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ORIGINAL ARTICLE

Safety of biologic agents after rituximab therapy in patients with rheumatoid arthritis

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Abstract The safety of other biologic therapies in rheumatoid arthritis (RA) following B cell-depletion therapy with rituximab has not been established. This retrospective chart review of patients attending an outpatient rheumatology clinic aimed to assess the incidence of adverse events in patients receiving biologic agents to treat RA after an inadequate response or intolerance to rituximab. The charts of 22 patients (18 female; mean age 59 years) were reviewed. Duration of RA was >2 years. Before rituximab, patients had failed one ($n = 10$), two ($n = 4$) or three ($n = 7$) biologic therapies: 1 patient started on rituximab as a first-line biologic. Eighteen patients stopped rituximab due to an inadequate clinical response, while four patients stopped due to adverse events. The mean time to starting a new biologic after rituximab was 4 months, although five patients were started within 1 month of the last rituximab infusion. Abatacept (41%) was the most common biologic used after rituximab. The mean follow-up time from the last rituximab infusion was 14 months. Adverse events occurring after rituximab therapy, but before initiation of a new biologic, included disseminated herpes zoster and aseptic meningitis (both required hospitalization). Adverse events recorded after starting a new biologic post-rituximab included rash, carbuncle, upper respiratory tract infection, urinary tract infection, pneumonia, and eczema, but none was classified as serious. Most of these events occurred in patients receiving abatacept. In conclusion, in this retrospective analysis, no serious adverse events were recorded in patients who received biologic agents following rituximab therapy.

Keywords B cell · Biologic therapy · Rheumatoid arthritis · Rituximab · Safety

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Introduction

Rheumatoid arthritis (RA), a systemic autoimmune disease characterized by chronic inflammation of the joints, affects approximately 1% of the Caucasian population and is associated with functional disability and a decreased life span [1]. The development of targeted biologic therapies, such as antitumor necrosis factor-α (anti-TNF-α) agents, represented a substantial advance in the treatment of RA. Even so, 25–40% of patients fail to respond to or become refractory to treatment with TNF inhibitors [2–4].

Treatment options for patients with an inadequate response to TNF inhibitors include rituximab, a genetically engineered monoclonal antibody that targets CD20-positive B cells [5, 6]. Rituximab is given as a course of two infusions of 1,000 mg, 2 weeks apart, and is licensed for use in combination with methotrexate in adults with moderate-to-severe active RA who have responded inadequately to one or more TNF inhibitors. In patients who develop an inadequate response to rituximab after one or more courses, further treatment options are limited, and many physicians return to biologic agents; in most cases, TNF inhibitors or abatacept. Given the long-lasting effects

of rituximab on B cell levels and the potential for protracted effects on the host immune defense system [7], there are some concerns that the use of a new biologic agent against a background of prior rituximab therapy may present an additional safety risk to the patient [8]. To investigate the safety of biologic therapy in patients who previously received and developed an inadequate response to rituximab therapy, we conducted a retrospective chart review of patients at a single US center.

Methods

The study was a retrospective chart review of patients with RA who received at least one infusion of rituximab and were then switched to another biologic agent (etanercept, adalimumab, infliximab, or abatacept) during a 2-year period (June 2006 to July 2008). All patients attended an outpatient rheumatology clinic affiliated to a community hospital near Philadelphia, PA, USA. Data collected included demographic information, duration of RA, and antirheumatic drugs used. Detailed information was collected on any adverse event reported during the study period.

Results

Charts were reviewed from 22 patients, of whom 18 (82%) were female. The mean (±SD) age of the patients was 59 ± 13 years, and all patients had RA of >2 years' duration. All but one patient had failed at least one biologic therapy before starting rituximab therapy (10, 4, and 7 patients had failed 1, 2, and 3 biologics, respectively).

Most patients ($n = 16$) had received a single course of rituximab (2 × 1,000 mg infusions given 2 weeks apart). Three patients had received two courses, and one patient was unable to complete a third course due to the development of aseptic meningitis following the first infusion of that course. The remaining two patients stopped rituximab after the first infusion of the first course due to adverse events (one case each of acute hypertensive reaction and cellulitis).

The reason for stopping rituximab therapy was inadequate clinical response in 18 patients and adverse events in the remaining four patients. Adverse events recorded during rituximab treatment, but before initiation of a new biologic, are listed in Table 1. Two events required hospitalization: one case of aseptic meningitis that occurred 1 week following the first rituximab infusion of Course 3 and one case of disseminated herpes zoster that occurred 1 month after the second rituximab infusion of Course 2. The patient with aseptic meningitis required hospitalization but improved with symptomatic treatment and was subsequently discharged; this patient also had a history of systemic lupus erythematosus. The patient with disseminated herpes zoster was also admitted to hospital but responded to antiviral therapy before being discharged home.

