Pulmonary Pharmacology & Therapeutics 37 (2016) 24–29

Contents lists available at ScienceDirect

Pulmonary Pharmacology & Therapeutics

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

Effect of rituximab on pulmonary function in patients with rheumatoid arthritis

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ARTICLE INFO

Article history:
Received 4 November 2015
Received in revised form
7 January 2016
Accepted 6 February 2016
Available online 8 February 2016

Keywords:
Rituximab
Rheumatoid arthritis
Pulmonary toxicity
Spirometry
Diffusion capacity
Lung injury

ABSTRACT

Background: Rituximab (RTX), a B-cell depleting monoclonal antibody is increasingly used in several antibody-mediated diseases. It has been reported to cause pulmonary toxicity, though mainly during polychemotherapy of malignant lymphoma. Prospective data on RTX-induced pulmonary complications in patients with rheumatoid arthritis (RA) are lacking.

Methods and methods: Serial spirometries and measurements of diffusion capacity of the lung for carbon monoxide (DLCO) in patients with RA before and 2, 4, 8, and 26 weeks after treatment with RTX were performed. A reduction from baseline of forced vital capacity (FVC) of $\geq$10%, or $\geq$15% of DLCO was defined as indicative for pulmonary toxicity.

Results: Thirty-three patients (mean (SD) age 59 (12) years, 27% males) were included. Mean (SD) FVC predicted and DLCO predicted at baseline were 108% (18%) and 88% (18%), respectively. In contrast to FVC, DLCO showed a progressive decline during follow-up with a maximum reduction of 6.1% (95%CI 2.5%, 9.7%; $p = 0.001$) at 26 weeks compared with baseline. After 26 weeks, 22% of the patients had a $\geq$15% DLCO decline. None of the patients reported increased dyspnea during follow-up. Risk factors for pulmonary function changes after treatment with RTX were cigarette smoking, repeated administration of the drug, and co-medication with Prednisone.

Conclusion: Although no cases of symptomatic lung injury were observed, the progressive DLCO decline seems to indicate the presence of subclinical RTX-induced pulmonary toxicity.

1. Background

Rituximab (RTX) is a chimeric monoclonal antibody with high affinity for CD20 surface antigens on B-lymphocytes. Binding of the antibody to CD20 causes cell lysis via activation of the complement cascade and natural killer cells [1]. As such, RTX remains a major step forward in the treatment of B-cell non-Hodgkin's lymphoma (NHL) in the last 20 years [2,3]. Furthermore, the drug is increasingly used in several antibody-mediated diseases with the advantage of a long-term effect, as the substance seems to persist in the body for several months [4,5]. RTX has demonstrated efficacy for the treatment of rheumatoid arthritis (RA) and is being used in combination with methotrexate in hose who inadequately respond to tumor necrosis factor (TNF) antagonists [6].

After several years of post-marketing surveillance experience, the safety profile of RTX is deemed to be well defined [4,7–10]. However, side effects were reported to occur preferentially in patients with NHL [4,11,12]. Knowledge on RTX-induced pulmonary toxicity is still scarce and limited to case reports and small case series including up to nine patients [13–27]. Since some of these adverse events are supposedly related to circulating tumor loads of NHL, fewer events are observed in non-oncological diseases [9]. Notably, current chemotherapy of NHL comprises cyclophosphamide and bleomycin, both well known to cause pulmonary toxicity. Moreover, the combination of mediastinal radiotherapy and

Abbreviations: BAL, broncho-alveolar lavage; FVC, forced vital capacity; DLCO, diffusion capacity of the lung for carbon monoxide; NHL, non-Hodgkin's lymphoma; RA, rheumatoid arthritis; RTX, rituximab; TNF, tumor necrosis factor.

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http://dx.doi.org/10.1016/j.pupt.2016.02.002
1094-5539/

polychemotherapy regimens are known to cause late toxic pulmonary effects leading to reduction of carbon monoxide lung diffusing capacity (DLCO) and decrease of total lung capacity [28]. In patients with RA, the focus of previous studies was on non-pulmonary infusion-related reactions and infections [10]. A prospective trial evaluating RTX and its potential effect on lung function has not been conducted so far.

The aim of the present study was to investigate the prevalence of pulmonary function changes in patients with RA during RTX therapy. Since DLCO decline is one of the earliest, although nonspecific, signs of interstitial lung disease, we performed DLCO measurements in addition to spirometry [29]. Furthermore, we attempted to identify risk factors for the development of pulmonary function changes.

2. Materials and methods

2.1. Subjects

Between January 2013 and January 2015, patients aged over 18 years with an established diagnosis of RA who were treated and followed up at the Department of Rheumatology of the University Hospital Zurich were asked to participate in the study after a treatment with RTX was suggested. RTX was considered for the treatment of RA by a study-independent physician of the Department of Rheumatology, if the response to a previous treatment with TNF antagonists and/or methotrexate was insufficient. Exclusion criteria were acute infections and pregnancy. After written informed consent was obtained, patients underwent a baseline evaluation including a medical history, physical examination, laboratory analyses (hemoglobin, leucocytes count, C-reactive protein, blood sedimentation rate), and pulmonary function tests with spirometry and measurement of diffusing capacity of the lung for carbon monoxide (DLCO). Thereafter, the first dose of RTX (1000 mg) was given intravenously over a period of 3 h after premedication with 1000 mg paracetamol, 125 mg methylprednisolone, and 2 mg clemastine. The second dose of RTX was administered 14 days later after analogue premedication. Study visits including spirometry and DLCO measurement were scheduled at two, four, eight and 26 weeks after initiation of RTX therapy.

