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Lack of magnetic resonance imaging lesion activity as a treatment target in multiple sclerosis: An evaluation using electronically collected outcomes

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ABSTRACT

Background: The appropriate treatment target in multiple sclerosis (MS) is unclear. Lack of magnetic resonance imaging (MRI) lesion activity, a component of the no evidence of disease activity concept, has been proposed as a treatment target in MS. We used our MS database to investigate whether aggressively pursuing MRI stability by changing disease modifying therapy (DMT) when MRI activity is observed leads to better clinical and imaging outcomes.

Methods: The Knowledge Program (KP) is a database linked to our electronic medical record allowing capture of patient and clinician reported outcomes. Through KP query and chart review, we identified all relapsing-remitting MS patients visiting between 1 January 2008 and 31 December 2014 with active MRIs despite DMT. Propensity modeling based on demographic and disease characteristics was used to match DMT switchers to non-switchers. KP and MRI outcomes were compared 18 months after the active MRI using mixed-effects linear regression models.

Results: We identified 417 patients who met criteria for our analysis. After propensity matching, 78 switchers and 91 non-switchers were analyzed. There was no difference in clinical or radiologic outcomes between these groups at 18 months.

Conclusions: We did not find a short-term benefit of changing DMT to pursue MRI stability.

1. Introduction

Multiple sclerosis (MS) is characterized by inflammatory demyelination and neurodegeneration in the central nervous system. Thirteen disease modifying therapies (DMTs) have regulatory approval to treat relapsing-remitting multiple sclerosis (RRMS), and several other therapies are in late-stage development (Dorr and Paul, 2015). The expanding range of MS treatment options, including highly effective agents, has led some to propose complete remission from RRMS, termed no evidence of disease activity (NEDA), as a treatment target (Havrdova et al., 2010). Operationally, NEDA has been defined as the absence of relapses, disability progression, new or enlarging (N/E) T2 lesions, and gadolinium enhancing (GdE) lesions. Additional disease status metrics, most notably brain atrophy $< 0.4\%$ per year, are sometimes included as part of the NEDA definition (Stangel et al., 2015; Montalban et al., 2015). A key strategy when treating to a NEDA target is to switch DMT when breakthrough disease occurs in the hope that a different treatment will be more effective.

A number of studies have investigated the benefits of changing DMT when breakthrough disease occurs (Carra et al., 2008; Castillo-Trivino et al., 2011; Gajofatto et al., 2009; Healy et al., 2010; Portaccio et al., 2009; Putzki et al., 2009; Rio et al., 2012). Treatment switches have generally been reported to have a positive effect on annualized relapse rate, with the exception of switching from natalizumab (Havla et al., 2011). Switching studies have typically focused on annualized relapse rates and have not reported on radiologic or other clinical metrics after treatment alteration. Further, the definition of breakthrough disease has been variable and has not necessarily required complete MRI lesion stability.

Abbreviations: MS, multiple sclerosis; DMT, disease modifying therapy; RRMS, relapsing-remitting MS; NEDA, no evidence of disease activity; N/E, new or enlarging; GdE, gadolinium enhancing; KP, knowledge program; EQ-5D, European Quality of Life 5-Dimensions; PS, Performance Scales; PHQ9, Patient Health Questionnaire 9; T25FW, Timed 25 Foot Walk; MRI, magnetic resonance imaging; GA, glatiramer acetate; IFN, interferon; IM, intramuscular; DMF, dimethyl fumarate; SC, subcutaneous; MM, mycophenolate mofetil; Stan Diff, standardized difference; SD, standard deviation; t_0, time of first active MRI

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Datasets such as Cleveland Clinic's Knowledge Program (KP), which is linked to our electronic medical record and includes patient and clinician reported outcomes, may be helpful in better understanding the utility of MRI quiescence as a treatment target in clinical practice. We utilized the KP to assess the hypothesis that treatment to a strict target of MRI lesion stability, with DMT alteration in the presence of any breakthrough disease, would lead to better clinical and imaging outcomes.

2. Methods

2.1. Patient population

The Mellen Center is a tertiary referral center for MS care at Cleveland Clinic. The KP is a Cleveland Clinic initiative to electronically collect patient and clinician reported outcomes at each clinical encounter (Katzan et al., 2011). Data collection began in 2007 and we have accumulated single-visit or longitudinal data on more than 16,000 patients. Prior to their visit, patients complete the European Quality of Life 5 Dimensions (EQ-5D) (Gottberg et al., 2006), Performance Scales (PS) (Schwartz et al., 1999; Marrie and Goldman, 2007), and Patient Health Questionnaire 9 (PHQ9) (Spitzer et al., 1999). Clinicians later record the Timed 25 Foot Walk (T25FW) (Rudick et al., 2002), as well as data related to the disease course and treatment. Unfortunately, relapse data and expanded disability status scale (Kurtzke et al., 1979) (EDSS) scores are not available in the KP.

