CORRESPONDENCE

The Treatment of Chronic Recurrent Oral Aphthous Ulcers

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Fumaric Acid Esters as an Additional Systemic Therapy Option

In symptoms that often prove so refractory to treatment and are so vexing for patients, for which no gold standard treatment exists (1), we would like to additionally mention the use of fumaric acid esters. Before 2005, a small working group around Professor Hagedorn conducted an uncontrolled open-label study with fumaric acid esters in 12 patients with recurrent benign aphthous ulcers (2). Only in one case did the treatment have to be stopped because of adverse effects; three patients experienced complete remission and eight an improvement of their symptoms owing to longer recurrence-free intervals, more rapid healing, or a reduction in the number of aphthous ulcers. Furthermore, several hypotheses were introduced regarding the mechanism of action of fumaric acid esters in recurrent benign aphthous ulcers.

The treatment back then was found to be relatively well tolerated (this was partly due to the low dosage—compared with that required to treat psoriasis—of 120–240 mg fumaric acid esters a day), and a number of otherwise treatment refractory patients responded well and experienced long term benefits.

Of course this is again all done off label. The long term safety of fumaric acid esters taken daily for many years was pointed out only in recent publications on the treatment of psoriasis vulgaris and enables the treating physician to balance risks and benefits. For this reason, fumaric acid esters represent a further helpful treatment option in otherwise refractory cases of recurrent benign aphthous ulcers—something that I wanted to draw readers' attention to, in spite of the low evidence level of the early study.

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Acatalasia Was Omitted

The list of important differential diagnoses of aphthous ulcers in the box on page 667 had one important omission: a congenital metabolic disorder that is characterized by total or near-total absence of enzyme activation of catalase in the erythrocytes, and which is listed in the Online Mendelian Inheritance in Man under #614097 as acatalasemia or acatalasia.

Acatalasemia was first found and described in Japan in 1948 by Takahara—an ear, nose, and throat specialist—in patients with progressive oral gangrene, because in these patients the local application of H₂O₂ (hydrogen peroxide) did not result in the usual release of oxygen. In addition to Japan (2), human acatalasemia has also been found and described in individuals in Switzerland, Hungary, Peru, and in Germany (3).

The disorder has an autosomal recessive pattern of inheritance; its incidence in Hungary was described to be 5:106. The treatment of these patients with aphthous ulcers and oral gangrene presents a particular therapeutic challenge.

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In Reply:

We thank Dr. Tsamaloukas for enriching our comprehensive list of differential diagnoses of chronic recurrent aphthous ulcers (1).

The “ulcerations and oral gangrene” affecting some patients with acatalasemia (Takahara’s disease)—a rare enzymopathy (estimated prevalence 1:31 250) (2) that is usually asymptomatic and has an autosomal recessive pattern of inheritance—are pronounced hemorrhagic mucosal necroses and ulcerations caused by H₂O₂ (3). For this reason, acatalasemia should be added to the group of “Other oral disorders” in our list.

We also thank Dr. Glaenz for his comment. We consider the reduction of neutrophil granulocytes in the epidermis and corium (4) and of the total lymphocyte number in the peripheral blood (5), that is caused by fumaric acid, as a possible mechanism of action of

fumaric acid esters in chronic recurrent aphthous ulcers. These events may be interpreted in the sense of an immunosuppressant effect (5).

Because of the large number of reported therapeutic approaches in chronic recurrent aphthous ulcers, however, we felt obliged to only include those therapeutic schemes in our article that have a higher evidence level (1). This didactic approach did not aim to cast aspersions on the value of such therapies, which in spite of long years of positive clinical experiences have not been considered in the planning of evidence based studies.

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Conflict of interest statement

The authors of all contributions declare that no conflict of interest exists.