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Rituximab-Induced Lung Disease: A Systematic Literature Review

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The anti-CD20 antibody rituximab has been reported to induce a heterogeneous spectrum of lung disorders. Our aim was to critically review data on the clinical presentations, causality assessments, and management strategies of lung diseases possibly related to rituximab.

Systematic literature review was performed on English-language reports in MEDLINE till September 2008.

We identified 45 cases of lung diseases ascribed to rituximab, with three "time to onset" patterns. The most common presentation (n=37) was acute/subacute hypoxemic organizing pneumonia starting 2 weeks after the last infusion (often around the 4^{th} cycle) and resolving in most cases provided glucocorticoid therapy was given early. ARDS occurred in 5 patients, within a few hours usually after the first infusion. In the remaining 3 patients, macronodular organizing pneumonia developed insidiously at a distance from rituximab therapy and responded to steroids. Eight patients died. Based on time to onset, symptoms, and responses to rituximab and other drugs discontinuation and rechallenge, 13 cases were highly compatible and 32 compatible with rituximab-induced lung disease.

Knowledge of these presentations of rituximab-induced lung disease should prove helpful for diagnosis and causality assessment purposes. Time-to-onset data, suggesting different pathogenic mechanisms, support closer clinical and perhaps radiological monitoring between infusions, particularly in patients with a history of reversible respiratory symptoms.

INTRODUCTION

Rituximab is a chimeric human-mouse IgG1 kappa monoclonal antibody with high affinity for CD20 surface antigens expressed by normal human pre-B and B lymphocytes but not by stem or plasma cells. Binding of the antibody to CD20 causes cell lysis via activation of the complement cascade and natural killer (NK) cells. Accelerated apoptosis and sensitivity to antineoplastic agents are also induced by the drug [1]. Rituximab may persist several months in the body. Peripheral B-cell depletion lasts 6 to 9 months after treatment in most patients [2].

Rituximab is the major step forward in lymphoma treatment during the last 20 years. It was approved by the Food and Drug Administration (FDA) in 1997 and by the European Medicines Agency (EMEA) in 1998 for low grade non-Hodgkin lymphoma (NHL) expressing CD20, chronic lymphocytic leukemia (CLL), and subsequently diffuse large B cell NHL[3]. In 2006, the EMEA approved rituximab for rheumatoid arthritis (RA) in adults [4]. Uses in idiopathic thrombocytopenic purpura (ITP) [5], autoimmune hemolytic anemia, Sjögren's syndrome, systemic lupus, and systemic vasculitis, are under evaluation. Patients with lymphoma are given one to six infusions of 375 mg/m^2 at intervals depending on the treatment protocol. In RA, 1000 mg are given twice, at a 2 weeks interval, followed by re-treatment 6 months later if needed.

From safety data on 960,000 patients treated worldwide up to 2007 [2, 6-8], rituximab was well tolerated. However, side effects were recorded in phase III controlled trials and postmarketing surveillance programs, with less severity in RA than in lymphoma [2, 9]. Infusion-related reactions (IRR) occurred in 9% to 15% of patients. IRR consist in flu-like symptoms, with respiratory manifestations in 30% of cases. Patients may experience anaphylactic shock or, more rarely, acute respiratory distress syndrome (ARDS), fatal in 0.04 to 0.07%. These serious side effects have led the pharmaceutical companies that market

rituximab to recommend a number of precautions (Table 1A) [10]. Although the rate of delayed neutropenia was slightly increased, the immediate risk of infection, namely pulmonary infections, was not increased and data were incomplete regarding the risk of delayed infection [11]. Severe delayed lung injury was noted with a rate of occurrence of 0.03% in the review by Kimby [2] and 0.01% in the Spanish pharmacovigilance database [9]. Of all side effects of rituximab, lung disease may have the highest reporting odds ratio (ROR) by far (ROR: 68.1, 95% confidence interval 23.8-194.9) [9].

We perform this study for several reasons: lung disease was not documented in the clinical trials, the drug being increasingly used as mentioned before [4], and case-reports of possible rituximab-induced lung disease are accumulating at a fast pace. The primary objective of this systematic literature review (SLR) was to obtain a comprehensive picture of the pulmonary side effects of rituximab and to provide diagnostic standard (for drug causality assessment) [12, 13].We also looked for time-to-onset that might help to develop protective measures for clinical practice.

