Journal of the Neurological Sciences 341 (2014) 22–27

Contents lists available at ScienceDirect

Journal of the Neurological Sciences

journal homepage: www.elsevier.com/locate/jns

Natalizumab treatment shows no clinically meaningful effects on immunization responses in patients with relapsing-remitting multiple sclerosis ☆

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ARTICLE INFO

Article history:
Received 1 November 2013
Received in revised form 4 March 2014
Accepted 18 March 2014
Available online 26 March 2014

Keywords:
Multiple sclerosis
Natalizumab
Immunization
Vaccines
Immunoglobulins
Lymphocytes
Immunity
Humoral

ABSTRACT

Natalizumab is an immunomodulatory drug approved for the treatment of multiple sclerosis. This randomized, multicenter, open-label study evaluated natalizumab's effects on immunization responses to a recall antigen (tetanus toxoid [TT]) and a neoantigen (keyhole limpet hemocyanin [KLH]) in patients with relapsing forms of multiple sclerosis (MS). Natalizumab-naive relapsing MS patients were randomized (1:1; n = 30 per group) to receive TT and KLH immunizations either without natalizumab treatment (control) or after 6 months of natalizumab treatment (natalizumab group). An adequate response to immunization was defined as an increase to at least twofold in specific serum immunoglobulin G (IgG) 28 days after the first immunization. All evaluable patients achieved protective levels of anti-TT IgG antibodies, and the proportion of responders to this recall antigen, as well as to primary immunization with KLH, was similar in the presence and absence of natalizumab. This indicates that natalizumab treatment does not appear to affect responses to primary or secondary immunization in a clinically meaningful way.

1. Introduction

Understanding immune responses with immunomodulatory therapy is important for the management of multiple sclerosis (MS) patients in clinical practice. Interferon beta-1a (Rebif®, EMD Serono Rockland, MA, USA) and teriflunomide (Aubagio®, Genzyme, Cambridge, MA, USA) do not appear to have an effect on immunization responses [1,2]. In contrast, fingolimod (Gilenya®, Novartis, East Hanover, NJ, USA) appeared to decrease the response to a pneumococcal vaccine, while responses to keyhole limpet hemocyanin (KLH) and influenza vaccines in patients treated with fingolimod were similar to or lower than responses in patients who received placebo [3–5]. In a small pilot study of patients treated with alemtuzumab (Lemtrada™, Genzyme, Cambridge, MA, USA) [6], humoral responses to recall antigens (pneumococcal vaccine and diphtheria, tetanus, and poliomyelitis vaccine) and a novel antigen (*Haemophilus influenza* type b and meningococcal group C conjugate vaccine) were consistent with historical controls. However, compared with patients who were vaccinated at least 6 months after alemtuzumab treatment, response was achieved in a smaller proportion of patients who were vaccinated within 6 months of treatment [7]. To our knowledge, no immunization data are currently available for glatiramer acetate (Copaxone®, Teva Neuroscience, Kansas City, MO, USA), mitoxantrone (Novantrone®, EMD Serono, Inc, Darmstadt, Germany), or dimethyl fumarate (Tecfidera™, Biogen Idec, Cambridge, MA, USA). With respect to natalizumab (Tysabri®, Biogen Idec, Cambridge, MA, USA), one report showed no decrease in the response to influenza vaccination [8].

Natalizumab, an established therapy for MS and Crohn's disease, is a recombinant humanized monoclonal antibody (Ab) that inhibits binding of the α4 subunit of the α4β1 and α4β7 integrins on mononuclear leukocytes to their endothelial receptors and prevents trafficking of mononuclear leukocytes across vascular endothelium [9–11]. Treatment with natalizumab has been associated with herpes infections as well as with progressive multifocal leukoencephalopathy [9,12–14].

Both de novo Ab responses to neoantigens (primary responses) and recall responses to memory antigens (secondary responses) involve

☆ Portions of this work were presented at the 63rd (2011) Annual Meeting of the American Academy of Neurology.

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http://dx.doi.org/10.1016/j.jns.2014.03.035
0022-510X/

activation of antigen-specific T and B cells in secondary lymphoid tissues [15]. While human and animal studies have shown that natalizumab increases the number of circulating lymphocytes, possibly due to trafficking effects [12,16–20], animal studies have not shown a significant effect of α4-integrin blockade on T and B cell trafficking into most lymphoid tissues [21]. Nonhuman primate studies have shown no significant effect of natalizumab on primary or secondary Ab responses [20]; however, it is important to evaluate its effects on primary and secondary immune responses in patients.

Owing to the potential effects of α4-integrin blockade by natalizumab on lymphocyte trafficking through primary and secondary lymphoid organs, it is important to provide additional data on the impact of natalizumab therapy on vaccination response in MS patients [21].

The objective of this study was to evaluate the effect of natalizumab on T-cell-dependent Ab responses to a recall antigen (tetanus toxoid [TT]) and to a neoantigen (keyhole limpet hemocyanin [KLH]) in patients with relapsing forms of MS. TT was used in this United States (US) study to assess recall Ab responses, as the majority of the US population receive childhood TT immunizations [22]. KLH, a strongly immunogenic protein isolated from the giant keyhole limpet, was used to assess primary immunization responses [23].

