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BRIEF COMMUNICATION

Fingolimod in pediatric multiple sclerosis: three case reports

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Abstract

Treatment for pediatric-onset multiple sclerosis (POMS) currently reflects treatment for adult-onset MS, despite some differences in its clinical course. First-choice treatment of POMS generally consists of interferon β-1a or glatiramer acetate, with therapies such as natalizumab or fingolimod reserved for second-choice treatment. In cases of severe disease, both fingolimod and natalizumab can be considered first-choice therapy. This paper presents three case histories of patients with POMS and highlights the different uses of fingolimod within the POMS treatment algorithm. The first and third cases are examples of escalation therapy, both in females aged 16 to 17 years, with fingolimod administering as second choice following disease progression. The second case is an example of using fingolimod as first-choice therapy, given to a 12-year-old male with severe disease. In all three cases, over a period of approximately 1 year after the initiation of fingolimod treatment, there was no further disease progression and no adverse events were recorded.

Keywords Fingolimod · First-choice therapy · Multiple sclerosis · Pediatric patients

Introduction

Multiple sclerosis (MS) generally manifests between the age of 20 and 40 years. However, between 3 and 10% of MS is pediatric-onset MS (POMS), i.e., MS with an onset before the age of 18 years [1–3]. POMS is associated with higher rates of inflammation and relapse than adult-onset MS (AOMS), and sufferers are likely to reach stages of irreversible disability at a younger age than those diagnosed in adulthood [2, 4, 5].

Despite the differences between POMS and AOMS in terms of clinical symptoms and disease course, treatment strategies for POMS currently follow the recommendations for AOMS, meaning that treatment is not necessarily suited to the developmental stages of younger individuals [4]. Until recently, treatment of POMS has been further confounded by the lack of clinical trials, owing to the rarity of the disease. Early diagnosis and appropriate treatment of POMS are clearly critical to help improve outcomes.

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Current first-choice therapies for POMS include immunomodulatory agents such as interferon β-1a (Avonex®, Biogen, Cambridge, MA, USA; and Rebif®, EMD Serono, Inc., Rockland, MA, USA) and glatiramer acetate (Copaxone®, Teva, Petah Tikva, Israel) [6]. However, relapses during first-choice therapy should prompt escalation to second-choice therapies such as fingolimod, natalizumab, or rituximab. Clinical trials are ongoing to evaluate the efficacy of ocrelizumab, alentuzumab, and dimethyl fumarate; however, these treatments have not been approved for POMS yet. Furthermore, patients with rapidly evolving severe relapsing-remitting MS should be prescribed second-choice therapies from the onset [7]. This report presents three case studies in POMS, which help to highlight the best therapeutic approach, the benefits of an early switch to effective second-choice treatment, and the use of fingolimod as first-choice treatment in severe cases of POMS.

Clinical cases

Case 1

A 16-year-old female with a confirmed diagnosis of severe MS in January 2018, according to the McDonald 2010 [8] and International Pediatric Multiple Sclerosis Study Group (IPMSSG) 2013 [9] criteria, was admitted to the Department

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of Neurology, Bambino Gesù Children's Hospital, Rome, Italy, in September 2017. The patient presented with migraine and upper limb paresthesia. A magnetic resonance imaging (MRI) scan upon admission showed multiple cerebral and spinal cord lesions.

First-choice treatment with glatiramer acetate was initiated in this patient in January 2018 but a suboptimal response to therapy was noted after 1 year of treatment as MRI scans of the brain, brain stem, and cervical spinal cord showed new lesions without any symptoms. In February 2019, following disease progression, her treatment was switched to second-choice therapy with fingolimod 0.50 mg/day orally. The patient was vaccinated against hepatitis B virus, rubella, and mumps before fingolimod initiation. No adverse events were recorded during the treatment, and an MRI scan performed in June 2019, in September 2019, and in February 2020, after 1 year of treatment, showed no further disease progression. During the progression of the disease, the Expanded Disability Status Scale (EDSS) was 3. At the last follow-up visit, the patient showed no disabilities and had a normal neurological examination (EDSS = 0) and subsequently continued fingolimod treatment.

Case 2

A 12-year-old male was admitted to the Department of Neurology, Bambino Gesù Children's Hospital, Rome, Italy, in January 2019 with optic neuritis in the left eye. An MRI scan upon admission provided evidence of numerous infratentorial and spinal lesions (Fig. 1), while autoimmunity screening was normal, and he was diagnosed with aggressive MS. In March 2019, treatment with first-choice fingolimod (0.25 mg/day orally) was initiated in this patient, with no adverse events recorded during the course of treatment. Subsequent MRI scans in September 2019 and April 2020, after 11 months of fingolimod treatment showed no signs of disease progression. At the onset, EDSS was 2. At the last follow-up visit, the patient had a normal neurological examination (EDSS = 0) and continues on fingolimod treatment.

