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# STUDY THE PREVALENCE OF NON-HEMATOLOGICAL SIDE EFFECTS OF RITUXIMAB IN RIYADH, SAUDI ARABIA

دراسة انتشار الآثار الجانبية غير الدموية لدواء الريتوكسيماب في الرياض، المملكة العربية السعودية

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**Abstract:**

***Background:*** *Rituximab (RTX) therapy has been used for hematological malignancies and autoimmune diseases for a long time, and its efficacy and safety are well documented. In spite of conflicting results from clinical trials regarding the association between RTX and infections, an increased incidence of infections or toxixity has recently been reported among patients receiving RTX for lymphomas. To date, there hasn't been any clinical experience linking RTX with different non-hematological side effects.*

***Objectives:*** *To investigate the prevalence of non-hematological side effects in in patients and outpatients receiving RTX in Riyadh, Saudi Arabia.*

***Methods:*** *A retrospective cross-sectional study was conducted from July 2020 to August 2021 at King Saud University Medical City (KSUMC), Riyadh, KSA. All consecutive patients who attended the KSUMC between July 2020 to August 2021 and referred with autoimmune or different types of cancer disease were included in this study.*

***Results:*** *RTX was commonly prescribed for different types of malignancies and autoimmune diseases. Non-hematological adverse reaction has been evaluated up to 1 year in patients who had been treated with RTX. The most common indications for RTX were DLBCL (36%), B cell lymphoma (20.2%), non-Hodgkin's lymphoma (NHL) (15.7%), chronic lymphocytic leukemia (10.1%), and Hodgkin's lymphoma (7.9%). An analysis of the association between RTX and infection among patients with hematological malignancies and autoimmune disorders was done. The most frequent adverse event was infection, infusion-related reactions. Infection rate of 34.8% was observed during the study and the infected patients had glomerulonephritis (9%), hepatitis B infection (6.7%) and renal toxicity (5.6%). Study results showed that RTX was well tolerated after one or more courses. Multiple courses did not result in increased serious infections.*

***Conclusion:*** *Data from this study indicate that RTX is a commonly used for autoimmune and cancers diseases with potential beneficial effects. Although RTX has a wide range of non-hematological adverse reaction, its well-tolerated therapy for autoimmune diseases. To clarify the association between RTX and infection, further research is needed.*

***Keywords:*** *Rituximab, non-hematological, autoimmune, infections, Hodgkin's lymphom*

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## INTRODUCTION:

Since the advances of genetic engineering, monoclonal antibodies (McAbs) have become more effective as therapeutic agents (Gklinos et al., 2021). RTX is one of the most important anti CD20 ( Cluster of derentiation 20 a protein in nature ) McAbs and it is also a standard therapy for a number of CD20-positive hematological malignancies and autoimmune diseases. It was first approved by the FDA (Food and Drug Administration) in 1997 and currently used for the treatment of CD20 positive B-cell non- Hodgkin lymphoma (NHL), chronic lymphocytic leukemia (CLL), moderate-to-severe rheumatoid arthritis (RA), microscopic polyangiitis (MP) and granulomatosis with polyangiitis (GPA) and pemphigus vulgaris (PV). The off-label use has been described in different neuroimmune diseases, including multiple sclerosis (MS), diseases of the spectrum of neuromyelitis optica, autoimmune neuropathies and myopathies, and the neuromuscular junction diseases (Uchida et al., 2004).

RTX is an unconjugated chimeric (murine / human) McAbs (IgG1) directed against the CD20 antigen (Gklinos et al., 2021). This antigen (CD20) is a transmembrane phosphorylated protein which plays a significant role in the activation and proliferation of B-lymphocytes (Reff et al., 1994). Except for immature B cells and plasma cells, it is expressed by mature B cells as well as mature NHL cells. Pluripotent hematopoietic stem cells, myeloid cells, and T lymphocytes/NK cells do not express CD20. The CD20 antigen is a very interesting target molecule for the immunotherapy of B-NHL (Weiner, 2010).