METHODS

Data Sources and Searches

According to Cochrane Reviews methodology, we conducted a SLR for case-reports in English or French indexed in MEDLINE PubMed between 1997 (the year of licensure of rituximab) and September 2008.

Study Selection

The following MeSH headings: “rituximab” AND “adverse effects” AND “interstitial pneumonitis”, OR “idiopathic interstitial pneumonitis”, OR “organizing pneumonia” were used. Then, we conducted a search using “rituximab” combined with “respiratory side effect”,

"drug reaction", or "pulmonary toxicity". The references of the articles retrieved by the PubMed search were manually searched. Abstracts from meetings with no corresponding full-length publication were not considered. For each reported case, we recorded the country and city in order to eliminate redundancies.

Data Extraction and Quality Assessment

From each case-report, we extracted six categories of data when available:

- patient characteristics (age, sex, geographic origin, and reason for rituximab therapy);
- treatment modalities (dosage, number of cycles, and cumulative dose);
- time-to-onset (time between the last rituximab infusions and respiratory symptoms), and whether symptoms occurred after previous cycles;
- tempo of onset (hyperacute: development of pneumonitis within hours after the first symptom; acute or subacute: over a few days; and chronic: over several weeks or months)
- respiratory and extra-respiratory manifestations (clinical and radiological features, computed tomography (CT) findings, cytological studies of bronchoalveolar lavage (BAL) fluid, and histological findings from transbronchial and/or open lung biopsies);
- therapeutic management (discontinuation of rituximab only or of all chemotherapy agents, steroid therapy) and course;
- whether subsequent treatment involved the use of rituximab (alone or with other chemotherapy agents) or of other chemotherapy agents without rituximab, and whether re-exposure to rituximab of patients with respiratory symptoms at one or more earlier cycles was intentional or unintentional (e.g., in patients with self-limited symptoms identified retrospectively).

Study quality was assessed independently by two reviewers, one with expertise in drug-induced lung diseases, and one with expertise in research methods. The following key design features were evaluated: presence of valuable data, especially for time to onset, exclusion of other causes, reintroduction conditions. Disagreements were resolved by independent adjudication.

Data Synthesis and Analysis

Numerical data are expressed as mean, range, and percentage. We used a chi-square test for independence to compare the two distributions, namely, time since the last infusion and tempo of onset since the first symptom.

RESULTS

Number of articles retrieved and numbers of included and excluded cases

We identified 52 cases [3, 14-41] (Figure 1**)** described in anecdotal case-reports and in eight case-series reporting two cases [16, 21, 29, 34-35], three cases [19, 33], four cases [38], or nine cases [39]. A few adequately documented cases occurred during clinical trials. Seven cases out of these 52 cases were excluded: insufficient detail about cases that occurred in clinical trials, n=2 [15]; time to onset too long to be compatible with causality of rituximab, n=2 (1 case each of fluctuant macronodular organized pneumonia 9 months after the last infusion in a patient with Castleman disease [16], and of constrictive bronchiolitis 10 months after the last infusion [14]); and manifestations not related to rituximab-induced lung disease (1 case each of heart failure ascribed to direct myocardial toxicity of rituximab [3], fludarabine-induced lung disease confirmed by a positive re-challenge test [3], and fatal hemoptysis complicating necrotizing lymphomatoid granulomatosis of the lung [41]). This left 45 cases of possible rituximab-induced lung disease for our study.

Characteristics of the 45 patients

Mean age was 65 years (43-80) and the male-to-female ratio was 2:1. Of the 45 patients, 17 (38%) were in Asia, 12 were in the Americas (and their ethnic origin was not reported), and 16 were in Europe. The rate of occurrence was 8.4% (9/107) in the Korean case-series [39] and 11% (4/36) in the Dutch case-series [38]. The reason for rituximab therapy was diffuse large B cell lymphoma in 30 patients, indolent lymphoma in 10 patients (mantle cell lymphoma, n=2 [20, 21, 39]; marginal zone lymphoma or MALT, n=3 [22, 32-33]; follicular lymphoma, n=4 [24, 32, 39]; and Waldenström's macroglobulinemia, n=1 [38]), CLL in 2 patients [3, 37], ITP in 2 patients [18, 26], and RA in 1 patient [16].

