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Original Article

The Use of Natalizumab in Pediatric Patients With Active Relapsing Multiple Sclerosis: A Prospective Study

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ABSTRACT

BACKGROUND: Pediatric multiple sclerosis (MS) has been increasingly recognized. In the absence of approved disease-modifying therapies (DMTs) for pediatric patients, clinicians resort to data extrapolated from clinical trials conducted in adults with MS. The objective of this article was to study the effectiveness and safety of natalizumab in with pediatric MS. **METHODS:** Patients with pediatric MS (aged less than 18 years) who had been treated with natalizumab were followed up prospectively as part of the national MS registry. Data of relapsing patients who had at least a one-year follow-up were analyzed. The primary outcome measure was the annual relapse rate after natalizumab treatment. Secondary outcomes measures included the mean change in disease progression measured by the expanded disability status scale and the proportion of patients with radiologic activity (gadolinium-enhancing or new T2 lesions) at the last follow-up visit. **RESULTS:** Thirty-two patients with pediatric MS had been treated with natalizumab for at least 12 months, of whom 72% were females. The mean age at onset and disease duration were 14.9 ± 2.6 and 5.1 ± 3.1 years, respectively. Most patients (n = 21, 66%) had breakthrough disease on first-line disease-modifying therapies. The mean number of natalizumab infusions was 34.5 ± 18. The annual relapse rate was significantly reduced (1.66 ± 0.5 vs 0.06 ± 0.25; $P < 0.001$), whereas the mean expanded disability status score improved (3.3 ± 1.3 vs 2.2 ± 1.0; $P < 0.001$) at the last follow-up visits. The proportion of patients with magnetic resonance imaging activity was significantly reduced (93.8% versus 12.5%; $P < 0.001$). No major adverse events were observed. **CONCLUSION:** In our pediatric MS cohort with aggressive or breakthrough disease, treatment with natalizumab was effective in reducing clinical and radiologic disease activity. Natalizumab has a similar clinical efficacy and safety profile as in adult MS.

Keywords: multiple sclerosis, pediatric, natalizumab, EDSS, Kuwait

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Introduction

As the criteria for the diagnosis of multiple sclerosis (MS) evolve, MS is being increasingly recognized in children and adolescents. The prevalence of pediatric-onset MS ranges from 2.7% to 11.3% of the total MS populations.[1-3] Children with MS predominantly present with more frequent relapses and a higher incidence of cognitive deficits than in adult MS cohorts,[4] which poses unique challenges in the management, especially given the lack of specific disease-modifying therapies (DMTs) proved by clinical trials for pediatric MS.[5-7] The American and European regulatory agencies have implemented guidelines for the inclusion of pediatric investigation plans for new pharmacologic agents, with the aim of ensuring safe and appropriate access to promising new therapies for children and adolescents.[8] Physicians are generally reluctant to use DMTs in children

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during periods of growth and physical development.[9] First-line medications, namely, interferon beta and glatiramer acetate (GA), are the standard care for patients with pediatric MS.[10,11] However, about 30% of treated patients were partial or nonresponders to first-line treatment and later on required a switch to a high-efficacy therapy.[12] Several observational studies have shown that natalizumab consistently reduces disease activity in patients with pediatric MS.[13-16] However, prospective data are limited, and there have been no regional published data about the use of natalizumab in pediatric cohorts. In our study, we aim to prospectively assess the effectiveness and safety of natalizumab in patients with pediatric MS in Kuwait.

Methods

We conducted a prospective study utilizing the national MS registry to evaluate patients with pediatric MS (less than 18 years) treated with natalizumab. The registry was established in 2010 in Kuwait and is composed of databases of all major hospitals.[17] The diagnosis in patients with pediatric MS was established based on the consensus definition proposed by the International Pediatric Multiple Sclerosis Study Group (IPMSSG).[18,19] Patients, who were identified from the registry, were followed up prospectively. As per the registry protocol, patients had at least two visits per year, excluding visits for suspected relapses. Neurological evaluation, including the assessment of expanded disability status scale (EDSS),[20] was performed every 6 months. Anti-John Cunningham virus (JCV) antibody (Stratify JCV performed at Unilabs, Denmark)[21] was performed every 6 months after the initiation of natalizumab. Magnetic resonance imaging (MRI) (1.5 T) brain and cervical spine with gadolinium were obtained at baseline, biannually for the first year and then annually. Relapses were defined as new or recurrent neurological symptoms not associated with fever or infection that lasted for at least 24 hours and were accompanied by new neurological signs found by the examining neurologist while disease progression was evident by an increase of at least 1.0 point on EDSS score.[22] MRI activity was defined as an increase evident by either gadolinium-enhancing or new T2 lesions. According to the hospital protocol, the indications for the institution of natalizumab in patients with pediatric MS were (1) one relapse and evidence of new brain MRI activity or a severe relapse with incomplete recovery despite being on first-line therapies (interferon beta or glatiramer acetate) for at least one year or (2) demonstration of rapidly evolving MS, with at least two relapses in the last year and appearance of new brain MRI activity in naïve patients. Patients received the standard adult dose of natalizumab (300 mg intravenously every 4 weeks).