Case 3

In April 2016, a 17-year-old female was admitted to the Department of Neurology, Bambino Gesù Children's Hospital, Rome, Italy, with hyposthenia on the right side of her body (EDSS = 3) and was diagnosed with MS based on the McDonald 2010 [8] and IPMSSG 2013 [9] criteria. The patient had a previous history of Epstein-Barr virus infection. An MRI scan upon admission showed multiple supra and subtentorial cerebral lesions.

First-choice treatment with interferon β1a was initiated in August 2016, and the patient remained stable until May 2018 when a follow-up MRI showed a new brain lesion. Subsequently, in August 2018, the patient was switched to second-choice treatment with fingolimod (0.50 mg/day orally). The patient was vaccinated against varicella 2 months before starting treatment and the second dose 1 month before therapy with fingolimod. No adverse events were recorded during treatment, and a follow-up MRI scan performed in January 2019, in September 2019, and in January 2020 after 1 year and 5 months of treatment showed no signs of disease progression. Neurological examination at the last follow-up visit was unremarkable (EDSS = 0), and the patient is currently on continued fingolimod treatment.

Discussion

The clinical cases presented here highlight different uses of fingolimod within the POMS treatment algorithm, with the first and third cases being examples of escalation therapy, while the second case being an example of use of Fingolimod as first-choice therapy. In all three cases, no adverse events were recorded during treatment, and no disease progression was seen at the last follow-up after initiation of fingolimod treatment, indicating that fingolimod was effective and well-tolerated in these patients over the time periods monitored.

Fingolimod is the first oral disease-modifying treatment available for MS and was approved in the USA and Canada for relapsing-remitting AOMS in 2010 and POMS (age 10 to 17 years) in 2018 [10]. A Cochrane review of six studies in AOMS found an advantage with fingolimod over interferon β-1a in terms of freedom from relapse, but no difference in freedom from disability [11]. Fingolimod was associated with more adverse events than interferon β-1a during the first 6 months of treatment, but the tolerability profiles were similar by 12 months [11]. Interestingly, this review also showed evidence of better quality of life during the first 6 months of treatment in patients taking fingolimod than in those taking interferon β-1a [11].

Data on fingolimod in POMS are still limited, but evidence for a potential benefit in this population is accumulating. The PARADIGMS study, which followed 215 patients with POMS for 2 years, found a significantly reduced annualized relapse rate with fingolimod compared with interferon β-1a (0.12 *vs*. 0.67; absolute difference, 0.55 relapses; relative difference, 82%; $P < 0.001$) but with a higher rate of serious adverse events (16.8% *vs*. 6.5%) [12]. A retrospective study of 17 patients with MS under the age of 18 years reported only one patient with a relapse and a new lesion on MRI after starting treatment with fingolimod and reported no adverse events [13]. In that case series, eight of 17 patients maintained their Expanded Disability Status Scale (EDSS) scores after treatment with fingolimod, and nine had improvements in their EDSS scores with treatment. However, the follow-up

