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Effectiveness and safety of natalizumab in real-world clinical practice: Review of observational studies

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ABSTRACT

Clinical trials have shown that natalizumab is highly effective for treating relapsing forms of multiple sclerosis (MS). The purpose of this analysis was to conduct a targeted review of data from country-specific observational studies and registries of natalizumab-treated patients with relapsing MS in order to more fully investigate the longer-term effectiveness and safety of this disease-modifying therapy in real-world clinical practice settings. A PubMed search was conducted on March 13, 2014, using the terms (natalizumab AND multiple sclerosis) AND (observational OR registry OR post-marketing OR clinical practice). Only English-language papers that reported effectiveness (in terms of effects on relapses, disability progression, and magnetic resonance imaging findings) and/or safety results from studies were included. Data from 22 studies/registries were included. Annualized relapse rates decreased by 73%–94% from baseline across the studies, with improvement maintained for up to 5 years during natalizumab treatment. Natalizumab effectiveness was also demonstrated via assessment of disability progression (Expanded Disability Status Scale), radiological measures, and no-evidence-of-disease-activity measures (clinical, radiological, and overall). Results were similar among patient groups stratified by level of disease activity. Safety outcomes were consistent with natalizumab's known safety profile. Data from country-specific observational studies and registries varying in size and scope support the effectiveness and safety of natalizumab in a broad range of patients in clinical practice.

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1. Introduction

Multiple sclerosis (MS) is a chronic, inflammatory, and degenerative autoimmune disease of the central nervous system that affects approximately 2.3 million people worldwide [1]. The socioeconomic burden of MS is considerable [2,3], and, over and above its detrimental health effects, MS reduces quality of life and negatively affects employment [2].

Natalizumab is a monoclonal antibody shown to significantly reduce annualized relapse rate (ARR) and the risk of 3-month confirmed Expanded Disability Status Scale (EDSS) progression relative to placebo in the phase 3 AFFIRM trial in patients with MS [4]. While randomized controlled trials like AFFIRM are considered the gold standard for evaluating interventions because of their ability to minimize or avoid bias [5], clinical trial populations may not fully represent patients treated in clinical practice. Trials often have strict inclusion and exclusion criteria and may exclude patients with certain characteristics or comorbidities. In addition, clinical trials are generally of limited duration, whereas MS is a chronic disease that requires long-term treatment. In contrast, observational studies and surveillance registries often have relatively long-term duration and can include patients who would be excluded from a clinical trial. Therefore, such studies can provide important supplementary information on the effectiveness and safety of drugs in real-world clinical practice.

A long-term, open-label, multinational, prospective study, the Tysabri Observational Program (TOP), enrolled natalizumab-treated patients in Europe, Australia, Canada, and Argentina [6]. Ninety percent of the patients in TOP were previously treated with a disease-modifying therapy (DMT) or immunosuppressant. Five-year interim results demonstrated the long-term effectiveness of natalizumab in clinical practice settings. Mean ARR was reduced from 1.99 over the year prior to baseline to 0.31 during treatment with natalizumab and remained low over 5 years [6]. Mean EDSS scores were stable. At 5 years, the cumulative probability of confirmed EDSS progression (≥1.0-point increase sustained for 6 months) was 14%, whereas the cumulative probability of confirmed EDSS improvement (≥1.0-point decrease sustained for 6 months) was 27%. Overall, 25% of patients discontinued natalizumab and 15% withdrew from TOP [6].

The purpose of this analysis was to conduct a targeted review of natalizumab data from country-specific observational studies and registries of patients with relapsing MS in order to more fully investigate natalizumab's longer-term effectiveness and safety in real-world clinical practice settings.

2. Methods

A PubMed literature search was performed for studies published through March 13, 2014 (with no limits applied). Search terms included (natalizumab AND multiple sclerosis) AND (observational OR registry OR post-marketing OR clinical practice). Only English-language articles and those that reported clinical effectiveness in terms of effects on relapses and disability progression, magnetic resonance imaging (MRI) outcomes, and/or safety outcomes from observational studies or registries of patients with relapsing MS initiating treatment with natalizumab in a clinical setting were included in the review. Papers identified by the search that reported studies only on other efficacy measures (e.g., fatigue or cognition), JC virus (JCV) or anti-JCV antibodies, diagnosis, treatment patterns, treatment persistence/adherence, anti-natalizumab antibodies, treatment with non-natalizumab agents, and cost-effectiveness analyses were excluded, as were reviews, consensus statements, and opinion pieces. A manual check of references for each article was conducted to identify additional relevant papers. Finally, further relevant publications known to the authors were included.

3. Results

3.1. Literature search

The PubMed search identified 119 records (Fig. 1), 18 of which reported effectiveness and/or safety results of observational studies or registries of patients with relapsing MS initiating treatment with natalizumab in clinical practice [7–24]. The remaining 101 papers did not meet the inclusion criteria and were excluded. Five additional reports were identified; two relevant papers were identified from the review of reference sections [25,26], and two relevant papers [27,28] and a conference presentation [29] were identified by the authors.

Of the papers, two reported similar measures for the same study at different time points [19,21]; only the most recent was included [19]. Two other papers reported different endpoints from the same study [13,25]; both of these were included and considered separate studies. Thus, data from 22 studies were reviewed (Table 1). Seven of the studies included were prospective, multicenter studies [10,11,14,15,26,28,29], 10 were retrospective [7–9,12,16,18,19,23,24,27], and eight (including some of the retrospective studies) were single-center studies [8,13,16,17,20,22,25,27]. Mean duration of follow-up ranged from 0.7 to 2.0 years, although this was not reported for all studies (Table 1).

3.2. Patient characteristics

The patient populations studied varied in size (30–3884 patients per study) and median age (range 29–41 years); across all studies, approximately 70% of patients were female (range 66%–78%) (Table 1). Fifteen of the studies were performed exclusively in relapsing patients (i.e., patients with relapsing-remitting MS, secondary progressive MS with relapses, or "active" [i.e., relapsing] MS) [7,9–18,20,22–24]. The remaining three studies primarily included relapsing patients (e.g., relapsing-remitting MS, progressive-relapsing MS, or secondary progressive MS with relapses; 79%–94%) as well as smaller proportions (6%–21%) of non-relapsing (e.g., primary progressive MS or secondary progressive MS) or nonspecified patients [8,19,21]. Taking these differences in patient populations into account, patients had a mean of approximately two relapses in the year before starting natalizumab treatment. Prior to natalizumab, mean EDSS score ranged from 2.7 to 4.8, and 36%–100% of patients had gadolinium-enhancing (Gd+) lesions (Table 1). Patients initiated natalizumab therapy because of either breakthrough disease activity on a prior DMT or aggressive disease activity, defined according to country-specific guidelines. In many studies, direct comparisons of the study population was made with that of AFFIRM, showing that patients in these studies were older (versus mean 36 years of age in AFFIRM), had a longer disease duration (versus median 5 years in AFFIRM), and had greater disease severity, as measured by ARR (mean 1.52 in AFFIRM) and EDSS score (mean 2.3 in AFFIRM) prior to starting natalizumab, even though many of these patients were transitioning from another DMT [7–11,15,29].

3.3. Clinical outcomes

Natalizumab substantially improved patients' clinical outcomes in each study. ARRs decreased from pre-natalizumab levels by 73%–94% during treatment with natalizumab [7–14,16–18,20,26,28,29], with improvement maintained for up to 5 years (Fig. 2A) [29]. During the studies, 51%–91% of patients achieved relapse-free status (Fig. 2B) [8,9,12–14,16,18,22–24,26–28]. EDSS

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