Herpes Virus Infections During Treatment With Etanercept in Juvenile Idiopathic Arthritis

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Incidence rates for varicella and herpes zoster were similar in patients with juvenile idiopathic arthritis receiving etanercept/methotrexate (n = 85, 184.9 patient-years [PY]) or methotrexate alone (n = 71, 199.4 PY); no complicated varicella or herpes zoster cases were reported; herpes labialis incidence was higher in patients receiving etanercept/methotrexate versus methotrexate alone (0.38 vs 0.24 PY).

Key words. etanercept; herpes simplex virus; juvenile idiopathic arthritis; varicella zoster virus.

The term juvenile idiopathic arthritis (JIA) comprises all arthritides of unknown cause, beginning before 16 years of age, which are classified according to the criteria of the International League of Associations for Rheumatology (ILAR) into mutually exclusive disease categories. Juvenile idiopathic arthritis has prevalence rates in developed countries varying between 16 and 150 per 100,000 and can lead to long-term disability and decreased quality of life [1]. Tumor necrosis factor (TNF) inhibitors (TNFi) are an effective treatment option, with etanercept (ETN) being the most commonly used [2]. The increased use of TNFi requires a better understanding of their long-term safety. It is well established that adult patients receiving TNFi have increased risk of bacterial and mycobacterial disease [3]. The risk of viral infections is less well investigated, and little is known about the effect of TNFi on chronic or latent viral infections, particularly in children. An observational study reported a 2-fold higher incidence of opportunistic infections (with herpes zoster being the most common) among children with JIA compared with children without JIA [4].

Herpes viruses are ubiquitous in most populations. Varicella, the primary infection of varicella zoster virus (VZV), usually results in mild to moderate illness. Herpes zoster (HZ) is the reactivation of latent VZV infection and is related to a decline of VZV-specific cell-mediated immunity. Most initial herpes simplex virus 1 (HSV-1) infections are asymptomatic; recurrent herpes labialis (HL) is often the initial manifestation. Varicella, HZ, and HL were occasionally reported in long-term follow-up studies on the use of ETN in JIA [5–8]. The aim of this study was to obtain incidence data of primary varicella, HZ, and HL in patients with JIA in a clinical practice setting and to compare rates in patients receiving ETN and methotrexate (MTX) with those in patients treated with MTX alone.

METHODS

Patients
In this retrospective observational study, we recruited 156 patients consecutively evaluated between March and September 2010 at the Rheumatology Division of the Bambino Gesù Children’s Hospital, Rome, with a diagnosis of JIA according to the ILAR criteria [1], treated with ETN/MTX or MTX alone and for whom informed consent was obtained. We excluded patients receiving ETN in association with other antirheumatic drugs or ETN monotherapy.

Eighty-five patients were receiving ETN (0.8 to 1 mg/kg per week) in combination with MTX and 71 MTX monotherapy. Methotrexate was used at 10 to 15 mg/m² per week. Etanercept was prescribed in patients with moderately to severely active polyarticular JIA (polyarthritis or extended oligoarthritis), with inadequate response to MTX [9]. Data on patient’s history, previous and
concomitant therapy, prior VZV-vaccination, or history of varicella, HZ, or HL episodes and antiviral therapy were collected by both review of medical patient charts and/or parents and patient interview. For varicella and HZ, physician diagnosis was required; for HL episodes, self-reporting of parents/patient of the classic herpetic lesions in or around the oral cavity was accepted.

Statistical Analysis
Data analysis was performed using Stata 11.1 (StataCorp LP). To compare differences between subgroups, the $\chi^2$ test or Fisher test were used. Differences in continuous parameters between treatment groups were compared by unpaired Student’s t test. Incidence rates were calculated as the number of varicella cases, HZ episodes, and HL episodes per patient-years of follow-up (under specific treatment); differences in incidence rates were compared by Mid-P exact test. For HZ and HL, patients were allowed to contribute with more than 1 episode. To calculate varicella incidence, patients with a prior history of primary varicella were excluded and density data censored at primary infection, resulting in a shorter follow-up. Patients without history of varicella were not excluded from the HZ analysis, to also include possible subclinical nonreported varicella cases. Kaplan-Meier survival analysis and Cox proportional hazard regression analysis were applied to investigate other possible risk factors for herpes virus infections.

RESULTS
Demographic features, age at treatment start, and treatment duration were comparable between the ETN/MTX and MTX groups (Table 1). Patients receiving ETN differed significantly from those treated with MTX alone in regard to severity of the disease as shown by the more frequent polyarticular course in the ETN/MTX group than in the MTX group ($P < .05$), reflecting the expected more severe disease of patients requiring treatment with ETN.

