Multiple Sclerosis and Related Disorders 18 (2017) 95–102

Contents lists available at ScienceDirect

Multiple Sclerosis and Related Disorders

journal homepage: www.elsevier.com/locate/msard

Long-term follow-up of a randomized study of combination interferon and glatiramer acetate in multiple sclerosis: Efficacy and safety results up to 7 years

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ARTICLE INFO

Keywords:
RRMS
Disease activity free status
Clinical trial
Interferon beta-1a
Glatiramer acetate

ABSTRACT

Background: To report the long-term results of the blinded extension phase of the randomized, controlled study of the combined use of interferon beta-1a (IFN) 30 μg IM weekly and glatiramer acetate (GA) 20 mg daily compared to each agent alone in relapsing-remitting multiple sclerosis (RRMS).

Methods: 1008 RRMS patients were followed on protocol until the last participant enrolled completed 3 years, allowing some subjects to be followed for up to 7 years. The primary endpoint was reduction in annualized relapse rate. Secondary outcomes included time to confirmed disability, Multiple Sclerosis Functional Composite (MSFC) score and MRI metrics.

Results: Similar to the core study, combination IFN + GA was not superior to the better of the single agents (GA) in risk of relapse. Both the combination therapy and GA were significantly better than IFN in reducing the risk of relapse. The combination was not better than either agent alone in lessening confirmed EDSS worsening or change in MSFC. Also similar to the core result, the combination was superior to either agent alone in reducing new lesion activity, but the 3 year MRI result did not presage a clinical benefit over the extended observation interval.

Conclusion: Combining GA & IFN did not produce a significant clinical benefit over the entire study duration. The earlier effect on reducing MRI activity did not result in a later clinical advantage. The combination showed a sustained advantage in reducing disease activity free status.

1. Introduction

The CombiRx study was a double blind, placebo controlled, randomized clinical trial comparing the combination of interferon beta-1a (IFN) and glatiramer acetate (GA) to either agent alone in treating relapsing-remitting multiple sclerosis (RRMS). The study was planned to assess clinical and magnetic resonance imaging (MRI) activity over three years. Subjects were followed in the blinded protocol until the last subject completed the three years. This provided an opportunity to follow the earlier recruited participants in blinded fashion through seven years and allowed longer per protocol follow-up than any MS clinical trial. We previously reported the baseline characteristics of the study population (Lindsey et al., 2012) and the primary and secondary outcomes for the cohort at three years (Lublin et al., 2013). The combination of these two agents, the most commonly prescribed MS therapies at the inception of the study, did not achieve the primary outcome of reducing the risk of relapse over that of the better of the two monotherapies, GA. Both the combination and GA were superior to IFN in relapse reduction. There were no significant differences between the groups in time to relapse, development of confirmed disability or MS functional composite (MSFC). The combination was superior to either agent alone in reducing new lesion activity and the accumulation of total lesion volumes on MRI.

This report addresses whether the MRI benefits seen at three years

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http://dx.doi.org/10.1016/j.msard.2017.09.012
Received 13 June 2017; Received in revised form 31 August 2017; Accepted 13 September 2017

translated into clinical differences in the longer studied cohort. The trial design allowed for the longest on protocol blinded assessment of study metrics, both clinical and MRI, and a composite measure of disease activity.

2. Materials and methods

2.1. Study population and design

At the start of the 3-year core study, eligible participants with a confirmed diagnosis of RRMS (by Poser or McDonald criteria), aged 18–60 years, with an Expanded Disability Status Scale (EDSS) score of ≤ 6, and with at least 2 relapses in the prior 3 years were randomized (2:1:1) to combination IFN + GA or each single agent plus matching placebo (Bhanushali et al., 2014). There was no dual placebo arm; all participants received at least one active agent. All participants administered 8 injections weekly: GA (Copaxone; Teva Pharmaceuticals, Petah Tikva, Israel) 20 mg was given subcutaneously daily and IFN (Avonex; Biogen-Idec, Weston, MA) 30 μg used intramuscularly weekly, with matched placebo preparations provided by the respective manufacturers. Those who completed the 3-year placebo-controlled core study were eligible for inclusion in the extension phase with up to 7 years of total follow up on blinded medication. Study design, randomization allocation, baseline characteristics, and core study results have been reported (Lindsey et al., 2012; Lublin et al., 2013). The results of the extension phase of the trial are provided here.

2.2. Protocol and procedures

CombiRx enrolled 1008 participants from January 2005 through April 2009. The protocol and 4 amendments were approved by the 68 US and Canada center's applicable central or institutional review boards and the NIH appointed data and safety monitoring board (DSMB). Informed consent was obtained prior to screening and enrollment procedures.

