

Discontinuation of Etanercept After Successful Treatment in Patients with Juvenile Idiopathic Arthritis

To the Editor:

Etanercept (ETN) has been used to treat patients with juvenile idiopathic arthritis (JIA) with demonstrated efficacy and safety^{1,2}. However, few studies have addressed the appropriate time and the way to discontinue the drug once the disease is inactive. We analyzed the progress of patients with JIA after discontinuation of ETN and the clinical response to reintroduction of the drug in those who relapsed.

A retrospective chart review 2004 to 2009 revealed that therapy with ETN had been discontinued in 26 patients with JIA due to inactive disease (16 female, 10 male). The mean age at discontinuation of drug was 11 ± 2 (range 2.6–18.8) years. The clinical subtypes of JIA were 11 cases of enthesitis-related arthritis, 7 rheumatoid factor-negative polyarthritis, 2 systemic JIA with polyarticular involvement, 1 psoriatic arthritis, and 1 persistent oligoarticular arthritis. Inactive disease was defined according to the criteria of Wallace, *et al*³, which required no joints with active arthritis, no fever or other clinical signs attributable to JIA, no active uveitis, normal erythrocyte sedimentation rate or C-reactive protein concentration, and no disease activity on the physician's global assessment.

For the purposes of the study, before considering the disease inactive we also required a 3-month period since the last dose of oral or intraarticular steroids was administered. All patients were examined at least every 2 months. They were considered to have a relapse when active arthritis was detected on the physical examination. In 14 patients the withdrawal of drug was performed abruptly, and in 12 in a progressive way, either by reducing the dose or by increasing the interval between doses. Given that the disease remained inactive during the tapering process the date of discontinuation considered for analysis was the day the drug was completely stopped. ETN was restarted on all patients who relapsed.

Remission time was evaluated according to the Kaplan-Meier survival curve; comparison of qualitative data was done using the log-rank test; and the association between quantitative variables was analyzed using a Cox regression model.

The mean duration of therapy with ETN was 19 ± 8.4 (range 9.6–38.5) months. The disease persisted at an inactive stage for a mean 14.7 ± 8.6 (range 1–36) months before ETN was interrupted. In total, 24 patients had inactive disease for more than 6 months, thus meeting the criteria for clinical remission on medication³. Eighteen cases (69%) relapsed at a mean 5.8 ± 5.3 (0.6–15.9) months after drug discontinuation, whereas in the other 8 (31%) patients the disease remained inactive for a mean of 21 ± 14.7 (range 5–44.5) months. After withdrawal of ETN the disease remained inactive in 9 children for at least 12 months, reaching the definition of clinical remission off medication³; 4 of them relapsed between 1.5 and 4 months later and 5 continued in remission a mean 17 ± 13 (range 1.1–32.5) months until the end of the study.

The survival curve (Figure 1) shows that 50% of the patients continued to have inactive disease at 6 months and 39% at 12 months after drug discontinuation. No significant differences were observed in the time to relapse between the group in whom the drug was tapered and the group in whom ETN was discontinued abruptly (11 vs 14 months, respectively; $p = 0.48$). Similarly, no association was found between the duration of inactive disease prior to drug withdrawal and the time to relapse ($p = 0.23$). Due to the small sample size, differences between the clinical subtypes could not be evaluated. Patients who relapsed were started again on ETN and all responded satisfactorily, although 6 of the 18 cases received intraarticular or small and transient doses of oral steroids.

It can be concluded that the majority of patients (69%) relapsed after discontinuation of ETN, the probability of remaining symptom-free at 6 months was 50%, and the response to reintroduction of treatment was satisfactory. Unlike the results of Prince, *et al* in 19 patients with JIA⁴, the period of remission after discontinuation of ETN in patients was associated neither with the duration of inactive disease before the withdrawal nor with the method used (tapering vs abrupt cessation). Some studies on

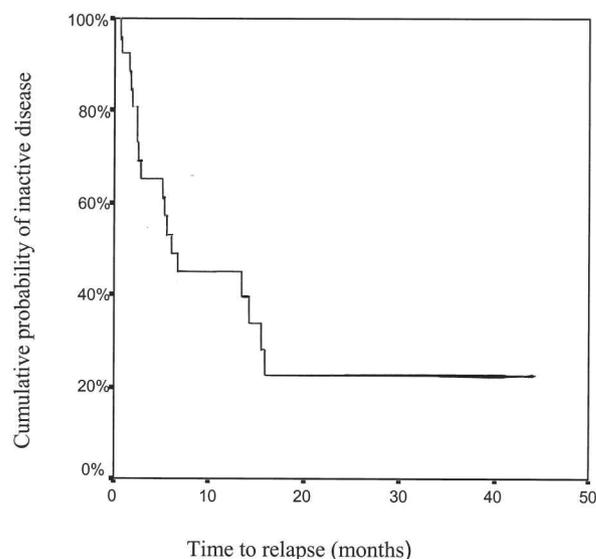


Figure 1. Cumulative probability of maintaining inactive disease after discontinuation of etanercept treatment in 26 patients with JIA.

adults with rheumatoid arthritis^{5,6} or ankylosing spondylitis^{7,8,9,10} have also shown a high incidence of relapse after discontinuation of anti-tumor necrosis factor drugs and a good response upon their reintroduction.

The 12 patients in whom the drug was reduced progressively did not relapse until its complete withdrawal, which suggests that low doses of ETN may be sufficient to maintain remission. In our opinion ETN can be discontinued after an as-yet undetermined period of disease inactivity, given that even if there is a relapse of disease patients will respond to its reintroduction.

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