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CLINICAL TRIAL

Therapy Optimization in Multiple Sclerosis: A cohort study of therapy adherence and risk of relapse

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Abstract
Objectives: The objective of the Therapy Optimization in MS (TOP MS) Study was to prospectively assess the relationship between MS disease-modifying therapy (DMT) adherence and MS relapse risk over 2 years.
Methods: Potential participants were recruited for TOP MS by specialty pharmacies who dispensed glatiramer acetate and beta interferons for MS nationwide. Signed IRB-approved informed consents were returned to the pharmacies. TOP MS used electronic data capture with monthly patient entries. Adherence, measured by medication possession ratio (MPR), was derived from pharmacy shipment records. Logistic regression examined the association between protocol-defined relapses and DMT MPR ($\leq$0.5; $>$0.5-$<$0.9; $\geq$0.9).

Abbreviations: 95% CI, 95% Confidence Interval; DMT, disease-modifying therapy; FG, fingolimod; FSS, Fatigue Severity Scale; GA, glatiramer acetate; ICF, informed consent forms; IFNβ, interferon beta; MPR, medication possession ratio; NZ, natalizumab; OR, Odds Ratio; PDQ-5, Perceived Deficits Questionnaire (5 items); PHQ-9, Patient Health Questionnaire (9 items); Self-Assessed Kurtzke, Self-Assessed Expanded Disability Status Scale [EDSS]; TOP MS, Therapy Optimization in MS

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Results: TOP MS enrolled 3151 persons with MS, and 2410 completed the full 2 years. Across all therapies, the mean MPR for the 2-year completer cohort of 2049 who maintained the same DMT was 0.9 ± 0.2 (range: 0.1–1.0), with 63.8% reaching a 2-year MPR >0.9. Evaluated by categories of MPR, the proportion of participants remaining relapse-free for 24 months increased with increasing MPR, and the proportion with ≥ 1 relapses declined with increasing levels of MPR ($p<0.0008$). Regression analysis revealed the odds of relapse for a patient in the MPR ≥ 0.9 MPR group was 64% that of a patient in the MPR ≤ 0.5 category ($p=0.02$). Use of ≥ 1 DMT prior to the current one was an independent predictor of relapse.
Conclusions: The study provides class III evidence that improvement in adherence to DMT for MS is associated with improved clinical outcomes as measured by relapse reduction.

1. Introduction

When treating a chronic disease like Multiple Sclerosis (MS), optimizing the full benefit of medication requires that patients conform to physician recommendations about dosage and frequency of treatment; this is defined as medication adherence (Sabeté, 2003; Cramer et al., 2008). The disease-modifying therapies (DMT), first introduced for treatment of MS 20 years ago, were FDA-approved to reduce the number and frequency of relapses and delay confirmed disability (Johnson, 2007). Recent research in patients with relapsing-remitting MS suggests that, like those with many other diseases, more than 25% do not adhere to their medication (DiMatteo, 2004; Kleinman et al., 2010; Halpern et al., 2011).

While many of the investigations into DMT adherence have used arbitrary categories of good and poor adherence with cutoffs of 75–85%, these cutpoints have not been prospectively linked to disease outcomes (Cramer et al., 2008; Halpern et al., 2011; Devonshire et al., 2011; Steinberg et al., 2010). In a cross-sectional study of MS patients, from the Neurology Department at Henry Ford Hospital, Cerghet et al. used generalized estimating equation methods to look at the relationships between DMT adherence and outcomes. They found patients with higher adherence had better mental health, greater likelihood of employment, and lower disability scores (Cerghet et al., 2010). Others have explored the association between DMT adherence and the occurrence of MS relapses retrospectively with administrative claims databases and their results suggest an inverse relationship between DMT adherence and relapses (Steinberg et al., 2010; Oleen-Burkey et al., 2011).

The objective of the Therapy Optimization in MS (TOP MS) Study was to prospectively assess the relationship between adherence to MS DMT and the risk of MS relapses over a 2-year follow-up period in a community-based cohort.

2. Materials and methods

TOP MS was a prospective, open-label, observational cohort study designed to include approximately 3000 MS patients who were initiating or continuing DMT dispensed by their cooperating specialty pharmacies. This 24-month usual-care study of MS patients was sponsored by Teva Pharmaceuticals, Inc., with guidance from a steering committee of MS neurologists (authors).

2.1. Standard protocol approvals, patient consents, and registration

The study protocol and informed consents were reviewed and approved by Sterling Institutional Review Board (IRB). Written informed consent forms (ICF) were mailed by the specialty pharmacies to all potential study participants; those returned to the respective pharmacies initiated the enrollment process. The TOP MS study was registered with ClinicalTrials.gov (NCT00819000).

2.2. Inclusion and exclusion criteria

TOP MS inclusion criteria included males and females, 18 years of age or older, with a diagnosis of MS and a DMT prescription dispensed by a participating specialty pharmacy between 2008 and 2010. Eligible patients had to be treated with approved doses of glatiramer acetate (GA; Copaxone, Teva Pharmaceuticals, USA, Inc., North Wales, PA), interferon β-1b (IFNβ-1b; Betaseron, Bayer Healthcare Pharmacueticals, Inc., Montville, NJ), interferon β-1a (IFNβ-1a Intramuscular [IM]; Avonex, Biogen Idec, Inc., Cambridge, MA or IFNβ-1a Subcutaneous [SC]; Rebif, EMD Serono, Inc., Rockland, MA). During the 2-year follow-up, patients could change to natalizumab injection (NZ; Tysabri, Elan Pharmaceuticals, Inc., South San Francisco, CA), IFNβ-1b (Extavia, Novartis AG, Novartis Pharmaceutical Corporation, East Hanover, NJ) or fingolimod (FG; Gilenya, Novartis Pharmaceutical Corporation, East Hanover, NJ) and remain in the study.

Exclusion Criteria for TOP MS included: 1) any condition that might interfere with participation or with assessments for the 24-month follow-up; 2) any contraindication to GA or IFN-β therapy, including pregnancy, trying to become pregnant or breast feeding; and 3) receiving any experimental drug in the 30 days prior to enrollment.

2.3. Study procedures

Potential participants for TOP MS were recruited by specialty pharmacies providing services throughout the United States. Patients expressing interest in the study received mailed copies of the ICF explaining the procedures.

TOP MS used electronic data capture. Enrollment produced log-on instructions for the study website where responses were entered by participants monthly throughout