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The Reply:

We thank Kalfus and Frank for their interest in our observation.[1] We agree that 3 selected cases and 24 historical controls do not provide strong evidence such as a large, prospective, randomized, controlled study would do. However, we believe that such a study would be difficult to conduct, particularly in terms of keeping patients over decades in certain treatment arms. Furthermore, we agree that hereditary angioedema has a tendency to wax and wane: periods of time with more attacks may alternate with periods with fewer attacks. We believe, however, that the continuous and considerable increase in the number of attacks over a long time at the ages of the women described in our article seems unusual and does not reflect the variations of attacks in the course of hereditary angioedema as seen in other patients. Among the reported patients, the increase in attacks started after the beginning of treatment with C1 inhibitor concentrate. For that reason, and because none of the factors known to increase the number of attacks of hereditary angioedema could be identified that could have explained the increase, we considered that the frequent injections of C1 inhibitor concentrate might constitute the reason for the unusual course of disease in those patients.

If, indeed, the slow and continuous increase in attacks actually were a sequela of frequent injections of C1 inhibitor concentrate, a continuation of the frequent injections with an even higher weekly dose of C1 inhibitor concentrate (1000 U C1 inhibitor every 3-4 days, as suggested by Drs. Kalfus and Frank) might perhaps not be able to solve the problem of the potentially increased disease activity as reported in those patients.

Konrad Bork, MD[a]
Jochen Hardt, PhD[b]
[a]*Department of Dermatology*
[b]*Department of Medical Psychology and Medical Sociology*
Johannes Gutenberg University Mainz
Mainz, Germany

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Reference

1. Bork K, Hardt J. Hereditary angioedema: increased number of attacks after frequent treatments with C1 inhibitor concentrate. *Am J Med*. 2009;122:780-783.