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Clinical Trials in Pediatric Multiple Sclerosis: Pending Landscape and Challenges

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Abstract

Until recently, pediatric clinical trials were not required for new therapeutics. As a result, children were often prescribed medications off-label based on data from adult studies, or were unable to receive potentially beneficial therapies because of a lack of official approval for use in the pediatric population. As this was deemed unethical and detrimental in some cases, legislation was recently approved that now mandates pediatric studies for all new therapeutics.

Implementation of clinical trials in pediatric MS is especially germane as there are a number of emerging oral and intravenous therapies that may be more tolerable and effective than the platform injectable therapies. As pediatric MS trials are now being designed, challenges regarding their feasibility have been identified. These include sample size limitations, determination of appropriate study endpoints and pediatric MS-specific outcomes, and fear about the unknown impact of these new agents on the maturing immune, reproductive, and central nervous system. In this commentary, we discuss the pending landscape of pediatric MS trials and their anticipated challenges.

Introduction

The last 20 years have borne witness to significant advances in the care of patients with relapsing-remitting multiple sclerosis (RRMS). Subcutaneous and intramuscular injection of interferon-beta and subcutaneous injection of glatiramer acetate have level 1A evidence for a reduction in relapse rate and for suppression of new lesions on brain MRI. Intravenous natalizumab has been shown to have an even more dramatic impact on clinical and MRI evidence of multiple sclerosis (MS) disease activity, but duration of exposure is limited by the risk of brain infection with JC virus. The last few years have seen approval of several new oral therapies for RRMS, and approval in some countries of even more powerful immunosuppressive therapies, such as alemtuzumab.

The advent of formal therapeutic trials in pediatric MS is urgently needed. To date, there have been no pediatric clinical trials, and all MS therapies used in the population are prescribed off-label. Though retrospective studies have provided important information on the safety of interferon-beta, glatiramer acetate, and natalizumab in the pediatric population, formal clinical trials are required for efficacy data.

Discussion

Legislation in the United States [1,2] as well as regulatory authorities such as the Federal Drug Authority and the European Medicines Agency, now require pediatric investigation plans (PIPs) that design Phase III pediatric studies for any new medication. These requirements are particularly germane to emerging therapies for MS. However, although 3-5% of all patients with MS do experience their first clinical symptom in childhood or adolescence, pediatric MS is still rare and PIPs must consider this. Additional challenges to implementing clinical trials in the pediatric MS population include determination of appropriate study endpoints and study design and concern about the impact of these new agents on the maturing immune, reproductive, and central nervous system. These considerations have been discussed in a recent position paper of the International Pediatric Multiple Sclerosis Study Group (IPMSSG) [3].

As the overall incidence of pediatric onset MS is low (0.18-0.51/100,000 per year) [4-6] enrolling an adequate number of patients for clinical trials will be challenging and will require multi-center international support. With patients enrolling from multiple centers, consensus definitions must be employed when diagnosing a patient with MS [7]. With a limited group of potential study participants, trials will have to be designed with appropriate endpoints such that they can be properly powered to provide informative results. In its position paper, the IPMSSG suggested that the clinical metrics of time to next relapse or annualized relapse rate should be used as primary outcomes in phase III clinical trials as these would most easily translate to clinical practice [3].

With the prospect of pediatric clinical trials on the horizon, Verhey et al. performed a study aimed to estimate the sample sizes required for pediatric studies using both clinical and radiologic metrics [8]. Prospective data from a national study of children and adolescents followed from their incident demyelinating attack were used, and sample size estimates were generated using outcomes of time to next relapse and annualized relapse rate (ARR) for placebo-controlled trials of 12 and 24 months' duration. Using the cohort's calculated ARR of 0.69 over two years of follow-up, Verhey et al. found that a sample size between 75 and 115 patients would be required per arm to detect a 40% treatment effect over placebo in a two-year study using ARR as a primary outcome[8]. This number is less than the sample sizes required for similar studies done in the adult population, which may

be a result of the higher relapse rate seen in the early stages of MS in patients with pediatric onset [9]. For instance, in FREEDOMS, a phase III placebo-controlled trial of oral fingolimod that used ARR as the primary outcome, about 425 patients per study group (1250 patients divided amongst 3 groups) were required to provide 95% power to detect a relative reduction of 40% or more in ARR as compared to placebo after 24 months [10].

