The CombiRx trial of combined therapy with interferon and glatiramer acetate in relapsing remitting MS: Design and baseline characteristics

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ARTICLE INFO

ABSTRACT

Background: Interferon-β1a (IFNB) and glatiramer acetate (GA) are distinct therapies which are both partially effective for relapsing MS. It is not known if combining the two treatments would be more effective.
Objective: To review the rationale, design, and baseline characteristics of the CombiRx study of combined treatment with IFNB and GA.
Methods: The key inclusion criteria included a diagnosis of relapsing MS, at least 2 episodes of MS activity in the previous 3 years, expanded disability status scale of 0–5.5, and no prior treatment with either IFNB or GA. Subjects were randomized to IFNB+GA, IFNB monotherapy, or GA monotherapy in a 2:1:1 ratio.
Results: From 2005 to 2009, we enrolled 1008 subjects. The participants were 72.4% female and 87.6% Caucasian with a mean age of 37.7 years. The median duration of symptoms was 2 years at entry into the study, and the mean EDSS was 2.1. On the baseline MRI, the mean total lesion load was 12.2 ml, and 40% of the participants had enhancing lesions.
Conclusion: We have recruited a population of patients with clinical and MRI characteristics typical for early MS. The study results will aid in deciding on the optimum early treatment. This trial should serve as a model for future studies of combination therapy.

1. Introduction

Multiple sclerosis (MS) is a chronic disease of the central nervous system that affects approximately 350,000–400,000 persons in the United States and 2.5 million persons worldwide. The typical form of the disease begins in young adulthood, has a relapsing–remitting course, and often causes substantial neurologic disability over time (Compston and Coles, 2008; Noseworthy et al., 2000). There are several treatments approved for relapsing–remitting MS (RRMS), but none are ideal. Interferon-β (IFNB) has a good safety profile and reduces relapse rate by 32% (Jacobs et al., 1996). Glatiramer acetate (GA) likewise is safe for long-term use

and reduces relapse rate by 29% (Ford et al., 2010; Johnson et al., 1995). More recently developed treatments, such as natalizumab and fingolimod, may have better efficacy but have safety concerns and side effects which limit their use.

As more agents have been tested in MS, it appears that no single therapy is likely to have the desired combination of efficacy and safety. One reasonable approach to this problem is combination therapy (Tullman and Lublin, 2005). The concurrent use of two effective drugs with different mechanisms of action could have an additive or synergistic benefit without additional side effects. IFNB and GA are an obvious choice for combination therapy, since both have good safety, modest efficacy as monotherapy, and probable different mechanisms of action.

An ideal study of a combination therapy should compare the combination to either drug as monotherapy. It should also be randomized and blinded and have an adequate sample size and duration to discern meaningful differences in the treatment groups. We report here the design and baseline characteristics

of such a study of the combination of IFNB and GA. Future reports will correlate these baseline characteristics with the genetic studies, biomarkers, and clinical course collected as part of this study.

2. Materials and methods

2.1. Study design

CombiRx is a 3-arm, randomized, double-blind, placebo-controlled, multi-center, Phase-III trial of combination therapy utilizing a partial 2×2 factorial design with a 2:1:1 randomization balance (Table 1). With the partial factorial design, there is no arm with no active treatment. The monotherapy arms have a matched placebo injection. Participants were followed for a minimum of 36 months and up to 7 years, if they continued into the extension phase of the trial (Fig. 1). The major inclusion and exclusion criteria are given in Table 2. Diagnosis of MS was made according to the McDonald criteria (McDonald et al., 2001; Polman et al., 2005). Participants had to have experienced 2 clinical relapses in the prior three years or one clinical relapse with subsequent MRI activity.

2.2. Randomization

Eligible participants were randomized using a distributed Data Entry System (DES), where the sites and participants were masked to the assigned treatment arm. Participants were randomized to one of the three treatment arms in a 2:1:1 ratio (combination:single agent:single agent) within site using a permuted block design, with block sizes of 4 or 8.

2.3. Medications

All participants receive at least one active medication, and all participants take the same number of injections. Interferon-β1a is given 30 μg intramuscularly once a week, and glatiramer acetate is given at 20 mg subcutaneously daily. Matched placebo preparations were provided for the active medications by their respective manufacturer.

