Documents

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Efficacy and Safety of Donidalorsen for Hereditary Angioedema
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Abstract
BACKGROUND Hereditary angioedema is a rare disorder characterized by episodic, potentially lifethreatening swelling caused by kallikrein-kinin dysregulation. Long-term prophylaxis can stabilize this system. Donidalorsen, an antisense oligonucleotide, specifically reduces prekallikrein expression. METHODS In this phase 3, double-blind, randomized trial, we assigned patients with hereditary angioedema to receive donidalorsen (80 mg subcutaneously) or placebo once every 4 or 8 weeks. The primary end point was the time-normalized number of investigator-confirmed hereditary angioedema attacks per 4 weeks (attack rate) from week 1 to week 25. RESULTS A total of 90 patients received donidalorsen every 4 weeks (45 patients), donidalorsen every 8 weeks (23 patients), or placebo (22 patients). The least-squares mean time-normalized attack rate was 0.44 (95% CI, 0.27 to 0.73) in the 4-week group, 1.02 (95% CI, 0.65 to 1.59) in the 8-week group, and 2.26 (95% CI, 1.66 to 3.09) in the placebo group. The mean attack rate from week 1 to week 25 was 81% lower (95% CI, 65 to 89) in the 4-week group than in the placebo group (P<0.001) and 55% lower (95% CI, 22 to 74) in the 8-week group than in the placebo group (P = 0.004); the median reduction in the attack rate from baseline was 90% in the 4-week group, 83% in the 8-week group, and 16% in the placebo group. The mean attack rate during weeks 5 to 25 was 87% lower (95% CI, 72 to 94) in the 4-week group than in the placebo group (P<0.001) and 60% lower (95% CI, 25 to 79) in the 8-week group than in the placebo group. Donidalorsen administered every 4 weeks resulted in an improvement in the least-squares mean total score for the change at week 25 on the Angioedema Quality-of-Life Questionnaire (scores range from 0 to 100, with a score of 100 indicating the worst possible quality of life) that was 18.6 points (95% CI, 9.5 to 27.7) better than that with placebo (P<0.001). The most common adverse events were erythema at the injection site, headache, and nasopharyngitis; 98% of adverse events were mild or moderate in severity. CONCLUSIONS Donidalorsen treatment reduced the hereditary angioedema attack rate, a finding that supports potential prophylactic use for hereditary angioedema. Copyright © 2024 Massachusetts Medical Society.

Index Keywords
antisense oligonucleotide; adolescent, adult, aged, angioneurotic edema, clinical trial, controlled study, double blind procedure, drug therapy, female, human, male, middle aged, multicenter study, phase 3 clinical trial, quality of life, randomized controlled trial, subcutaneous drug administration, young adult; Adolescent, Adult, Aged, Angioedemas, Hereditary, Double-Blind Method, Female, Humans, Injections, Subcutaneous, Male, Middle Aged, Oligonucleotides, Antisense, Quality of Life, Young Adult

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