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Review

Multiple sclerosis in the real world: A systematic review of fingolimod as a case study

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ABSTRACT

Introduction: The aim of our study was to systematically review the growing body of published literature reporting on one specific multiple sclerosis (MS) treatment, fingolimod, in the real world to assess its effectiveness in patients with MS, evaluate methodologies used to investigate MS in clinical practice, and describe the evidence gaps for MS as exemplified by fingolimod.

Methods: We conducted a PRISMA-compliant systematic review of the literature (cut-off date: 4 March 2016). Published papers reporting real-world data for fingolimod with regard to clinical outcomes, persistence, adherence, healthcare costs, healthcare resource use, treatment patterns, and patient-reported outcomes that met all the eligibility criteria were included for data extraction and quality assessment.

Results and discussion: Based on 34 included studies, this analysis found that fingolimod treatment improved outcomes compared to the period before treatment initiation and was more effective than interferons or glatiramer acetate. However, among studies comparing fingolimod with natalizumab, overall trends were inconsistent: some reported natalizumab to be more effective than fingolimod and others reported similar effectiveness for natalizumab and fingolimod. These studies illustrate the challenges of investigating MS in the real world, including the subjectivity in evaluating some clinical outcomes and the heterogeneity of methodologies used and patient populations investigated, which limit comparisons across studies. Gaps in available real-world evidence for MS are also highlighted, including those relating to patient-reported outcomes, combined clinical outcomes (to measure overall treatment effectiveness), and healthcare costs/resource use.

Conclusions: The included studies provide good evidence of the real-world effectiveness of fingolimod and highlight the diversity of methodologies used to assess treatment benefit in clinical practice. Future studies could address the evidence gaps found in the literature and the challenges associated with researching MS when designing real-world studies, assessing data, and comparing evidence across studies.

Contents

Abbreviations: AHSCT, autologous hematopoietic stem cell transplant; ARR, annualized relapse rate; BVL, brain volume loss; DMT, disease-modifying therapy; EDSS, Expanded Disability Status Scale; GA, glatiramer acetate; HRQoL, health-related quality of life; IFN, interferon; MS, multiple sclerosis; NA, not applicable; NEDA, no evidence of disease activity; NS, not significant; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRO, patient-reported outcome; RCT, randomized controlled trial; RRMS, relapsing–remitting multiple sclerosis; RWD, real-world data; SR, systematic review.

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1. Introduction

In multiple sclerosis (MS) research, randomized controlled trials (RCTs) have demonstrated the efficacy of MS treatments according to relapses, disability, and magnetic resonance imaging (MRI) outcomes, and in some cases according to patient-reported outcomes (PROs) [1–3]. The protocol-driven approach to data generation in RCTs provides high-quality evidence in a carefully selected group of patients who are treated under ideal, controlled conditions [3,4]. In the real world, however, the population of patients with MS who are eligible to receive disease-modifying therapies (DMTs) is much more heterogeneous than that treated in RCTs [4], and patient medication-taking behavior and patient monitoring are not constrained by protocol [4,5]. These factors can influence clinical outcomes, and as a result, data generated from RCTs may not be generalizable to the clinical practice setting [4,6].

Real-world studies complement RCTs by investigating a more diverse group of patients than those included in clinical trials, providing real-world data (RWD) that can be generalized across the population of patients with MS who are treated and monitored according to standard clinical practice [4]. Real-world studies are often observational in nature, and can collect RWD prospectively during routine patient visits or retrospectively from existing data sources, such as patient registries, medical records, or administrative claims databases [4,7]. Medical records and registries generally report clinical information collected by physicians [7]. Conversely, administrative claims databases, which capture diagnosis codes and payment data for the insured population, may require proxy measures to identify patients with MS and certain clinical outcomes, such as relapses [7–10]. RWD expand the evidence base for MS, give insight into the short-term and long-term safety and effectiveness of DMTs for MS as well as patient persistence with, and adherence to, therapies in clinical practice, and can provide insight into healthcare resource use and costs that are often not measured in RCTs [3,4,7,11].

Injectable, infusible, and oral therapies, which can have different mechanisms of action, are approved to treat patients with MS, and several new treatments are in development [1,12]. A need therefore exists to understand the comparative benefits of different DMTs in this complex and evolving landscape. Fingolimod (Gilenya®, Novartis Pharma AG, Basel, Switzerland), the first oral therapy approved to treat relapsing MS, has demonstrated efficacy in reducing relapses, delaying disability progression, and improving MRI and brain volume loss (BVL) outcomes in phase 3 RCTs compared with placebo or intramuscular interferon (IFN) beta-1a [13–16]. There is also a growing body of RWD being generated for fingolimod in clinical practice from administrative claims databases, MS registries, and patient records [3]. Using fingolimod as a case study, our aim was therefore to systematically review the published literature presenting RWD for this DMT, to assess effectiveness, and to explore the methodologies and data sources used to assess MS treatments in clinical practice. A similar approach could be used to assess the body of RWD for other DMTs being used to treat MS in clinical practice.

Various aspects of MS have already been reviewed, including disease biomarkers and the role of inflammation and neurodegeneration in fatigue [17–19]. In this review, we evaluate the RWD for fingolimod for several effectiveness outcomes of interest (clinical outcomes, treatment persistence/adherence, healthcare costs, healthcare resource use, treatment patterns, and PROs), grouping studies into those that assess outcomes after fingolimod initiation (including fingolimod single-arm studies) or according to the DMT against which fingolimod was assessed. We present the diverse range of methodologies and data sources being used to investigate MS in clinical practice, the challenges of investigating MS in the real world, and the evidence gaps, as exemplified by fingolimod [5]. Finally, we conclude with a summary of our