To obtain the annual relapse rate (ARR), we included only relapsing patients with pediatric MS who had at least one-year follow-up after natalizumab institutions. Pretreatment ARR was defined as the number of relapses that occurred in the year before natalizumab initiation, whereas on-treatment ARR was calculated as the number of relapses per duration of therapy.

Patients' demographics (age, gender), clinical characteristics (course of the disease, disease duration, relapse rate, EDSS score), and treatment parameters (prior DMT use, number of natalizumab infusions, adverse events, anti-JCV results) were obtained. The primary outcome measure of the study was to determine the ARR before and after natalizumab treatment. Secondary outcomes measures included the change in disease progression measured by EDSS scores and the proportion of patients with radiologic activity (gadolinium-enhancing or new T2 lesions) at the end of the observational period. Patients with primary or secondary progressive MS were excluded. The study was approved by the institutional ethical committee. Assents and parental consents forms were obtained from all patients.

All analyses were performed using SPSS 19 for Windows. Simple descriptive statistical tests (mean and standard deviation) were used to describe the numerical values of the sample. The significance of the differences of mean ARR and EDSS scores before and after treatment were compared by using the paired-sample Student t test, whereas χ^2 tests were used for categorical variables (MRI activity); P value < 0.05 was regarded as significant.

Results

Of 35 patients with pediatric MS who had been treated with natalizumab, three received less than 12 natalizumab infusions and were excluded. Data from 32 relapsing patients with pediatric MS were analyzed. Baseline demographics and clinical characteristics of the studied cohort are outlined in Table. The mean age at onset and disease duration were 14.9 ± 2.6 and 5.1 ± 3.1 years, respectively. Most patients (66%; n = 21) were escalated to natalizumab after having breakthrough disease while on first-line therapies (indication "a"). Natalizumab was initiated in 11 naïve pediatric patients who had a rapidly evolving disease (indication "b"). The mean number of natalizumab infusions was 34.5 ± 18 in the studied cohort. No major adverse events were observed.

With respect to the primary outcome measure, the ARR decreased significantly from 1.66 ± 0.5 in the year before natalizumab treatment to 0.06 ± 0.25 ($P < 0.001$) at the end of the observational period. The mean EDSS in our patients decreased from 3.3 ± 1.29 (range 2-6) at initiation of natalizumab treatment to 2.2 ± 1.0 (range 1-5) at last visit ($P < 0.001$). The proportion of patients with MRI activity was significantly reduced from 93.8% to 12.5% ($P < 0.001$) at the end of observational period. The proportion of patients with no evidence of combined clinical and radiologic activities was 84% (Figure).

We have not seen any major adverse events, apart from two patients who experienced mild headaches following the infusions, which subsided with acetaminophen, and one patient who experienced mild infusion-related

TABLE.
Baseline Demographic and Clinical Characteristics of Pediatric MS Who Were Treated With Natalizumab for at Least 1 Year (n = 32)

Variables	n (%), Mean ± S.D. (Range)
Gender	
Female	23 (66%)
Male	9 (34%)
Mean age of onset (years)	14.9 ± 2.6 (8-17)
Mean age at start of natalizumab initiation (years)	15.7 ± 1.9 (8-17)
MS duration (years)	5.1 ± 3.1 (1-11)
Mean number of natalizumab infusions	34.5 ± 18 (6-79)
Anti-JCV antibody status	
Negative	29 (90.6)
Positive	3 (9.4)
Prior use of DMTs	21 (65.6)
IFN-β 1a IM	6 (18.8)
IFN-β 1a SC	5 (15.6)
IFN-β 1b SC	9 (28.1)
Others	1 (3.1)

Abbreviations:
DMT = Disease-modifying therapy
IFN = Interferon
IM = Intramuscular
JCV = John Cunningham virus
MS = Multiple sclerosis
N = Number
SC = Subcutaneous