In adult MS trials, the Expanded Disability Status Scale (EDSS) has been used as a primary endpoint and as a measure of disability. The EDSS was developed in 1983, ranges from 0 (normal neurologic exam) to 10 (death due to MS), and measures impairment in eight functional systems [11]. Though it is generally accepted as an endpoint in adult studies, it may not be an ideal endpoint in pediatric studies as children do not tend to accrue functional disability as quickly as adults. For example, in one multicenter observational study of childhood-onset MS, it was found that pediatric MS patients took approximately ten years longer to reach the secondary progressive phase with irreversible disability as compared to patients with adult-onset disease [12].

The EDSS does not provide a detailed assessment of cognitive impairment, a major concern in pediatric MS. Furthermore, current and emerging therapies have not been shown to influence cognitive outcome. The biological mechanisms that underlie cognitive decline remain to be fully defined, and may be distinct from those processes that subserve relapse frequency. As such, selection of cognitive measures as outcomes in pediatric MS trials may serve to indicate a lack of efficacy of therapies that do meaningfully impact relapsing disease.

Although Phase III studies are powered on clinical endpoints, MRI endpoints are commonly employed as secondary endpoints and are also often measured in phase II studies. There is a relative paucity of data on the natural history of new lesion accrual in pediatric MS patients, a particular challenge given issues of serial imaging in young patients. In terms of the sample size needed for studies using MRI metrics, Verhey et al. estimated the sample size required for a phase II placebo-controlled trial using the outcome of a 50% relative reduction in new T2 lesion formation as 90 patients per arm for a study of 6-months' duration [8]. It is anticipated that MRI metrics will serve as key secondary outcomes in the inaugural therapeutic trials in pediatric MS.

Selecting the appropriate clinical trial design with regard to placebo-controlled or superiority trials is also challenging. While placebo-controlled trials would allow for smaller sample sizes, some may find this unethical as children have now been safely treated off-label with interferon and glatiramer acetate for many years and there is observational and retrospective data to support their efficacy in pediatric MS. Censoring may also be a problem in placebo-controlled trials as patients may drop out or switch therapy at the time of a relapse. One trial design that might address these concerns would involve use of time to next relapse as the primary outcome. Though use of this outcome would require a larger sample size than if annualized relapse rate was used, this may be a more appropriate outcome measure in pediatric placebo-controlled trials as patients treated with placebo would be allowed to switch to active treatment after a relapse. This design would allow for shorter placebo exposure and possibly greater acceptance by families and treating physicians.

Trials designed to determine the appropriate dosing for pediatric patients are also needed. While this data might be generated by Phase I or II dose-finding studies, a dose-toxicity component might also be built into a Phase III trial such that the patients initially enrolled are treated with a dose escalation plan. These studies would provide valuable information on toxicities that are unique to children (effects on puberty, growth, and immune system maturation), and on drug metabolism, which may vary considerably in the pediatric population.

Unlike therapeutic trials in adult MS, trials in pediatric MS will require consent of both the patient and their guardians. Nothing is yet known regarding endorsement of trials by pediatric MS patients or their families. Clinicians recruiting children for studies must consider protocol complexity and the emotional distress of the parents and patients involved [13]. As it has been shown that recruitment for a study is enhanced when a treating physician is in support of enrollment and there is verbal explanation of the study, referring clinicians should continue to be involved in the design of clinical trials in the pediatric population [14].

Conclusions

Despite the obvious challenges in designing and recruiting patients for pediatric MS clinical trials, the benefit of collecting safety information, pharmacokinetics, and efficacy data specific to pediatric patients is significant. Data from the initial clinical trials in the pediatric population will in turn inform not only on the efficacy and safety of the therapy under study, but will inform on feasibility of pediatric MS trials, and on pediatric MS-specific outcomes. As a result, a thoughtful approach to clinical trial design is required and the choice of agents to study will require discussion amongst leaders at various MS centers around the world. With this approach, therapeutics with new mechanisms of action and improved tolerability may become realistic treatment options for pediatric patients with MS.

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