EDITORIAL

# Kallikrein Inhibition for Hereditary Angioedema

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Management of hereditary angioedema due to C1 inhibitor deficiency has evolved. During the past 10 years, those affected have progressed from underrecognized disability and premature death, through evidence-based hospital treatment, toward self-administration and independence from unscheduled hospital care. Encouraging results from the use of lanadelumab for the prevention of angioedema associated with C1 inhibitor deficiency, reported by Banerji et al. in this issue of the *Journal*,[1] promise a major step toward achieving this independence from ongoing medical care for all affected by the disorder.

Hereditary angioedema is associated with unpredictable subcutaneous or submucosal swellings.[2] These have a slow onset, last 2 to 5 days, and typically result in a period of disablement or disfigurement during which work, education, or leisure activities are curtailed. Thus, hereditary angioedema has considerable implications for physical, psychological, and economic health, affecting not only the individual patient but also the well-being of family members who frequently act as informal caregivers.[3]

Advances in therapies to treat acute attacks of angioedema have resulted in a welcome increase in the number of people coming forward for diagnosis and treatment, although many remain undiagnosed. This is important, because premature deaths can be reduced by knowledge of the diagnosis.[4,5] However, the parenteral administration of treatment for an attack is inconvenient, and full resolution takes up to 24 hours. Therefore, if disability is to be avoided, prophylaxis is necessary, particularly for those with frequent episodes.[4]

C1 inhibitor deficiency, whether inherited (owing to heterozygous mutation of the *SERPING1* gene) or acquired (owing to depletion of C1 inhibitor by complement-activating monoclonal antibodies or autoantibodies), is believed to result in loss of inhibition of plasma kallikrein, leading to increased cleavage of high-molecular-weight kininogen and the release of bradykinin. Bradykinin increases local capillary permeability, resulting in angioedema.[2] Lanadelumab is a recombinant fully human monoclonal antibody and the first therapeutic agent to allow sustained inhibition of kallikrein.

Kallikrein is implicated in other forms of bradykinin-mediated angioedema — namely, angioedema associated with angiotensin-converting–enzyme inhibitors, acquired C1 inhibitor deficiencies, and some idiopathic angioedemas[6] — and has a central role in the generation of inflammation and pain. The ability to provide sustained inhibition of kallikrein could therefore have potential for a much wider range of disorders, although of course this remains to be seen, particularly in view of the multiplicity and redundancy of the various interacting inflammatory pathways.

Current prophylactic options for hereditary angioedema are unsatisfactory. Attenuated androgens, fibrinolytic agents, and intravenous C1 inhibitors are used but have incomplete efficacy and carry the risk of adverse effects. Attenuated androgens (anabolic steroids) such as danazol, stanozolol, and oxandrolone probably work by increasing intrinsic C1 inhibitor production and promoting bradykinin degradation through an increase in aminopeptidase P. They show good

efficacy at higher doses. However, adverse effects are common, and androgens are contraindicated in pregnancy and for prepubertal children.[7,8] At the lower doses currently recommended, efficacy is likely to be less good.[8] Tranexamic acid is a popular option for children but has an incomplete evidence base and poor efficacy.[7] Intravenous C1 inhibitor (Cinryze) prophylaxis, at a dose of 1000 units twice weekly, showed a 50% median reduction in angioedema frequency among patients who had, on average, weekly attacks while receiving placebo. The severity and duration of attacks and the use of treatments for acute attacks also decreased.[9] Much better control is possible when the dose and frequency of C1 inhibitor administration are individualized.[10] Nevertheless, the need for intravenous access and safety concerns, particularly with respect to the use of indwelling ports, limit the usefulness of this approach. For all these reasons, a safe, effective prophylactic agent is desperately needed.

Kallikrein inhibition with lanadelumab given by fortnightly subcutaneous injection would be convenient and widely accessible. Early safety indications are encouraging, with no indication of antibody formation or the anaphylactoid events associated with short-term inhibition of kallikrein; therefore, self-administration could be feasible. Most exciting, the preliminary study by Banerji et al. suggests an unprecedented level of protection against angioedema. If this proves reproducible in larger studies currently under way, and if the treatment will be affordable, lanadelumab could herald a transformation in the way that we manage hereditary angioedema and in the life prospects for families affected by this devastating disorder.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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