Modalities of rituximab administration

Overall, rituximab was given in a mean dosage of 375 mg/m^2 per IV cycle on one day or two consecutive days. The interval between cycles was 8, 15, or 21 days. Rituximab was used alone in 7 patients [20-21, 24, 26, 33, 37, 40] and with stable-dosage methotrexate for maintenance therapy of RA in 1 patient [16]. The 37 other patients received rituximab in combination with multiple chemotherapy regimens (COP, CHOP, CEOP, CVP, ACVBP, VNCOP, fludarabine, cladribine, growth factors [A: adriamycin; B: bleomycin; C: cyclophosphamide; E: epirubicin ; H: doxorubicin; N: mitoxantrone; O: vinblastine; P: prednisone; V: etoposide]).

Time-to-onset data

The mean time from the first rituximab infusion to onset of the respiratory manifestations (n=21) was 3 months (12 weeks), with a peak at the fourth cycle (Figure 2A) and a mean cumulative dosage of 1600 mg/m^2. The histogram of times-to-onset from the last

rituximab infusion clearly shows three peaks (Figure 2B). The first peak, with 5 patients [17-19], occurred a few hours after the infusion (day 1), i.e., reflected early-onset forms. The second peak, with 29 patients, occurred exactly on day 15, and 8 additional cases occurred a few days before (day 8 to day 15) or after (day 15 to day 21) this second peak. Thus, 37 patients experienced delayed-onset forms [3, 20-39]. Finally, the third peak reflected late-onset forms occurring 1 to 3 months after the last infusion, in 3 patients [16, 33, 40].

Tempo of onset

The tempo of onset (Table 2) was usually acute or subacute (36 patients) [3, 20, 21, 23-39]. In 6 patients, the onset was hyperacute [17-19]; and in 3 patients, the onset was chronic [16, 33, 40]. The distributions of tempo of onset and of time-to-onset from the last rituximab infusion showed a nearly perfect match (Table 2) and were significantly linked ($P<10^{-16}$): the 5 early-onset cases were hyperacute, 36 of the 37 delayed-onset cases were acute or subacute, and the 3 late-onset cases were chronic.

Symptoms and course

Early-onset hyperacute forms (n=5)

All 5 patients in this group had ARDS with PaO_2 values less than 50 mm Hg. A single patient underwent lung biopsy, which showed diffuse alveolar damage and intra alveolar hemorrhage [19]. All 5 patients required mechanical ventilation and received bolus of steroids. Two patients died.

Of the 5 patients, 4 were receiving combination chemotherapy regimens and 4 experienced ARDS after the first rituximab cycle. The recommended premedication was given to 4 patients; for the remaining patient, this information was not available. Re-challenge

was performed in 2 patients and was negative in both, despite the absence of additional precautions [19].

Delayed-onset acute forms (n=37)

Of the 37 patients in this group, 34 had non-Hodgkin's lymphoma, 2 had chronic lymphocytic leukemia, and 1 had ITP. Rituximab was used alone in 4 patients and with combination chemotherapy in 33 patients. Onset occurred after the third, fourth, or fifth cycle in 18 of the 32 patients for whom this information was available and on day 15 after the infusion in 29 of the 37 patients. Earlier infusions had been followed in 9 patients by respiratory symptoms consisting of coughing, dyspnea, or reversible bronchospasm [3, 20-21, 25-26, 31, 33, 38]. These symptoms were not consistently present after the first cycle. They occurred repeatedly in 8 patients (twice in 3 patients, three times in 2 patients, four times in 2 patients, and 5 times in 1 patient).

The clinical and radiological features are shown in Table 3. The main manifestations were dyspnea and fever. Hypoxemia with PaO_2 values less than 60 mm Hg was the rule. CT of the chest showed focal alveolar densities in 54% of patients, usually at multiple sites and in combination with ground-glass attenuation (32%). Positron emission tomography was performed in 7 patients and consistently showed an early increase in tracer uptake [31, 33, 38]. Findings were negative from microbiological studies (n=40), including those on BAL fluid. Failure of empirical antibiotic treatment was mentioned for 20 patients.

The BAL fluid cytology results were available for 9 patients [22, 28-30, 34, 37-38]. A consistent finding was lymphocytosis (13% to 90%) with a predominance of CD4+ T cells. Histological data were obtained (Table 3) by surgical lung biopsy in 6 patients [3, 23-25, 32-33] and by transbronchial lung biopsy in 5 patients [27, 31, 35-37]. According to the ATS/ERS classification [42], the predominant histological pattern was organizing pneumonia

(8/11, 72%) [23-25, 27, 31, 32-33, 37], isolated (n=5), or associated with nonspecific interstitial pneumonia or usual interstitial pneumonia. None of the patients had nonspecific interstitial pneumonia or usual interstitial pneumonia as the only histological pattern.

Of the 37 patients in this group, 10 required mechanical ventilation [20, 23, 24, 25, 28, 29, 31, 32, 33, 35]. Six patients died, including 2 with a history of respiratory symptoms after previous cycles [25, 31]. Of the 6 patients who died, only 1 was receiving rituximab alone, for follicular lymphoma [24]. The 31 survivors made a full recovery with clinical resolution within a few days and of imaging resolution within a few weeks. In 27 patients, simultaneous steroid therapy was given.

Rituximab was reintroduced in 15 patients with previous respiratory manifestations, either intentionally or unintentionally (Table 4). Rechallenge was positive in 4 patients with rituximab alone [20, 31, 26, 38] and in 8 patients with rituximab and combination chemotherapy [3, 25, 31, 34, 38-39]. Rechallenge was negative in 3 patients who concomitantly received high-dose steroids (1 mg/kg) independently from the recommended prophylactic methylprednisolone therapy. Finally, 9 patients experienced no further respiratory symptoms when their chemotherapy was restarted without rituximab [22, 25, 27, 29, 38-39].

Late-onset chronic forms (n=3) [16, 33, 40]

Mean time to onset in these 3 patients was 8 weeks from the last rituximab infusion. The symptoms started after the second, third, and fifth cycles, respectively. None of these patients was receiving anticancer chemotherapy. The diagnoses were RA [16], gastric MALT lymphoma [33], and Waldenström's macroglobulinemia [40]. Clinically silent pulmonary macronodules and BAL fluid lymphocytosis were the only manifestations. Lung biopsy was performed in all 3 patients and consistently showed organizing pneumonia. Steroid therapy

ensured a full recovery in all 3 patients. None of these patients was rechallenged with rituximab.

DISCUSSION

Our systematic review confirms that rituximab can cause pulmonary toxicity. We identified three clinical presentations based on time-to-onset and symptoms. The most common presentation by far was acute or subacute organizing pneumonia occurring about 2 weeks after the last infusion and rapidly causing hypoxemia but responding favorably to early steroid therapy. More rarely, the pulmonary toxicity of rituximab manifested as early and potentially fatal ARDS or as chronic macronodular organizing pneumonia.

Causality

Although there is no consensus regarding the best method for assessing causality [43], the criteria generally used to evaluate drug-induced lung disease [12, 13, 44] (Table 5) support a causal link with rituximab in all 45 patients. The time to onset, clinical and radiological features, and cytohistological findings were consistent with drug-induced lung disease. Other causes of pneumonia were considered and ruled out in most patients. The histological data and course excluded pulmonary lymphoma relapse, lymphoma-related organizing pneumonia [45], rheumatoid lung disease, and other respiratory diseases. Doubtful cases were excluded [14-16]. Respiratory tract infection was ruled out by negative microbiological studies including tests for opportunistic pathogens in BAL fluid, and by negative response to antibiotics. Exacerbation of a cardiac or previous respiratory disease was excluded [3]. The full recovery achieved by survivors of the acute-subacute episodes after rituximab discontinuation should be interpreted with caution. Five patients received steroid therapy, which is known to improve lung disease due to other causes. Only 7 patients were taking rituximab alone. In the other patients, it is unclear which drug or drug combination was

responsible for the respiratory manifestations. Indeed, similar times to onset and features of pneumonitis have been reported with the associated drugs [46]. The results of rechallenge with the drug (Table 4), usually considered a major causality criterion for drug-induced hypersensitivity pneumonitis [13, 47], must be interpreted according to the circumstances, which varied across patients. In 13 patients, the data were highly compatible with drug causation. In the 32 remaining patients, the data remained compatible with drug causation. Five among these 32 patients had a negative rechallenge but either received steroids in an unspecified dosage (n=3) [30, 39] or had ARDS, i.e. a manifestation probably unrelated to hypersensitivity [19].

Pathogenic mechanisms and precautions for use

The three clinical presentations of rituximab-induced lung disease may differ regarding the underlying mechanism. Early onset ARDS is probably unrelated to hypersensitivity. Indeed, immediate hypersensitivity would be expected to produce symptoms within a few minutes after the beginning of the infusion, in most cases after at least one previous cycle. Instead, ARDS symptoms started after a few hours, suggesting an IRR related to cytokine release and/or tumor lysis syndrome [10]. This mechanism is consistent with the occurrence of early onset ARDS in patients receiving multiple cytotoxic agents and at the first cycle, i.e., when the tumor burden is greatest, or with circulating malignant B cells. Similarly, early onset ARDS is exceedingly rare in patients treated by rituximab alone for systemic diseases. Also supporting this mechanism is the negative response to rechallenge in 2 patients and the inconsistent efficacy of premedication, only 10% in clinical trials [4]. Therefore, close monitoring is in order at the first cycle, particularly in patients receiving combination chemotherapy for high-burden lymphoma. Recommendations concerning serious side effects should be followed (Table 1A) [10]. Higher dose steroid therapy may deserve consideration.

Acute or subacute rituximab-induced lung disease, most notably organizing pneumonia, probably reflects a hypersensitivity reaction to the potentially immunogenic chimeric anti-CD20 antibody. Arguments that support a hypersensitivity reaction include the recurrence and increasing severity of the symptoms from one infusion to the next, occurrence during the third month on average, responsiveness to steroid therapy (delayed onset 15 days after the methylprednisolone infusion and favorable outcome with steroid therapy), rash and eosinophilia, BAL fluid lymphocytosis, and histological pattern of organizing pneumonia in many patients [48]. The potential for severity lies in the risk of a delayed diagnosis, with the initial reversible symptoms being overlooked as a result of inadequate knowledge of this complication.

Given the potential severity of rituximab-induced lung disease and the strong suspicion of underlying hypersensitivity, we suggest a number of recommendations (Table 1B). First, patients should be told that respiratory disease may develop, with the risk being greatest about 15 days after the last infusion and around the fourth cycle. Second, respiratory symptoms should be looked for routinely after each infusion. Third, any clinical manifestation, however mild, should prompt a chest radiograph. Finally, when the findings support a diagnosis of rituximab-induced lung disease, steroid therapy should be started immediately, as it seems to improve the outcome. Furthermore, instead of the currently recommended methylprednisolone infusion at each rituximab administration, a longer period of steroid therapy with tapering of the dose to avoid a rebound reaction may be appropriate.

Late-onset organizing pneumonia (which may occur up to several months after the last rituximab infusion) may be related either to toxicity of the drug, whose biological half-life is poorly known but probably long, or to immune system restoration [49]. Although not severe,

these forms require histological confirmation as the nodules may suggest a malignancy or a chronic infection in these immunocompromised patients.

In conclusion, our study confirms the pulmonary toxicity of rituximab. Our data should prove helpful to clinicians for assessing causality in patients with respiratory symptoms after rituximab therapy. Three distinct clinical presentations according to time-to-onset were identified suggesting different underlying mechanisms. For each other we suggest specific recommendations. Pulmonologists must ensure the early diagnosis and treatment of rituximab-induced lung disease and inform other specialists of this complication and of the need for close monitoring of the respiratory status.

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Table 1: Recommended precautions when using rituximab

IRR: infusion-related reaction

A. Recommendations of the pharmaceutical company for preventing IRRs modified from Smolen et al. (10)

- Give 1 g of acetaminophen (paracetamol), an antihistamine, and 100 mg of methylprednisolone (MP) 60 min before the rituximab infusion, which should be started 30 min after the end of the MP infusion.
- Mild side effects: decrease the infusion rate
- Serious side effects
    - Stop the infusion immediately
    - Symptomatic treatment
    - Look for lab features of tumor lysis syndrome
    - Restart on a case-by-case basis, in a lower dosage and at a slower rate, under close monitoring
    - In the event of a recurrence, definitive treatment discontinuation is recommended.