The study was approved by the Ethics committee of the Canton of Zurich, Switzerland (KEK-ZH 2011-0198) and is registered at ClinicalTrials.gov (identifier: NCT01632124).

2.2. Pulmonary function tests

Spirometry and DLCO were measured according to performance standards based on the statements from the American Thoracic Society (ATS) and the European Respiratory Society (ERS) [30,31]. Values of DLCO were adjusted for the patient's current hemoglobin value, and the patients were asked to withhold cigarette smoking at least 4 h before pulmonary function testing. Lung volumes and DLCO were measured with a commercial ZAN300 CO Diffusion system (nSpire Health GmbH, Oberthulba, Germany).

2.3. Outcome measures

Primary outcome measures were the absolute change in forced vital capacity (FVC) and DLCO in percent predicted as compared to baseline. A relative reduction of FVC of $\geq$10% from baseline or a fall of $\geq$15% from baseline of DLCO was chosen as indicative of a possible interstitial lung disease as a consequence of RTX induced pulmonary toxicity [32,33]. In this case a high-resolution computed tomography (CT) of the chest was performed. When radiological signs of interstitial lung disease (ground glass opacities, reticular, or nodular changes) were present, bronchoscopy with bronchoalveolar lavage (BAL) was done.

2.4. Statistical analysis

Continuous variables were summarized as mean (SD) or median (25th–75th percentiles) as appropriate, and categorical variables summarized using percentages. The change in FVC and DLCO (% predicted) at each time point compared to baseline was assessed using mixed-effects multilevel models with a patient-level random intercept and a random-effect for each follow-up visit. Global tests were used to determine whether the change in each outcome varied over follow-up. The effect of patient characteristics (smoking, sex, age, previous RTX administrations prior to study inclusion versus first administration, methotrexate and prednisone use) on the change in FVC and DLCO at each time-point was assessed by adding an interaction term between the characteristic of interest and follow-up visit to the model for the corresponding outcome and adjusting for the baseline value of the outcome. A two-sided p-value less than 0.05 was considered statistically significant for the primary outcomes. All analyses were performed using Stata version 14.0 (College Station, TX: StataCorp LP.).

3. Results

Thirty-three patients (mean age 58.8 years ± 11.7 years, 27% males) participated at the baseline visit and at the first study visit which was scheduled two weeks after the first rituximab administration. The study flow-chart displaying drop-outs at the different stages is shown in Fig. 1. Baseline characteristics of these patients are displayed in Table 1. At baseline visit, pulmonary symptoms consisted of chronic cough (n = 6, 18%), sputum production (n = 4, 12%), and dyspnea on exertion (n = 7, 21%). Most of the patients have been receiving repeatedly RTX (n = 26, 79%), and 14 patients (42%) were concurrently treated with methotrexate. Baseline pulmonary function tests are displayed in Table 2. FVC and DLCO were below 80% of the predicted value in one (1%) and in ten patients (30%), respectively.

The evolution of FVC and DLCO (% predicted) during follow-up compared to baseline is displayed in Fig. 2. A statistically significant progressive decrease of DLCO at four (−3.9%, 95%CI 0.7%, 7.1%; p = 0.017) and eight weeks (−3.3%, 95%CI 0%, 6.6%; p = 0.049) was observed, culminating in a mean reduction by 6.1% (95%CI 2.5%, 9.7%; p = 0.001) at 26 weeks compared to baseline (Table 3). By contrast, there was no decline of FVC occurred during the observation period with a mean change of −0.6% (95%CI −3.7%, 2.5%; p = 0.69) at 26 weeks compared with baseline (Table 4). After 26 weeks, 6 patients (22%) reached the endpoint of DLCO decline of $\geq$15% from baseline, whereas a decline of FVC $\geq$ 10% compared to baseline was observed in only 2 patients (7%) (Tables 3 and 4). In patients who experienced a DLCO decline of $\geq$15%, a chest CT was performed in three patients revealing no pathologic findings corresponding to the observed lung function changes. Pulmonary symptoms were observed only in two patients with lonely cough but pulmonary function decline. However, these patients had no lung function decline over follow-up.

Risk factors for pulmonary function changes after treatment with RTX were cigarette smoking, previous administrations of RTX prior to study inclusion (repeated cycles), and co-medication with prednisone (Figs. 3 and 4). However, cough (p = 0.76), sputum (p = 0.84), dyspnea on exertion (p = 0.99), DLCO at baseline (p = 0.45), and FVC at baseline (p = 0.56) were independent of the fact if the patient was previously exposed to RTX or not. A significant DLCO decline in smokers was only observed after two weeks. However, this effect seemed to vanish over time. Sex, age and co-