2. Materials and methods

2.1. Study design

In this phase 4, randomized, multi center, open-label study, eligible MS patients, naive to natalizumab, were randomized (1:1) to receive TT and KLH immunizations either 2 months prior to natalizumab treatment or after 6 months of natalizumab treatment (Fig. 1). Patients enrolling in the study agreed to delay treatment with natalizumab for approximately 2 months if randomized to the control/immunization-only group. All nine US sites used an interactive voice response system to randomize patients at the baseline visit. Randomization was stratified by site. Planned enrollment was approximately 46 patients; 23 patients per group.

The study protocol and amendments were reviewed and approved by each site's institutional review board. The study was performed in accordance with the Declaration of Helsinki and International Conference on Harmonisation Guideline on Good Clinical Practice and is registered with ClinicalTrials.gov, number NCT00536120.

2.2. Patients

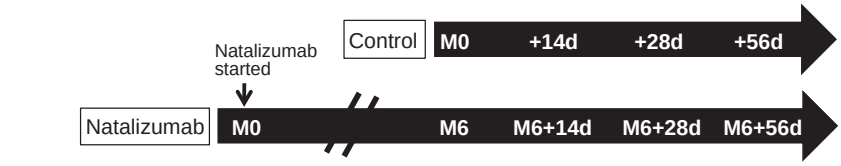
Patients 18–60 years old who were diagnosed with a relapsing form of MS, eligible to receive natalizumab per approved labeling, and previously vaccinated against TT were eligible for the study. Written informed consent was obtained from each patient prior to evaluations performed for eligibility. Exclusion criteria included the following: [1] TT immunization <2 years prior to screening, [2] hypersensitivity to TT, KLH, or other immunizations or their components [3], significant infectious illness within 30 days prior to screening [4], prior treatment with natalizumab, rituximab, any murine protein, or any therapeutic monoclonal Ab [5], treatment with cyclophosphamide within 1 year prior to screening [6], treatment with intravenous (i.v.) or intramuscular (i.m.) immunoglobulin (Ig), or immunosuppressant medications within 6 months prior to screening [7], treatment with systemic corticosteroids within 4 weeks prior to screening, and [8] treatment with immunomodulatory medications (interferon-β and glatiramer acetate) within 2 weeks prior to screening.

2.3. Interventions

Patients randomized to natalizumab treatment prior to immunization (natalizumab group) received natalizumab, 300 mg i.v. every 4 weeks for 6 months, starting at the baseline visit, and received immunizations after the seventh natalizumab infusion. Natalizumab treatment continued for 2 months after the first immunization during which their immune responses were measured. Patients randomized to the control group received immunizations beginning at the baseline visit and their immune responses were measured over the following 2 months. Both groups received a single intramuscular TT vaccine administered per approved label at the investigational site and both groups received three subcutaneous Immucothel® (KLH) (Biosyn Arzneimittel AG, Fellbach, Germany) vaccines, each separated by 2 weeks (Fig. 1). KLH was supplied by Biogen Idec. The first TT and KLH vaccines were given on the same day. For patients randomized to the natalizumab group, samples for Ab assessments were collected prior to natalizumab infusion, and all immunizations were administered after completion of the 1-hour natalizumab post-dosing observation period. All eligible patients from both groups could enroll in TYSABRI® Outreach: Unified Commitment to Health (TOUCH®) after the study ended.

2.4. Antibody measurement

TT and KLH Ab levels were measured using an enzyme-linked immunosorbent assay by Focus Diagnostics (Cypress, CA, USA). The upper limit of detection for the anti-TT Ab assay was 7.0 IU/mL in this clinical assay, which is not validated for diluted samples.



TT vaccine		X			
TT Ab assay	X	X		X	X
KLH vaccine		X	X	X	
KLH Ab assay	X	X	X	X	X

Fig. 1. Study design. Patients were randomized 1:1 to the control group or natalizumab group. Control group patients received immunizations shortly after randomization and agreed to delay initiation of natalizumab until after day +56; patients randomized to natalizumab were treated with natalizumab for 6 months prior to immunizations. In the natalizumab group, baseline levels were drawn at month 0 prior to the initiation of natalizumab therapy. Blood for pre-immunization anti-KLH and anti-TT Ab levels was drawn just prior to the first immunization in both groups; baseline and pre-immunization time points are equivalent in the control group. Patients received three KLH immunizations separated by 2 weeks, and one TT immunization. A pre-planned assessment of anti-KLH Ab levels occurred at 14 days (after one KLH immunization), 28 days (after two KLH immunizations), and 56 days (after three immunizations) after first immunization. A pre-planned assessment of anti-TT Ab levels occurred at 28 days and post hoc at 56 days after the first (only) immunization. M: month; d: days; KLH: keyhole limpet hemocyanin; TT: tetanus toxoid; Ab: antibody.