The exact mechanism of action of RTX in eliminating tumor cells is still unclear (Johnson and Glennie, 2003). Topics discussed include cytotoxic mechanisms through complement-mediated lysis, cell-mediated cytotoxicity, apoptosis, inhibition of proliferation, and possible sensitization of chemotherapy. In addition, *in vitro* experiments performed on CD20-positive cell lines show that RTX triggers a variety of signals (chemo-sensitization e.g. increased phosphorylation of tyrosine and activation of protein kinase C) after binding to B-lymphocytes and via antiproliferative or apoptotic effects (Abulayha et al., 2014). The *in vivo* administration of RTX quickly leads to a destruction of B cells through cellular cytotoxicity, complement activation, and induction of apoptosis (Edwards and Cambridge, 2006). Consequently, circulating B-lymphocytes are rapidly depleted, and remain low or undetectable for 3–6 months after the last dose of RTX (Pescovitz, 2006).

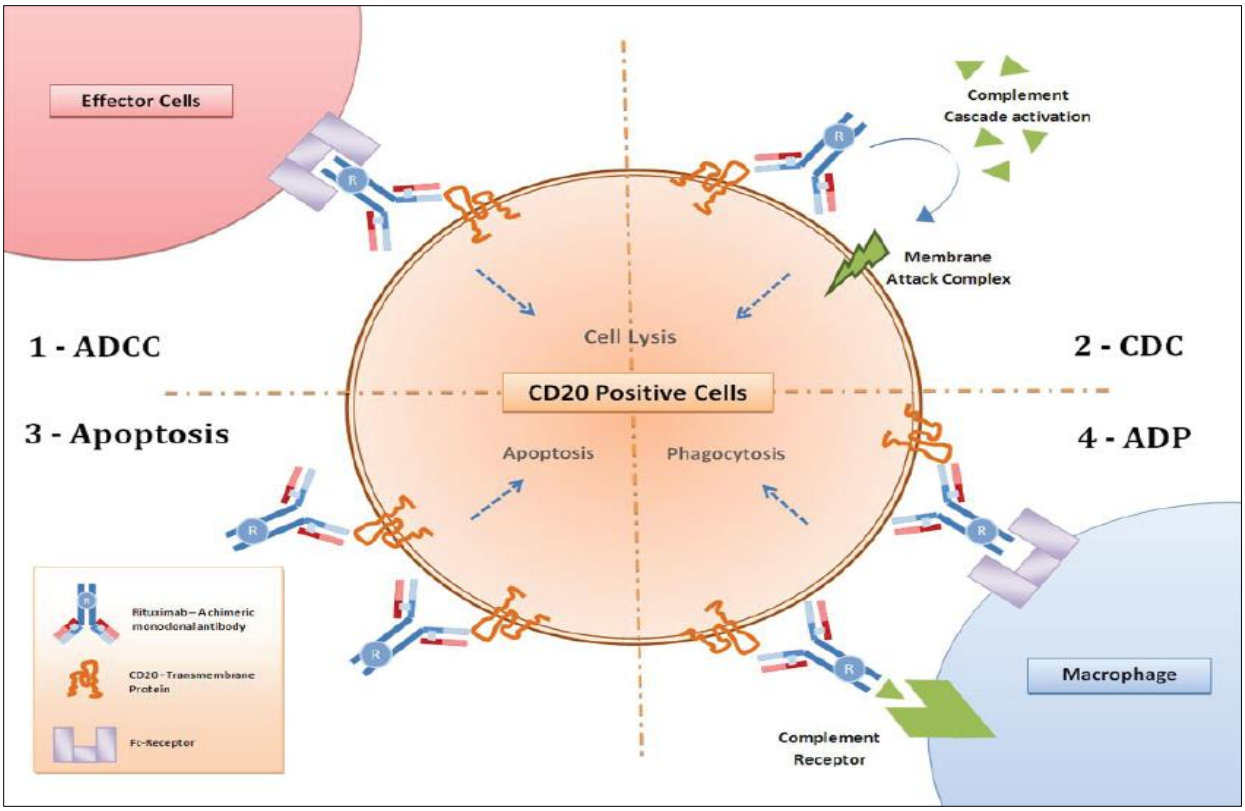


**Fig. 1: Mechanism by which rituximab, a chimeric monoclonal antibody, targets the CD 20 receptor. (Adopted from Kasi P.M. et al., 2012).**