B. Our recommendations

- Prevent hyperacute lung disease by increasing the glucocorticoid dose given before the rituximab infusion.
- Acute and subacute lung disease
    - Inform the patients of the risk of respiratory disease, which is greatest on day 15 and around cycle 4.
    - Routinely monitor respiratory symptoms between infusions.
    - Obtain radiograph immediately if any symptom occurs, however mild.
    - Diagnostic evaluation and prompt glucocorticoid therapy if suspicion of rituximab-induced lung disease.

Table 2: Distribution of cases by time to onset after the last rituximab infusion and by tempo of respiratory symptom development after the first symptom

Time since last infusion / Tempo of development	Early (D1)	Delayed (D7- D21)	Late >D30	Total
Hyperacute *	5	1		6
Acute/Subacute †		36		36
Chronic‡			3	3
Total	5	37	3	45

*development over a few hours, †development over several days, ‡ development over several weeks or months

Table 3: Clinical, computed tomography (CT) and histological findings in patients with acute or subacute rituximab-induced lung disease

Clinical features from 35 patients (3, 20-39)	**n**	**%**
Cough	**16**	**43**
Dyspnea	**30**	**85**
Fever	**23**	**62**
Crepitant rales	**13**	**35**
Hypoxia	**15**	**37**
PaO_2 < 60 mmHg	**8**	**> 50**
Chest pain	**1**	
Rash and hyperéosinophilia	**2**	
Predominant CT pattern from 35 patients (3, 20-39)	**n**	**%**
Focal alveolar pattern ≥1	**19**	**54**
Ground-glass opacities	**12**	**34**
Diffuse alveolar pattern	**3**	**8.5**
Macronodules	**1**	
Histological Pattern* from 11 patients (3, 23-25, 27, 31, 32-33, 35-37)	**n**	**Isolated pattern**
Organizing pneumonia	**8**	**5**
Nonspecific interstitial pneumonia	**4**	**0**
Usual interstitial pneumonia	**2**	**0**
Diffuse alveolar damage	**2**	**0**
Intraalveolar hemorrhage	**2**	**0**

* evaluated by lung biopsy

Table 4: Results of rechallenge with rituximab (RTX) and/or other drugs in patients with any clinical pattern of lung disease (n = number of patients)

Reintroduction	n	Causality
Positive to RTX alone (20, 21, 26, 38)	**4**	**Highly compatible N=13**
Negative to chemotherapy without RTX (22, 25, 27, 29, 38-39)	**9**	
Positive to chemotherapy with RTX (3, 25, 31, 33, 38-39)	**8**	**Compatible N=32**
No rechallenge	**19**	
Negative to RTX* (19, 30, 39)	**5**	

*RTX rechallenge with glucocorticoid therapy in an unspecified dosage (n=3) or after a hyperacute episode of lung disease (n=2)

Table 5: Modified criteria for assessing drug causation of lung disease from Mayaud et al. (13)

Intrinsic criteria from the clinical analysis

- Timing
- Clinical manifestations
- Exclusion
    - site specific of the treated disease
    - infection
    - other condition or exacerbation of a previous condition (e.g., heart failure, pulmonary embolism)
- Favorable outcome after discontinuation of the suspected drug
- **Positive accidental or intentional rechallenge**

Extrinsic criteria from the literature

- Same criteria as the intrinsic criteria when the pattern of lung disease has been reported previously with the same drug
- Rate of occurrence, interpreted according to the time the drug has been on the market

Confrontation of intrinsic and extrinsic criteria

- Similarity of the clinical presentation, time to onset, and course

Figure legends

Figure 1: Flow chart showing the total number of cases retrieved by the literature search, the number of excluded cases, and the number of included cases.