Following enrollment, participants were followed every 12 weeks with neurological assessments by a treating clinician and examining clinician, both blinded to treatment assignment. Relapse assessments occurred every 12 weeks and as needed, EDSS examinations occurred every 12 weeks in the core study through Month 42 and every 6 months thereafter in the extension. MSFC was performed quarterly in the core study and annually in the extension study. MRI was performed at study entry, months 6, 12, 24, 36, 48 and 60 and at the End of Study (EOS) visit in the extension if it had been more than 12 weeks since the prior MRI; the variable amount of data on MRI available, especially at years 5 and year 7, relate to when patients had EOS scans (Fig. 1).

2.3. Study outcomes

2.3.1. Annualized relapse rate

The primary outcome of the core trial was the annualized relapse rate (ARR), with 3 exacerbation definitions determined centrally according to the relapse assessment and EDSS data provided by the center: protocol-defined exacerbations (PDE), non-protocol defined exacerbations (NPDE) and suspect exacerbations (SE), differing by the time of EDSS confirmation and amount of change in EDSS (Fig. 2).

2.3.2. Confirmed worsening

Confirmed worsening was defined as a minimum 1.0 increase in the EDSS from baseline if baseline EDSS ≤ 5.0, or minimum increase of 0.5 for baseline ≥ 5.5, confirmed at 2 successive quarterly visits through month 42 and 1 successive semi-annual visit in the extension phase. The time of confirmed worsening was taken as the onset of the first recorded change and only the first occurrence of worsening was used for the analyses.

2.3.3. MSFC

The MSFC score was determined centrally using the pooled baseline population of the core study as the reference standard in accordance with the protocol specified by the MSFC training manual (http://www.nationalmssociety.org/For-Professionals/Researchers/Resources-for-Researchers/Clinical-Study-Measures/Multiple-Sclerosis-Functional-Composite-(MSFC)).

2.3.4. MRI outcomes

MRI of the brain with and without contrast was acquired using a previously described standardized protocol and semiautomated processing and segmentation approach (Wolinsky et al., 2000; Lublin et al., 2013; Wolinsky et al., 2013). In this multimodal analysis system total lesion volume is defined as the sum of the T1-hypointense and T2-hyperintense lesion volume components. Combined unique lesion activity (CUA) was defined as the sum of the number of new enhanced lesions at a given imaging session and the number of new unenhanced T2 and substantially enlarged unenhanced T2 lesions with reference to the immediately prior scan session, where the unenhanced new or substantially enlarged images found were subjectively defined when compared to images from the prior imaging session and could not be explained by partial volume effects or errors in alignment in post-registered paired image sets. In the CUA assessment, lesions that enhanced on T1 weighted images were counted once and only once, and new lesions on T2-weighted images that also enhanced on T1-weighted images were not included in the CUA to avoid double counting. Atrophy was assessed as change in the normalized cerebrospinal fluid (nCSF) calculated as the percentage of the total intracranial contents that segmented as CSF over the total segmented intracranial contents;, where the calvarium is not expected to change in size over the course of the clinical trial. Increasing nCSF is a reflection of reduction of the intracranial contents analogous to the inverse of the brain parenchymal fraction; the larger change the nCSF from baseline the greater the intracranial tissue loss.

2.3.5. Clinical and disease activity free status

Clinical activity free status (CAFS) was defined as participants without relapse and without confirmed worsening. Disease activity free status (DAFS, also sometimes referred to as NEDA- no evident disease activity) was defined as CAFS plus no new MRI activity (absence of CUA). DAFS was a post-hoc analysis.

2.3.6. Safety outcomes

Safety was assessed quarterly and as necessary by recording all adverse events both serious and non-serious. Estimated glomerular filtration rate (eGFR) monitoring was added in 2008. Safety was monitored by an external safety monitor and the DSMB.

2.4. Statistical analysis

Descriptive measures are presented as means, medians, standard deviations (SD) and minimum and maximum (range) values, as applicable. Comparisons at baseline among the treatment arms, as well as power and sample size estimations for the primary trial are described elsewhere (Lublin et al., 2013). A significant but slight difference in mean age occurred at the start of the core study. ARR was calculated for each treatment arm by dividing the total number of relapses by the total person years within each arm. Confidence intervals for ARR were calculated using a Poisson regression model. The risk of relapse (hazard rate) was evaluated using a covariate adjusted Cox proportional hazards model with the Anderson Gill modification to allow for multiple relapses within participants with its associated confidence interval (Therneau and Grambsch, 2000).

Covariate adjusted for age and baseline EDSS score logistic regression was used to evaluate confirmed worsening and CAFS, and adjusted for age, baseline EDSS, and presence of gadolinium enhanced (Gd^+)