2.4. Outcome measures

The primary objective of the core study is to determine whether combined treatment is more effective than either agent alone in treating RRMS, as determined by the number of relapses during 36 months of follow up. The primary analysis will compare the relapse hazard rate between the treatment groups using a Cox Proportional Hazards Model with Anderson–Gill Modification. Secondary outcome measures include confirmed progression on the expanded disability status scale (EDSS), change in the Multiple

Table 1
Treatment combinations in CombiRx Primary Trial.

	Active IFNB	Placebo IFNB
Active GA	Arm 1 (500): active IFNB+active GA	Arm 2 (250): active IFNB+placebo GA NA
Placebo GA	Arm 3 (250): active IFNB+placebo GA	

Table 2
Major inclusion and exclusion criteria.

Inclusion criteria
Age 18 and 60 years, inclusive
Expanded disability status scale (EDSS) score of 0–5.5, inclusive
Diagnosis of relapsing–remitting MS by either the Poser or McDonald criteria
At least 2 exacerbations in the prior three years; one exacerbation may be an MRI change meeting the McDonald MRI criteria for dissemination in time

Exclusion criteria
Any prior use of interferon beta or glatiramer acetate
Acute exacerbation within 30 day of screening
Steroids for acute exacerbations (> 100 mg/day) within 30 day of screening visit or chronic systemic steroid use
Evidence of progressive MS
IVIg, azathioprine, methotrexate, cyclosporine, mitoxantrone, cyclophosphamide, mycophenolate or plasma exchange in the twelve weeks prior to study drug dosing or 4 aminopyridine in the four weeks prior to study dosing
Any previous treatment with natalizumab, cladribine, T cell vaccine, alemtuzumab, daclizumab, rituximab, altered peptide ligand or total lymphoid irradiation
Any prior history of seizure or significant cardiac, hepatic, pulmonary, or renal disease; immune deficiency; or other serious medical conditions
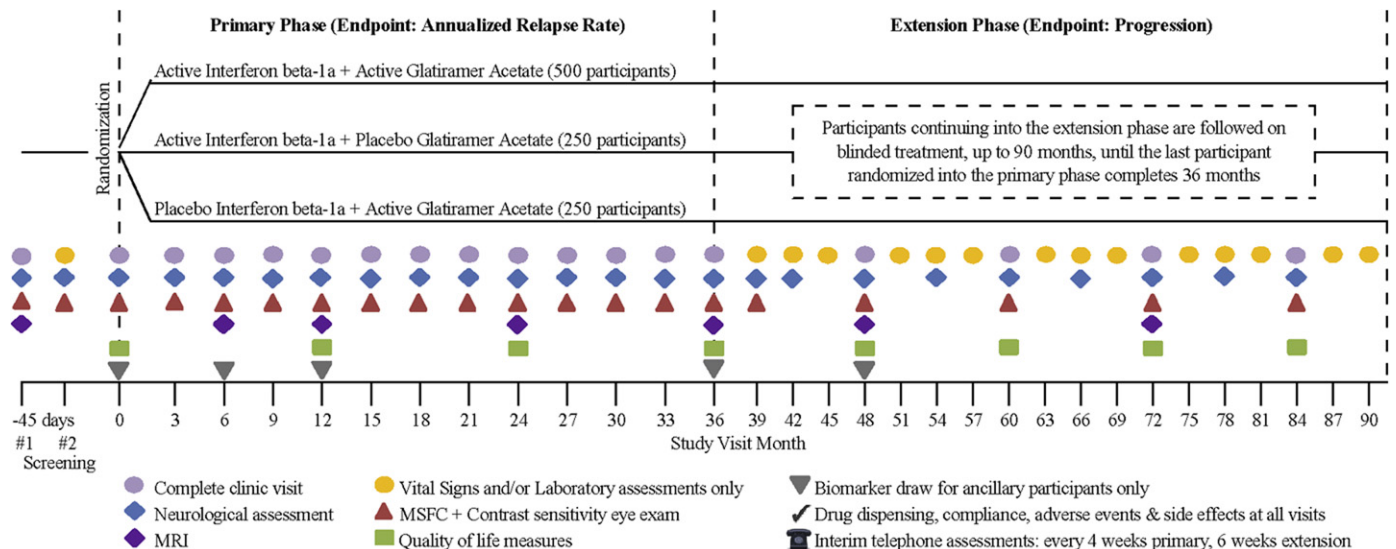

Fig. 1. Study timeline and assessments.