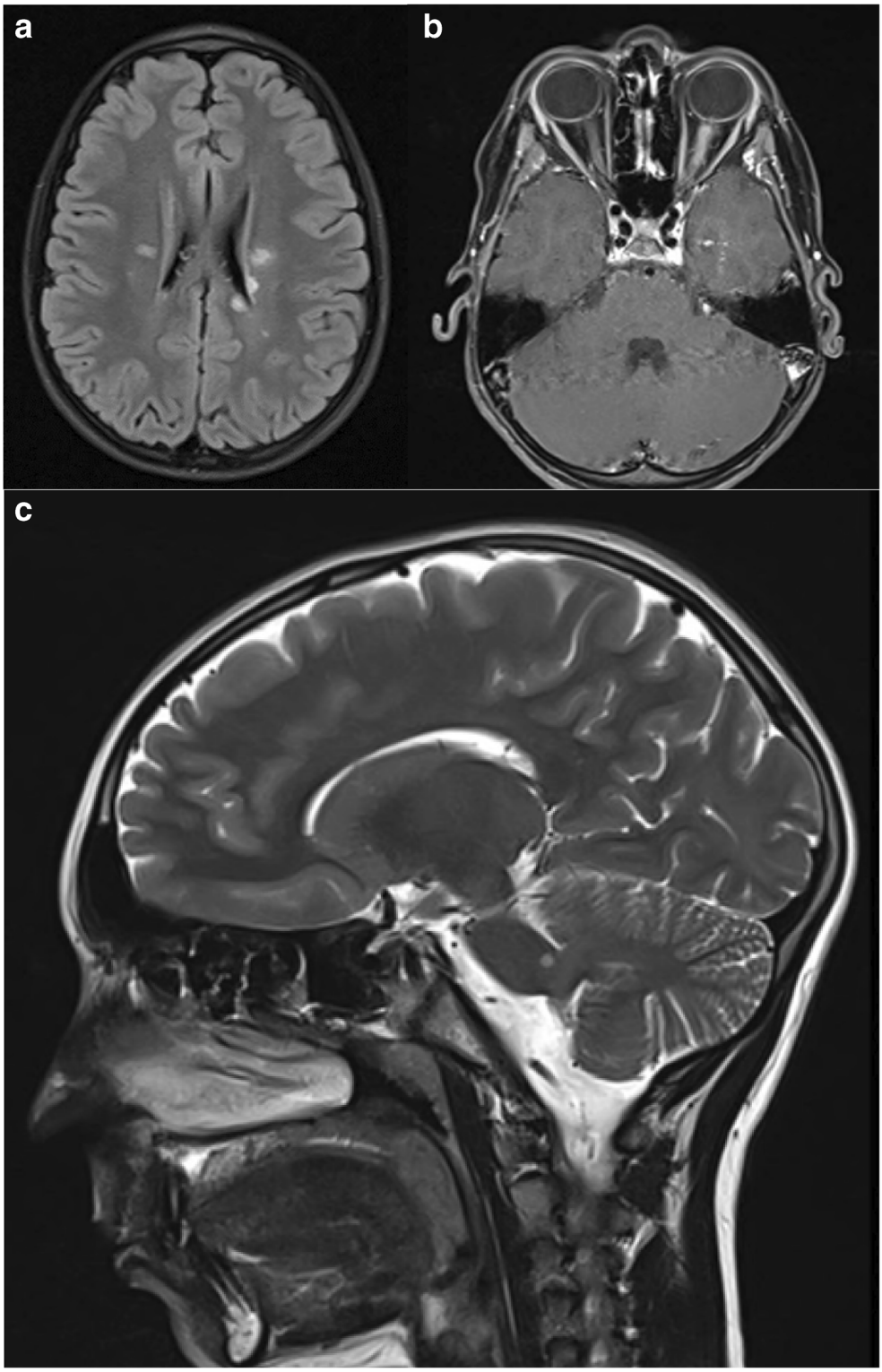

Fig. 1 **a** Axial T2 FLAIR MRI showing multiple periventricular lesions, **b** axial T1 contrast-enhanced MRI showing abnormal enhancement throughout the left optic nerve, and **c** sagittal T2 MRI showing a lesion in the right middle cerebellar peduncle. Abbreviations: MRI, magnetic resonance imaging; FLAIR, fluid attenuated inversion recovery

time was <18 months in these patients, and the mean follow-up time was 8.6 months [13], which is similar to the 9-month follow-up time in the three patients reported here.

The three cases presented here reflect topics widely discussed in the management of POMS: (1) when to initiate therapy and choice of escalation therapy versus induction therapy at onset and (2) early identification of suboptimal responders. As for the choice of therapy, a part from fingolimod, natalizumab is approved as second-choice therapy in POMS. Several observational studies have shown that natalizumab

consistently reduces disease activity in POMS [14–17]. Ocrelizumab, alentuzumab, and dimethyl fumarate have not been approved for use in children, although randomized controlled clinical trials are underway to evaluate the efficacy and safety of ocrelizumab and dimethyl fumarate in POMS.

At present, no criteria for identifying suboptimal responders have been validated. In the absence of validated criteria, Cohen and colleagues suggested a combination of three parameters that include clinical course, subjective impressions of the patient and physician concerning impairments in function affecting daily activities, and significant MRI changes indicating persistent inflammatory disease [18].

Fingolimod is reported to be effective and well-tolerated upon oral administration, has a good safety profile, and was, therefore, the preferred choice for the treatment of the three patients described here. Importantly, our case studies demonstrate the feasibility of treatment with fingolimod for POMS as either first- or second-choice treatment. However, the results must also be viewed with caution given the short follow-up in each case to date. Further studies are required to fully determine the place of fingolimod and indeed all currently available second-choice treatments in the management of POMS.

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Code availability Not applicable.

Author contribution Michela Ada Noris Ferilli was involved in data collection and writing and reviewing the manuscript drafts. Laura Papetti was involved in data collection, and Massimiliano Valeriani was involved in writing and reviewing the manuscript drafts and final editing of the manuscript. All authors have read and approved the final draft of the manuscript before submission.

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Data availability Not applicable.

Declarations

Conflict of interest The authors declare that they have no conflicts of interest.

Ethics approval and consent to participate Ethical approval was obtained from the local ethics committee of the Bambino Gesù Children's Hospital, Rome.

Consent for publication Informed consent to publish was obtained from legal guardians.

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