Effects of Danazol on Clinical Improvement of Patients with Human T-cell Lymphotropic Virus Type I Associated Myelopathy/Tropical Spastic Paraparesis (HAM/TSP/TSP): A Placebo-Controlled Clinical Trial

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Abstract

Objective(s)
HTLV-I associated myelopathy/tropical spastic paraparesis is (HAM/TSP) is an endemic disease observed in Japan, Africa, Caribbean basin and North-east of Iran. It is usually presented as a chronic and progressive spastic paraparesis (HAM/TSP). There are some options for treatment of HAM/TSP patients. The aim of this study was to compare the effects of danazol controlled with placebo in relieving the symptoms and signs of HAM/TSP patients.

Clinical
Among 77 patients with definite diagnosis of HAM/TSP based on clinical and para-clinical findings, 71 patients had the required criteria for entering the study. Severity of symptoms and the degree of motor disability were determined before the beginning of treatment based on motor disability grading (MDG) in both groups of patients and were followed in 1 month intervals during 6 months for changes in symptoms and their motor disability.

Results
Among 38 patients of the first group, after 6 months therapy with Danazol, mean difference of MDG0 (before starting treatment) and MDG6 (after six months), which is the indicator of motor improvement of the patients, was 0.89. Meanwhile among the 33 patients treated with identical appearing placebo there was no significant difference between MDG0 and MDG6 (P< 0.001). Moreover, there was a significant difference in improvement of symptoms between two study groups.

Conclusion
This study showed that danazol provides relative effects on improving motor disabilities and the symptoms of HAM/TSP patients and can be considered according to its lower side effects compared with other suggested treatments such as corticosteroids and also its lower costs in particular patients.

Keywords: Danazol, HTLV-I, Myelopathy
Introduction

HTLV-I is endemic in well-defined geographical regions throughout the world such as south of Japan, Sub-Saharan Africa, Caribbean countries and Brazil (1). In 1992 North of Khorasan, a province of Iran, (North east of Iran) was concluded as an endemic area for HTLV-I infection. Most of the infected individuals remain asymptomatic, but it may cause various neurologic and non-neurologic presentations. Less than 5 percent of infected individuals will develop a chronic progressive paraparectic syndrome named HAM/TSP; a chronic inflammatory disease in central nervous system characterized by sphincter dysfunction, gait disturbances, spasticity, pain, and paresthesia (2). Other neurologic involvements such as neuropathy, cerebellar atrophy, myopathy, encephalopathy, meningitis, and cranial nerve paresis are rarely reported (3). No therapy has been shown to be completely effective on improvement of disease manifestations and progression. However different studies have recommended various treatments mostly based on immunomodulatory strategies and down-regulation of pro-inflammatory cytokines, including corticosteroids, plasmapheresis, danazol, pentoxifylline, interferons and some anti-viral agents such as zidovudine and lamivudine (4, 5). Nevertheless, many problems such as considerable side effects of corticosteroids and expensive costs of interferons limit their administration in many patients.

In this study, regarding the endemic infection of HTLV-I in North-east of Iran and high prevalence of HAM/TSP patients and its associated disabilities in the region, we decided to investigate the therapeutic effects of danazol on these patients. Previous studies have shown some clinical improvements using danazol but the main problems with most of these studies are the limited number of cases, short duration of treatment and absence of control group (4, 6). Therefore we performed a placebo-controlled clinical trial on 71 patients with definite HAM/TSP/TSP diagnosis and examined the effects of danazol compared with placebo effects after 6 months. It should be noted that for a long time, danazol has been used as a treatment in endometriosis, and has well known side effects; hence prescribing danazol does not have any interference with ethical issues.

Materials and Methods

Before starting the treatment, HTLV-I associated myelopathy was proved in patients. In order to do so, all patients referred to neurology clinic of Ghaem Medical Centre in Mashhad, Iran with spastic paraparesia, were screened using ELISA test for HTLV-I infection that was positive in 79 patients. In the next step, western blot (WB) test was performed, the result of which showed that among 79 patients, there were 77 positive, 1 negative and 1 indeterminate. Then polymerase chain reaction (PCR) test was performed to find HTLV-I genome in peripheral white blood cells on all patients. It was positive in 77 patients that had already positive WB and ELISA test results and was negative in patients with negative and indeterminate WB results. For ruling out the other causes of spastic paraparesia, brain and cervical and thoracic spinal cord MRI were performed in all patients and their CSF was studied for inflammatory patterns and Anti-HTLV-I anti-body. Apart from definitive diagnosis of HAM/TSP, the other criteria for entering the study include cases who: 1- have the age less than 65 and more than 20 years old, 2- are not pregnant or breast feeding if females, 3-do not have any chronic diseases like congestive heart failure, chronic renal failure, hypertension and/or history of liver function abnormalities, 4- have cooperation for a six month treatment period, 5-have suspended other treatments for HAM/TSP e.g. corticoids, at least four month before entering the study. So the patients with definitive diagnosis of HAM/TSP who did not fulfill these criteria or did not agree on taking CSF samples for confirming the diagnosis were excluded from the study. Side effects of the medications and other choices were explained to the patients and a written
Danazol in HAM/TSP

consent was obtained. The Local Research Ethics committee approved the study (80264).

This is a placebo-controlled clinical trial and the patients were divided in 2 study groups in a way that except for the treatment, they were equal in other variables such as age, duration of symptoms, onset of the disease, severity of the disease and sex ratio. In the first group danazol was prescribed 400 milligrams per day (the initial dose was 200 mg per day that is increased to 400 mg during two weeks) for 38 patients and in the second group identically appearing placebo was prescribed, which were, produced in the same form for 33 patients.

Both groups were carefully examined in the beginning of treatment and in one-month intervals during 6 month for monitoring the presence of side effects of the drug, effects of treatment based on motor disability grading (Table 1) and the value of patients' satisfaction in improvement of their symptoms. The degree of motor disability is expressed based on MDG. MDG0 (the degree of motor disability before the beginning of the treatment) also indicates the severity of the disease. The difference between MDG0 and MDG6 (the degree of motor disability after 6 month of treatment) represent the degree of improvement. Also before and during the treatment, liver function tests were evaluated.

Patients' satisfaction in relieving symptoms (pain, paresthesia, urinary problems and gait disturbances) is determined by the patient in percent. So the degree of improvement was categorized in 5 groups: 1-no efficacy (no improvement), 2-mild efficacy (less than 25% improvement), 3-moderate efficacy (25-50% improvement), 4-good efficacy (50-75% improvement), and 5-excellent efficacy (75-100% improvement).

Results

Among 77 patients with definitive HAM/TSP diagnosis, only 71 patients had the criteria for entering the study. Their mean motor disability grading (Table 2) before starting treatment (MDG0) was 4.2.

Mean MDG0-MDG6 (the difference between MDG before starting treatment and MDG after six months) in patients treated with danazol was 0.89 and in patients treated with placebo was near zero. Data analysis exhibited a significant difference in MDG improvement between the two groups ($P<0.001$). Also there was a significant statistical difference in improvement of all the symptoms including pain, muscle stiffness, urinary problems and gait disturbance in patients treated with danazol compared with the second group that were treated with matching placebo (Table 1).

Among the patients treated with danazol, 8 patients developed the following side effects: gastrointestinal disturbances such as nausea and epigastric pain in 2 patients, lower limb edema in 2 patients, hypertension in 1 patient, skin rash in 1 patient, mild increase of liver enzymes in 1 patient and hirsutism in 1 patient.

Discussion

According to the results, danazol has both positive subjective (reducing pain, muscle stiffness, urinary problems and gait disturbances) and objective (based on clinical findings of MDG improvement) effects. Although it was not in the range of good and excellent improvement, but these relative effects are noticeable according to the lower side effects compared with corticosteroids, and its lower costs compared with interferons.

It is not precisely clear how danazol can improve signs and symptoms of HAM/TSP patients but it probably affects the regulating immune system. In fact, after many years using danazol for treatment of endometriosis, its regulatory effects were found in certain immune processes. Danazol may induce a decline in serum immunoglobulines (7), level of serum C3 (8) and CA125 (9, 10). It may also increase the serum level of C4 (8), and inhibits Interlukine-
1(IL-1) and Tumor Necrosis Factor (TNF) production (11). So danazol is recommended in some immune system diseases like autoimmune hemolytic anemia (12), hereditary angioedema (13), systemic lupus erythematososis (8), idiopathic thrombocytopenic purpura (14, 15) and HAM/TSP (4-6).

Some effects of danazol (like inhibition of IL-1) are dose-dependent, but the appropriate dose of danazol in HAM/TSP patients is not identified yet and this study does not answer to this question.

Data analysis showed no difference in the degree of drug effectiveness based on age ($P=0.22$), sex ($P=0.94$), severity ($P=0.62$) and duration of disease ($P=0.73$) in HAM/TSP patients. Also the performed tests for evaluating danazol effects represented higher value in improving muscle stiffness ($P<0.001$) and lower value in improving paresthesia ($P=0.007$). In other words, patients had less satisfaction for improving of paresthesia.

Side effects of danazol were seen in 8 patients. Fortunately these side effects were resolved soon after stopping the medication. No life-threatening side effect was seen in our patients, which is similar to the other studies in which danazol had been used for treatment of endometriosis. For minimizing the side effects and increasing the tolerance of the drug, it is recommended to start with low doses and then increase it gradually. In case of some irreversible complications like hirsutism and voice change, the medication should be stopped as soon as possible permanently.

**Conclusion**

As a suggestion danazol can be used for treatment of HAM/TSP patients. It is particularly recommended in patients who are not able to use corticosteroids or interferon because of their side effects and expensive costs. But it should be considered that danazol has probably lower effectiveness than these medications. Its effect is not related to the severity of symptoms or age and sex of the patients.

As mentioned above, this study does not demonstrate the most effective dose and duration of the treatment with danazol; hence further studies need to be conducted.

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**References**