There were 3 cases of HZ, 2 in the ETN/MTX group and 1 in the MTX group, with comparable crude incidence rates (Table 1). All patients received oral acyclovir for a minimum of 7 days. No cases of multidermatomal zoster, herpes zoster ophthalmicus, or postherpetic neuralgia were reported.

There were 11 case of varicella in the ETN/MTX group and 10 in the MTX group, with comparable crude incidence rates (Table 1). The number of patients with a prior clinical history of varicella or vaccinated against VZV was similar in the 2 groups. Two patients, 1 in each group, developed varicella despite receiving 1 dose of VZV vaccine before treatment. All patients developing varicella received acyclovir, none required hospitalization, and all episodes resolved without complications. Kaplan-Meier survival analysis did not show significant differences in the estimated time to varicella or to first HZ episode. Neither varicella nor HZ showed significant associations with age at disease onset, age at treatment start, concomitant glucocorticoids, or varicella vaccination in univariate analysis, with confirmation on multivariate Cox regression analysis for varicella (not applied to HZ because of the small number of episodes).

There were 70 HL episodes in 15 patients in the ETN/MTX group and 48 HL episodes in 10 patients in the MTX group, with a higher incidence rate in the ETN/MTX group (Table 1). Two patients in the ETN/MTX group required long-term therapy with acyclovir to reduce the frequency of recurrences. No patients withdrew from treatment. In univariate analysis, there was no significant

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Abbreviations: ETN, etanercept; HL, herpes labialis; HZ, herpes zoster; MTX, methotrexate; PY, patient-years; SD, standard deviation; VZV, varicella zoster virus.
association of HL with age at disease onset, age at treatment start, and concomitant glucocorticoids, whereas there was a statistically significant association between HL and polyarticular involvement ($P = .024$), not confirmed by multivariate Cox regression analysis.

**DISCUSSION**

In our study population, the crude HZ incidence rate was 0.011 per patient-year in the ETN/MTX group. In the long term-follow-up of the clinical trial with ETN in JIA [5] and in data from national registries for ETN in JIA [6–8], the HZ rates per patient-year ranged from 0.001 to 0.017, suggesting that incidence rates are similar in a clinical practice setting and in clinical trials. The lack of association between HZ and concomitant glucocorticoids, a well known risk factor, could be explained by the limited number of HZ cases observed and the limited use of glucocorticoids in our population.

Herpes labialis and primary varicella were common events. This finding is consistent with the relative high prevalence of HSV-1 infection and the high incidence of varicella in Italy [10, 11]. The crude incidence rate of varicella was 0.15 in the ETN/MTX group. This rate is much higher than those reported in clinical trials and registries [5–8], which ranged from 0.001 to 0.01. It is important to note that mass varicella vaccination is not performed in Italy resulting in high varicella incidence. Data from 2009 show an incidence of 339.5 cases per 100,000 children aged 0–14 years; data from the Italy’s Paediatric Sentinel Surveillance System of Vaccine-Preventable Diseases show an incidence ranging from 4.053 to 6.655 per 100,000 children in the period 2000–2005 [11]. Therefore, incidence figures of varicella in this study are in line with those of the general Italian population. In our patient cohort, incidence rates for varicella and HZ under ETN/MTX treatment were comparable with those under MTX monotherapy. Primary varicella cases (as well as the few HZ) occurring during ETN treatment were not severe and were not associated with bacterial superinfection. All of our cases were treated with acyclovir, which might have prevented complications.

In data from national registries from ETN-treated patients, only a few cases of HL have been reported [5–8]. It is possible that underreporting of minor infections, such as HL, explains the relative high incidence rates we found for HL compared with other observational studies. Even though HL cannot be considered a serious infection, frequent recurrences can negatively affect quality of life; indeed, if there are more than 6 recurrences per year, oral antiviral therapy may be considered.

The main limitations of our study are the size of the population and the observational character. Our analyses are based on a limited number of infective episodes. Ideally, multicenter studies are necessary to better estimate the burden of HL recurrences in JIA patients receiving ETN and to confirm that this TNFi is not associated with an increased risk of HZ and of complicated varicella.

**CONCLUSIONS**

Our data suggest that varicella and HZ occurring during treatment with ETN, when treated with oral antiviral therapy, should not be considered a major concern, even in a setting of high VZV infection incidence, such as Italy. Nevertheless, because few serious VZV infections in patients treated with ETN have been reported, it is reasonable to follow the recommendation to administer 2 doses of VZV vaccine [12] before starting therapy in subjects without prior VZV infection and to continue close clinical surveillance of infections.

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