New biologic therapy was initiated a mean of 4 months (range 1–12 months) after the cessation of rituximab; five patients (23%) began treatment within 1 month of their last rituximab infusion. Abatacept was the most common biologic agent used after rituximab ($n = 9$; 41%); the other biologic therapies used were etanercept ($n = 6$), adalimumab ($n = 5$), and infliximab ($n = 2$). The mean follow-up time after the last rituximab infusion was 14 months (range 7–24 months). Adverse events recorded in patients receiving biologics after rituximab are shown in Table 2. A total of seven adverse events occurred in six patients, three of whom were receiving abatacept. None of the seven adverse events recorded during this period was considered serious and none required inpatient hospitalization. Occurrence of an adverse event did not appear to be related to the number of prior rituximab courses or to the duration of the new biologic therapy. The period between the last rituximab infusion and the first dose of the new biologic varied from 1 to 12 months among patients who experienced an adverse event. Among the five patients who began treatment with a biologic within 1 month of their last

Table 1 Adverse events during rituximab treatment before initiation of new biologic therapy

Adverse event	No. of rituximab courses received	Time of onset of adverse event after last rituximab infusion	No. of biologic therapies before rituximab
Aseptic meningitis[a]	2.5[b]	1 week	1
Disseminated herpes zoster[a]	2	1 month	1
Cellulitis	0.5[c]	1 week	3
Sinusitis	1	4 months	1

[a] Patient required hospitalization

[b] Patient did not receive second infusion of third course

[c] Patient did not receive second infusion of first course

Table 2 Adverse events reported after starting a new biologic therapy

Adverse event	Biologic therapy	Duration of biologic therapy before onset of adverse event (months)	No. of rituximab courses received	Time from last rituximab infusion to first dose of biologic (months)	No. of biologic therapies before rituximab
Rash (erythema nodosum)	Etanercept	5	2.5[a]	4	1
Carbuncle	Abatacept	9	1	3	2
Urinary tract infection	Adalimumab	1	0.5[b]	1	1
Upper respiratory tract infection	Abatacept	1	1	4	1
	Abatacept[c]	1	0.5[b]	12	3
Pneumonia	Abatacept[c]	5	0.5[b]	12	3
Eczema	Infliximab	6	1	3	1

[a] Patient did not receive second infusion of third course

[b] Patient did not receive second infusion of first course

[c] Two adverse events (upper respiratory tract infection and pneumonia) occurred in the same patient

rituximab infusion, only one patient developed an infection (a mild urinary tract infection).

Discussion

The results of this retrospective chart review indicate that patients who have an inadequate response to rituximab or who are unable to tolerate rituximab can be restarted safely on a new biologic therapy (TNF inhibitor or abatacept). To date, no serious adverse events requiring hospitalization have been recorded among 22 patients who were treated with etanercept, adalimumab, infliximab, or abatacept following one, two or three courses of rituximab therapy. There was no clear pattern to the type of nonserious adverse events (five infections and two dermatologic events) recorded during biologic therapy post-rituximab. These types of adverse events are typically observed in patients receiving TNF inhibitors [9, 10] or abatacept [11]. Occurrence of an adverse event appeared unrelated to the number of prior rituximab courses received or to the interval between stopping rituximab and starting the new therapy. Indeed, there was only one mild infection among the five patients who started a new biologic 1 month after stopping rituximab. Similarly, the type and duration of new therapy did not appear to predict the occurrence of an adverse event.

Overall, although the patient numbers are small, there is no evidence from this review of any increase in the incidence of nonserious or serious adverse events in patients who are treated with a biologic agent following a period of rituximab therapy compared with the incidence during rituximab treatment. This finding is consistent with long-term follow-up data from the rituximab clinical trial program: a recent analysis, involving 185 patients who received rituximab plus methotrexate and who subsequently received another biologic agent, with follow-up for at least 48 months, showed that 13 serious infections occurred during rituximab therapy (6.99 events/100 patient years), compared with 10 serious infections after initiation of a new biologic (5.49 events/100 patient years) [12]. The infections were reported to be variable and typical for patients with RA; no opportunistic or fatal infection occurred.

Our study is limited by a number of factors, including: the small size of the patient cohort; the use of a single sampling center; the retrospective nature of the analysis; and the relatively short follow-up period. Nonetheless, the results provide supportive evidence from real-life practice that biologic agents can be safely given to patients who have discontinued therapy with rituximab. Further results from the clinical trial program extension studies and from national registries and other postmarketing surveillance will be required before firm conclusions can be drawn regarding the safety of biologic therapies after rituximab.

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