RCT: randomized control trial

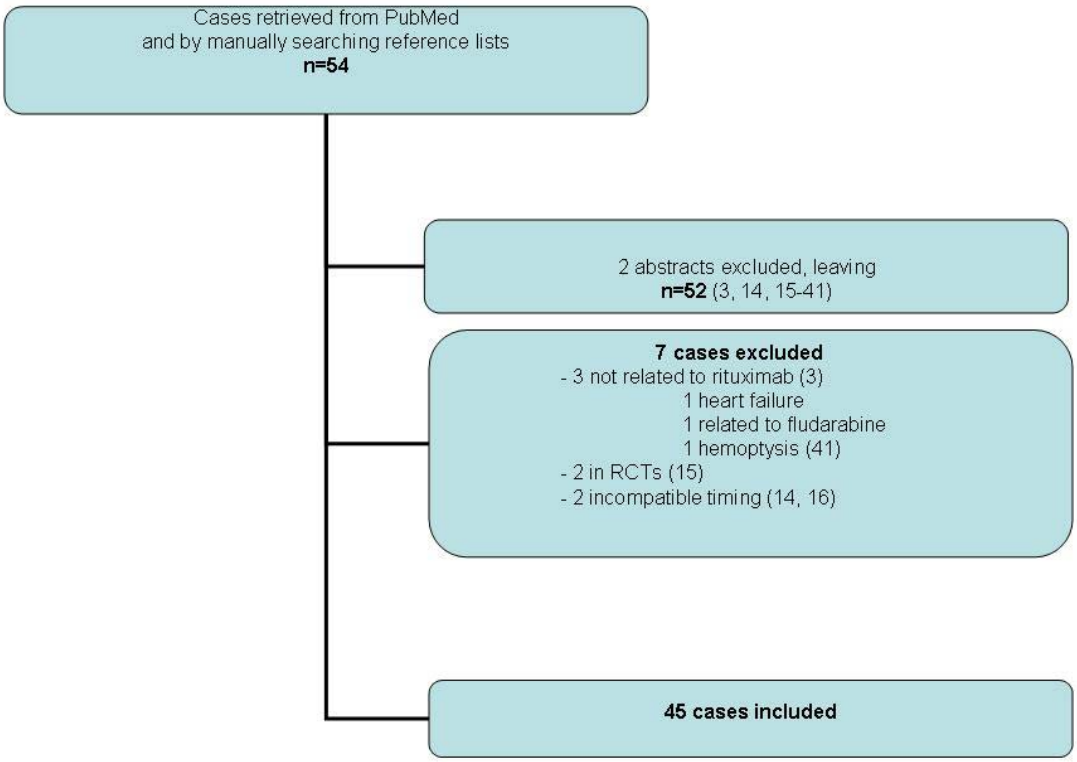
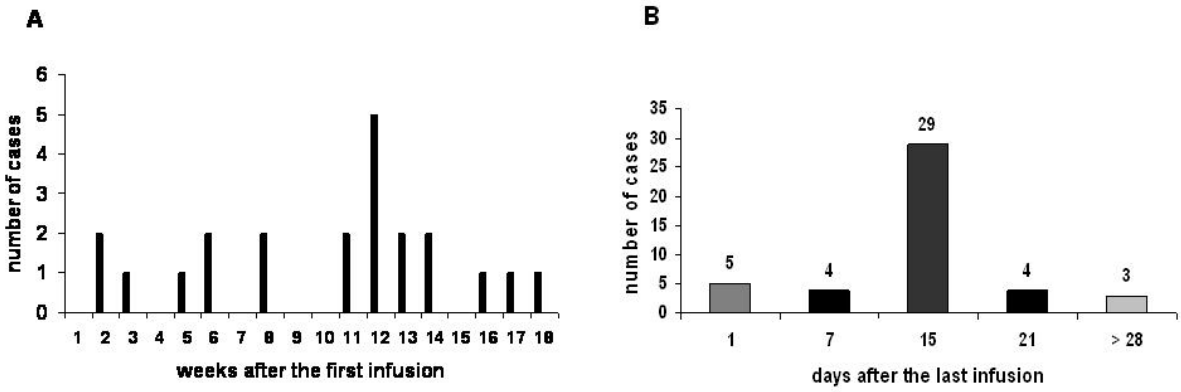


Figure 2: Time to onset of the respiratory manifestations from the first (A) and last (B) rituximab infusion. Delayed acute and subacute forms: ■


A
number of cases
0
1
2
3
4
5
6
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
weeks after the first infusion
B
number of cases
0
5
10
15
20
25
30
35
5
4
29
4
3
1
7
15
21
> 28
days after the last infusion