Multiple Sclerosis and Related Disorders (2014) 3, 244–252

Available online at www.sciencedirect.com

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

Effects of rituximab on lymphocytes in multiple sclerosis and neuromyelitis optica

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Received 18 July 2013; received in revised form 8 October 2013; accepted 9 October 2013

KEYWORDS
Multiple sclerosis;
Demyelinating diseases;
Immunology;
Rituximab;
Monoclonal antibodies;
Neuromyelitis optica

Abstract
Objective: To investigate the effect of rituximab, a B-cell targeted therapy that is used in the treatment of multiple sclerosis (MS) and neuromyelitis optica (NMO), on other immune cells such as CD4+ and CD8+ T-cells in patients with MS and NMO.
Design, setting and patients: This is a retrospective study of all patients with MS or NMO who received at least one rituximab infusion at the UCSF MS tertiary care center between May 2005 and July 2011.
Main outcome measures: Linear mixed models were used to assess (a) how post-infusion cell counts changed over time compared to pre-infusion levels and one another; (b) whether the cell counts were different over multiple courses of rituximab; and (c) what was the dosing effect on the cell counts over time.
Results: Rituximab initially reduced CD4+ (by 26%, $p=0.0005$) and CD8+ (by 22%, $p=0.0006$) T-cells, although these changes were only transient. Subsequent treatments with rituximab did not result in a significant drop in CD4+ or CD8+ T-cells. Changes in other cell types were also typically more marked after the first cycle of rituximab than after additional treatments. The total dose of rituximab received did not appear to have a significant effect.

Abbreviations: MS, multiple sclerosis; NMO, neuromyelitis optica; NK, natural killer cells; EDSS, expanded disability status scale; WBC, white blood cells

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2211-0348/$ - see front matter
http://dx.doi.org/10.1016/j.msard.2013.10.003

Conclusions: Although transient, rituximab-induced decrease in CD4+ and CD8+ T-cells may increase the risk of infection in susceptible individuals.

1. Introduction

As recent data support that B-lymphocytes play a critical role in the pathophysiology of multiple sclerosis (MS) and neuromyelitis optica (NMO) (Archelos et al., 2000; Avasarala et al., 2001; Baranzini et al., 1999; Colombo et al., 2000; Cree et al., 2005; Duddy and Bar-Or, 2006; Genain et al., 1999; Lehmann-Horn et al., 2011; Polman et al., 2005) specific therapies targeting B-cells have been studied to treat both (Cree et al., 2005; Lehmann-Horn et al., 2011). One such drug is rituximab, a monoclonal antibody against CD20 that produces a rapid, profound, and long-lasting depletion of peripheral B-cells (Anderson et al., 1997; Bar-Or et al., 2008; Cragg et al., 2005; Cross et al., 2012; Kitsos et al., 2012; Meinl et al., 2006; Naismith et al., 2010; Reff et al., 1994). Data from MS trials suggest that its therapeutic effect is mediated through antibody-independent pathways (Hauser et al., 2008).

In contrast with its known effect on B-cells, the impact of rituximab on other immune cell types has not been carefully studied. Specifically, the impact of B-cell depletion on T-cells is of particular interest given that both interact closely.

The primary goal of this study is to improve our understanding of the effect of rituximab on other cell types such as CD4+ and CD8+T-cells and natural killer (NK) cells in patients with MS and NMO. Such information may help to better appreciate the safety profile of rituximab and provide a deeper understanding of the roles of B- and T-cells in various pathologies.

2. Materials and methods

2.1. Study design

This is a retrospective study of all patients who received at least one infusion of rituximab at the UCSF MS Center between May 2005 and July 2011. Rituximab treatment is most routinely administered as two separate infusions two weeks apart (a.k.a. cycle). Patients considered for inclusion were treated by different providers and the most common prescribing regimen changed over the time period of study. The earliest prescriptions were 375 mg/m^2 once weekly for four doses (4.9%), the majority (72%) were 1 g two weeks apart, and some (13%) were two doses 500 mg two weeks apart. Of the remaining patients screened for inclusion, one patient received 1 g followed by 500 mg two weeks apart and several had only one infusion (single dose 1000 mg, n=11; 500 mg, n=8). For simplicity, we grouped the doses into <2 g and ≥ 2 g per cycle. Our center recommends obtaining blood cell counts for CD19+, CD3+, CD4+, CD8+, CD56+/CD16+ cells and IgG and IgM levels at baseline. After treatment initiation, cell counts are monitored every 3 months and Ig levels annually in order to monitor biological efficacy and safety of rituximab. Laboratory tests were performed either at local laboratories or at UCSF. Re-dosing is typically considered yearly, based on tolerability and efficacy of prior treatment. For the present study, patients were identified through the UCSF MS center database and the charts of all patients who were prescribed rituximab were reviewed. Only patients who received at least one infusion of rituximab and had both pre- and post-first infusion laboratory test results available were included in this study. Demographic and clinical data, date and dose of infusions, and pre- and post-infusion laboratory results were collected. This study was approved by the UCSF institutional review board. The Board approved waiver of informed consent given minimal risk to subjects by retrospective design.

The following data were collected when available: cell counts (cells/μl) for CD19+, CD3+, CD4+, CD8+, CD56+/CD16+ cells, date of birth, date of disease onset, type of MS at the time of rituximab dosing, use of disease-modifying therapy including pulse steroids before and during rituximab therapy, date and type of relapses, and Expanded Disability Status Scale (EDSS) scores at baseline (i.e. during the visit preceding rituximab dosing) and after each rituximab cycle. A relapse was defined as the acute onset of new or previously experienced symptoms lasting at least one day, in the setting of previous clinical stability, excluding pseudo-exacerbations (Fay et al., 2012; Olsson and Link, 1973). EDSS scores were characterized as improved or worsened if there was a decrease or increase, respectively, of post-infusion EDSS scores by 0.5 point compared to before rituximab infusion (Kurtzke, 1983). The development of any adverse effects after rituximab, such as urinary tract infections or opportunistic infections, was also recorded.

2.2. Definition of laboratory tests

Because in some instances subsequent infusions of rituximab were administered before return of B-cell counts to normal (Morbach et al., 2010), baseline cell counts before any injection of rituximab was used as an individual's baseline. Post-infusion laboratory tests included all results available in patients' charts before the next rituximab dosing. Due to the irregular schedule at which laboratory tests were obtained, post-infusion tests were categorized based on the duration between the most recent rituximab treatment and the date of available post-infusion blood tests: 0–3 months (P1), 4–6 months (P2), 7–9 months (P3), 10–12 months (P4) and >12 months (P5) after rituximab treatment.

2.3. Patients with multiple rituximab cycles

For patients who received multiple cycles of rituximab, post-infusion data were compared with pre-infusion data