Long-term prophylaxis of hereditary angioedema with danazol

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To the Editor: Hereditary angioedema (HAE) is a rare genetic disorder that is characterized by recurrent attacks of subcutaneous or submucosal swelling.[1] HAE may lead to life-threatening conditions, with a mortality rate of 9.6% to 11.5% in those who develop laryngeal edema.[2,3] The fundamental abnormality of HAE types 1 and 2 is the deficiency or dysfunction of C1 inhibitor (C1-INH), a multifunctional serine protease inhibitor, caused by mutation in its coding gene, *SERPING1*.[1] These two types are collectively referred to as C1-INH-HAE.

The management of C1-INH-HAE includes on-demand treatment and short- and long-term prophylactic treatment. For long-term prophylaxis (LTP), which we focused on in this study, the 2017 version of the World Allergy Organization/European Academy of Allergy and Clinical Immunology guideline recommends plasma-derived C1-INH as the first-line drug and attenuated androgens for second-line use.[1] Novel therapeutic approaches, including anti-plasma kallikrein monoclonal antibody (lanadelumab) and plasma kallikrein inhibiting molecule (berotralstat), are also approved for LTP.[4,5]

Since being introduced to patients with HAE in 1986, danazol, a 17-alpha-alkylated attenuated androgen, remains the most commonly used drug for prophylaxis of C1-INH-HAE in China. The mechanism of danazol in the treatment of HAE is unclear, but it may enhance the synthesis of C1-INH in monocytes and hepatoma cell lines. Although there is evidence for the efficacy of danazol in C1-INH-HAE, there have been no reports on its application status for the treatment of C1-INH-HAE in China. The aim of this study was to review our experience using danazol as LTP for C1-INH-HAE.

We retrospectively analyzed LTP effects in 74 patients with C1-INH-HAE (type 1, $n = 73$; type 2, $n = 1$; males, $n = 35$) who were prescribed an individual course of danazol for between 2 and 26 years. Age at prescription ranged from 16 to 71 years. The diagnosis was based on the clinical history, low levels of C1-INH antigen (C1-INHa) and complement component 4 (C4), and mutations in *SERPING1*. The frequency and severity of C1-INH-HAE episodes before and during treatment, and the adverse effects of danazol, were documented in medical records. This study was approved by the Research and Ethics Board of Peking Union Medical College Hospital (No. S-K661). All participants provided signed informed consent.

Our danazol schedule started with a high dosage (600 mg/day) that was gradually reduced to the minimum effective dosage based on the incidence of swelling attacks and adverse effects of danazol. At the 600 mg/day dosage, 71 of 74 patients (96%) were free from attacks of C1-INH-HAE (defined as complete control), with 1 patient reporting >50% reduction in the frequency and severity of attacks (partial control), and 2 reporting <50% reduction in the frequency or severity of attacks (inadequate control). For the 71 patients who achieved complete control, the dosage was reduced to 400 mg/day, after which 57 of 71 (80%) maintained complete control, 13 (18%) had partial control, and 1 had inadequate control. The danazol dose was then reduced to 200 mg/day in the 57 patients with complete control, among whom 16 maintained complete control and 41 patients had partial control. The 200 mg/day dosage was then reduced to 5 days/week in the 16 patients with complete control, 12 of whom maintained complete control; of those, 4 patients continued to maintain complete control at 200 mg/day on a 3 day/week administration schedule. At a dosage of <200 mg/day, 14 patients achieved partial control. The therapeutic responses to different doses of danazol are summarized in [Supplementary Table 1, http://links.lww.com/CM9/B44]. During the study period, the maintenance dosage of danazol was 200 mg/day in 41 patients (55%), <200 mg/day in 16 patients (22%), 400 mg/day in 13 patients (18%), and 600 mg/day in 4 patients (5.4%).

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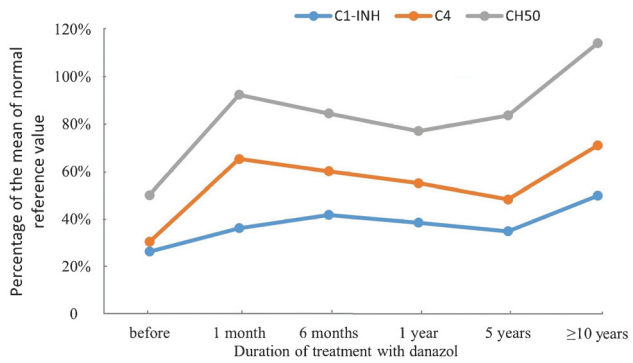

Figure 1: Changes in C1-INHa, C4, and total hemolytic complement activity (CH50) in patients receiving danazol treatment for HAE at six different time points: before treatment, 1,6 months, 1, 5, and ≥10 years. The levels of C4 and CH50 returned to normal ranges after treatment. The level of C1-INHa increased, but remained below the normal reference value throughout treatment. C1-INHa: C1 inhibitor antigen; C4: Complement C4.

Among patients with high adherence to maintenance treatment, no laryngeal edema occurred.

Using multinomial logistic regression, we determined that none of the following impacted the efficacy of danazol: sex, age of onset, severity of disease, or levels of C1-INHa or C4.

C1-INHa, C4, and total hemolytic complement activity (CH50) were measured before and after treatment with danazol. Because the assay methods for these parameters changed over the long observation period, we expressed the level of each parameter as a percentage of the mean of a normal reference value. Changes in each laboratory indicator over time are illustrated in [Figure 1]. C1-INHa levels remained under the normal range, increasing from 26% at baseline to 42% after 6 months of danazol administration, slightly decreasing to 35% at the fifth year, then rising again to 50% after >10 years of treatment. Both C4 and CH50 returned to normal ranges after 1 month of danazol treatment and remained there throughout the entire treatment period. It was unclear why all three parameters showed a slight decrease at the 5-year follow-up. Because there was no confirmed correlation between clinical improvement and levels of these complement proteins, adjustments to the titration of danazol were based on symptoms rather than laboratory parameters.

Adverse effects related to danazol are shown in [Supplementary Figure 1, http://links.lww.com/CM9/B44]. In total, 83 instances of adverse effects were observed, with 28 occurring in men and 55 in women. Hepatic impairment (28%) was the most common adverse effect in both sexes. Although we did not actively monitor patients using abdominal ultrasonography, none reported hepatomas by themselves. By reducing the danazol dose and using hepatoprotectants, any damage to liver function was reversible. Other frequent adverse effects were weight gain (17%), seborrhea (12%), and acne (11%), which were more common in women. Menstrual irregularities were reported by 24% of female patients.

Although lanadelumab has recently been approved for LTP use in China, it has not been priced; thus, danazol remains the main option for the LTP of HAE. Despite the adverse effects, danazol shows satisfactory efficacy for HAE in the majority of patients and has the advantages of oral administration and low cost. The reduction in danazol dosage should depend on clinical improvement rather than the levels of complement proteins. Close follow-up is necessary to observe adverse effects in patients treated with danazol.

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Conflicts of interest

None.

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