapy. Adışen et al [2016] reported slight improvement after six weeks of hyperbaric oxygen therapy.

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