The protocol was approved by our local institutional review board. The KP database was queried for patients 18 years of age or older who had RRMS and visited the Mellen Center between 1 January 2008 and 31 December 2014. We also required patients to have been on DMT during this timeframe and to have had at least two KP entries occurring at least 12 months apart.

2.2. Data acquisition

A chart review was performed on the resulting list of patients. Reports from magnetic resonance imaging (MRI) studies done after 1 January 2008 were reviewed, and the numbers of N/E T2 lesions and GdE lesions were recorded for each scan. The MRIs were ordered by the patients' clinicians and were used in real-time for assessment of disease status. The images were directly reviewed if the radiology report was ambiguous or did not specify the necessary information. The reviewer was blinded to whether the patient was a switcher or non-switcher at the time of the MRI assessment.

The charts of individuals with active MRIs were further examined to determine start and stop dates for each DMT the patient had taken. At the Mellen Center, each clinical note is prefaced with a header that specifies this information. For cases where the header was incomplete, the chart notes and medication record were reviewed in detail. To qualify for the analysis, the patient must have been on DMT for six months prior to their active MRI.

The resulting dataset was then scrutinized to determine which patients had sufficient data for the analysis. In order to qualify for the clinical analysis, the patient must have had a KP entry within ± 6 months of their active MRI (t_0) and also within ± 6 months of the time point 18 months after their active MRI. Similarly, to qualify for the radiologic analysis, an MRI within ± 6 months of the 18 month time point was required.

The medication data of the remaining patients was then examined and each patient was classified as either a "switcher" or "non-switcher" according to whether DMT was altered within 6 months of their active MRI. Treatment switches, if any, were made at the discretion of the treating neurologist. The progress notes of the switchers were reviewed to determine if disease activity was the reason for the switch. Switchers whose treatment was changed for non-efficacy reasons were excluded.

2.3. Statistical methods

To account for systematic differences between switchers and non-switchers, we performed a propensity analysis. To measure covariate balance between the two groups, we computed the standardized difference for each variable, both before and after propensity score matching (Austin, 2011a). We considered standardized differences less than 10.0 in absolute value to be balanced. For each continuous variable, we also compared density plots after propensity matching to ensure similar overall distributions in each treatment group.

To obtain propensity scores, we created a mixed-effects logistic regression model where the response variable was defined by whether or not the patient switched DMT. We included the following variables as fixed effects: age (years), gender, race, marital status (married vs. not married), smoking status, primary payer, median income by zip code, time since diagnosis (years), presence or absence of GdE lesions, number of N/E T2 lesions at the time of the first active MRI (1 vs. 2 or more), time on DMT at first active MRI (months), DMT at first active MRI (interferon beta, GA, other), and PS score at first active MRI. We included a random effect for each patient's MS neurologist. Propensity score matches were made using the predicted values on the logit scale from the final model, utilizing the optmatch package (Hansen and Klopfer, 2006) in R 3.1.1 (https://www.R-project.org). Matches of similar propensity scores were made where the ratio of switchers to non-switchers was allowed to vary from 1:2 to 3:1. We used a caliper width of one-fifth the standard deviation of propensity scores on the logit scale (Austin, 2011b).

To examine whether outcomes differed 18 months after the first active MRI, we created mixed-effects linear regression models for each of the outcomes: T25FW, PS score, PHQ9 score, and EQ-5D index. For each, the response variable was the value taken at the 18-month post-active MRI visit. The independent variable was an indicator variable that was 1 for patients that switched DMT and 0 otherwise. For each outcome, we adjusted for the value at the time of the first active MRI. We included a random effect for each propensity-matched group as well as a random effect for MS neurologist because we were unable to achieve complete balance in the two groups for this variable.

2.4. Missing data

We anticipated varying amounts of missing data. For the purpose of creating the propensity score model, we used multiple imputation (Rubin, 1987) to create and analyze 10 imputed datasets. Incomplete variables were imputed under fully conditional specification (Van Buuren et al., 2006) using the default settings of the mice 2.13 package (Van Buuren and Groothuis-Oudshoorn, 2011). Model parameters were estimated with mixed-effects logistic regression applied to each imputed dataset separately. Predicted values on the logit scale were averaged over the 10 analyzed datasets to obtain the propensity scores.

3. Results

A total of 5,735 patients with RRMS and KP data entries visited the Mellen Center between 1 January 2008 and 31 December 2014. Patients who did not meet criteria for the analysis were systematically eliminated from the dataset as illustrated in the Fig. 1.

We were left with 417 patients for the propensity analysis. Of