Despite the benefits of RTX in hematological malignancies and autoimmune diseases therapy, a number of serious adverse effects are being linked to the use of RTX in post-marketing studies, which frequently cause complications and require intensive care. It has an acute allergic and cytokine associated reactions (Witzig et al., 2002). Additionally, it has different hematological and non-hematological side effects (Einfeld et al., 1988). By causing a rapid depletion of B cells through cellular cytotoxicity and apoptosis induction deletion of immune cells, RTX inhibits the humoral immunity and consequently opportunistic infections risk increase (Kasi et al., 2012). Similarly, risk of certain viral infections increases (Aksoy et al., 2007). Additionally, some types of cancer patients, including those with hematological and non-hematological malignancies, may experience immune suppression due to the delayed onset of cytopenia or neutropenia caused by RTX (Cattaneo et al., 2006). In addition to hypergammaglobulinemia, hypogammaglobulinemia can also occur in patients who have received long-term treatment, such as those on maintenance therapy (Lim et al., 2005, Lim et al., 2008). Drug prophylaxis or preventive therapy strategies must be used for these cases when exposed to RTX (Edwards and Cambridge, 2006). The different hematological and non-hematological side effect of RTX was summarized in table 1.

**AIM**

- To investigate the prevalence of non-hematological side effects in *in patients* and outpatients receiving RTX in Saudi Arabia.
- To evaluate the general toxicity of RTX.

**SPECIFIC OBJECTIVES**

Assessing the safety of RTX infusion as mode of administration and investigate the occurrence of different non-hematological side effects in short and medium period (one year). In addition to the relation between multiple RTX courses and occurrence of different drug adverse effects or drug interaction.

Table 1: Different hematological and non-hematological side effect of Rituximab

| Hematological side effect of RTX | Non-hematological side effect of RTX |
|---|---|
| Lymphopenia<br>Leukopenia,<br>Neutropenia,<br>Thrombocytopenia,<br>Anemia. | Infusion reactions<br>Infections (viral, bacterial, fungal)<br>Renal: tumor lysis syndrome<br>Respiratory reactions<br>Cardiovascular: (supraventricular arrhythmias, tachycardia, peripheral edema, non-ischemic cardiomyopathy, hypertension)<br>Dermatologic reactions<br>Gastrointestinal: (diarrhea, nausea, and vomiting)<br>Neurological disorders: (dizziness, anxiety, depression, headache, and insomnia). |

**Literature Review**

As biologic agents have become available, the treatment of autoimmune diseases and hematological malignancies has become more precise and targeted. When compared to many other chemotherapeutic agents, such biologics have demonstrated relatively good tolerability. RTX is a monoclonal antibody that targets the B-cell marker CD20 and is commonly used to treat B-cell lymphoma, lymphoproliferative disorders, and inflammatory conditions that are resistant to conventional therapy, such as RA ( Rheumatoid Arthritis).

As a result of extensive use of RTX, the FDA has received 12,448 reports of adverse effects, including pyrexia ( increase in human body temperature ), febrile neutropenia, pneumonia, and anemia being the most common. This will increase the cost of health insurance and hospitalization responsibility especially when they require an ICU admission. Also, reports documented that, RTX had been implicated as the suspect drug that caused in about 4% of these cases (Zadeh et al., 2019, Kasi et al., 2012). The most common hematologic adverse effect of RTX was lymphopenia, which was the most common hematological adverse effect. There were also reports of leukopenia, neutropenia, thrombocytopenia, and anemia (Ram et al., 2009). The non-hematological adverse effects were infusion reactions, infections, