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Real-world persistence with fingolimod for the treatment of multiple sclerosis: A systematic review and meta-analysis

Daniel Kantor[a,*], Kristen Johnson[b], Maria Cecilia Vieira[b], James Signorovitch[c], Nanxin Li[c], Wei Gao[c], Valerie Koo[c], Emilie Duchesneau[c], Vivian Herrera[b]

[a] Kantor Neurology, 4851 W Hillsboro Blvd, Coconut Creek, FL 33073, USA
[b] Novartis Pharmaceuticals Corporation, 1 Health Plaza, East Hanover, NJ 07936, USA
[c] Analysis Group, Inc., 111 Huntington Ave 14th Floor, Boston, MA 02199, USA

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ABSTRACT

Objective: To systematically review reports of fingolimod persistence in the treatment of relapsing-remitting multiple sclerosis (RRMS) across data sources and practice settings, and to develop a consensus estimate of the 1-year real-world persistence rate.

Methods: A systematic literature review was conducted (MEDLINE, EMBASE, and abstracts from selected conferences [2013–2015]) to identify observational studies reporting 1-year fingolimod persistence among adult patients with RRMS (sample size ≥ 50). A random-effects meta-analysis was performed to estimate a synthesized 1-year persistence rate and to assess heterogeneity across studies.

Results: Of 527 publications identified, 25 real-world studies reporting 1-year fingolimod persistence rates were included. The studies included patients from different data sources (e.g., administrative claims, electronic medical records, or registries), used different definitions of persistence (e.g., based on prescriptions refills, patient report, or prescription orders), and spanned multiple geographic regions. Reported 1-year persistence rates ranged from 72%–100%, and exhibited statistical evidence of heterogeneity (I^2 = 93% of the variability due to heterogeneity across studies). The consensus estimate of the 1-year persistence rate was 82% (95% confidence interval: 79%–85%).

Conclusions: Across heterogeneous study designs and patient populations found in real-world studies, the consensus 1-year fingolimod persistence rate exceeded 80%, consistent with persistence rates identified in the recently-completed trial, PREFER*MS*.

1. Introduction

Multiple sclerosis (MS) is a chronic, progressive neurological disease caused by immune-mediated inflammatory damage to neurons' myelin [1]. The most common form, relapsing-remitting multiple sclerosis (RRMS), affects approximately 80–85% of patients with MS in the United States (US) [2,3]. Progressive damage to the central nervous system from relapses and incomplete remissions can result in clinical disability [4,5]. The main objectives of treatment are to avoid temporary disability, delay disease progression leading to permanent disability, and manage symptoms [6]. Disease-modifying therapies (DMTs) for RRMS have been demonstrated to be effective in delaying disease progression by reducing the frequency, severity, and duration of relapses [7–10], and can improve long-term outcomes for patients with RRMS [11,12]. However, the progressive nature of this disease makes long-term patient adherence to treatment of high importance in order to maintain treatment effectiveness [13].

In 2010, fingolimod, a sphingosine 1-phosphate receptor modulator, was the first US Food and Drug Administration-approved oral DMT for RRMS [14]. The safety and efficacy of fingolimod have been demonstrated in three pivotal Phase III clinical trials: the FREEDOMS and FREEDOMS II [15,16] and the TRANSFORMS trials [17]. The recently-completed 1-year Phase IV randomized, open-label PREFER*MS* trial expanded upon these trials and assessed treatment persistence of fingolimod as well as injectable DMTs among patients with RRMS [18,19]. At 12 months, 81.3% of the 852 RRMS patients who were randomly assigned to fingolimod stayed on fingolimod. The findings of the PREFER*MS* trial regarding the persistence rate with fingolimod are supported by a number of observational studies reporting similar results. For example, three recently completed real-world studies based on a retrospective chart review of a medical center in the US, a US commercial insurance claims database, and a patient registry in Sweden

* Corresponding author.
E-mail address: dkantor@kantorneurology.com (D. Kantor).

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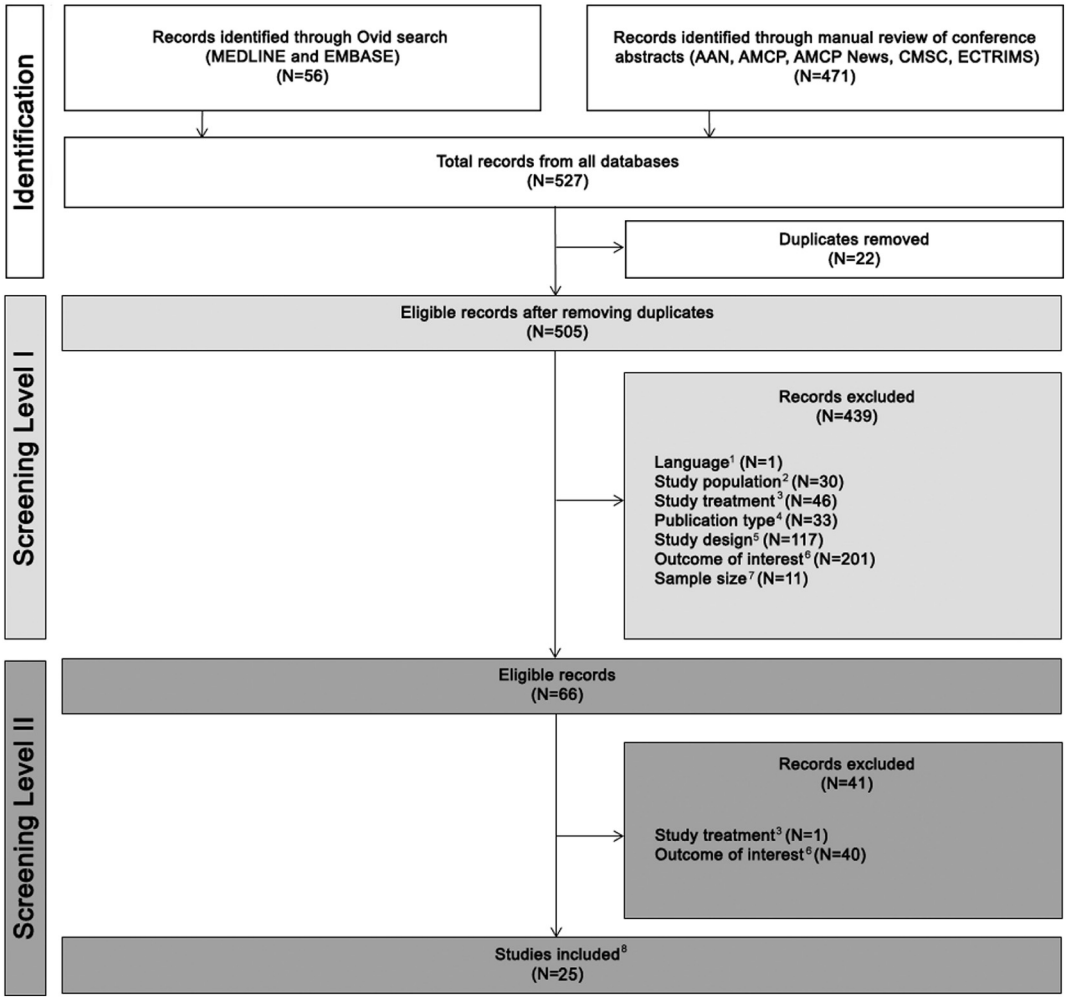

Fig. 1. PRISMA diagram for 1-year fingolimod persistence.

Abbreviations: AAN = American Academy of Neurology annual meeting; AMCP = Academy of Managed Care Pharmacy annual meeting; CMSC = Consortium of Multiple Sclerosis Centers annual meeting; ECTRIMS = European Committee for Treatment and Research in Multiple Sclerosis annual meeting.

Notes:

[1] Language: Studies that were not in English (level I: N = 1) were excluded.

[2] Study population: Studies in non-human populations (level I: N = 24), non-multiple sclerosis populations (level I: N = 2), and pediatric populations (level I: N = 4) were excluded.

[3] Study treatment: Studies that did not consider fingolimod (level I: N = 46; level 2: N = 1) were excluded.

[4] Publication type: Case reports (level I: N = 16), commentaries (level I: N = 1), guidelines and recommendations (level I: N = 3), reviews (level I: N = 12), and meta-analyses (level I: N = 1) were excluded.

[5] Study design: Economic studies (level I: N = 10) and clinical trials (level I: N = 107) were excluded.

[6] Outcome of interest: Studies that did not report persistence (level I: N = 201; level II: N = 10) and studies that reported persistence not evaluated at 1 year (level II: N = 30) were excluded.

[7] Sample size: Studies that reported 1-year fingolimod persistence in samples of < 50 patients with multiple sclerosis (level I: N = 11) were excluded.

[8] Sources of included studies: MEDLINE (N = 7), EMBASE (N = 1), conference abstracts (N = 17). One study (Hersh [49]) was excluded during the level II screening because only a conference abstract was available and it did not report the outcome of interest. This study was added back later when the full text manuscript became available which reported the outcome of interest.

reported the 1-year fingolimod persistence rates to be 81.1% [20], 79.1% [21], and 83% [22], respectively.

To our best knowledge, no recent studies have systematically reviewed the real-world persistence rate with fingolimod, which would be valuable evidence to augment persistence findings reported in clinical trials. The purpose of this systematic literature review and meta-analysis was to assess the consistency of reported fingolimod persistence rates across practice settings and data sources, and to develop consensus estimates of 1-year fingolimod persistence rates based on real-world evidence.

2. Methods

2.1. Systematic literature review

The systematic literature review was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The search was conducted in the MEDLINE and EMBASE databases to identify observational studies reporting persistence rates with fingolimod. In addition, proceedings of annual meetings of selected multiple sclerosis, neurology, and health economic conferences were searched for potentially relevant abstracts during 2013 through 2015. The meetings included those of the American Academy of Neurology (AAN), Academy of Managed Care Pharmacy (AMCP), Academy of Managed Care Pharmacy Nexus (AMCP Nexus),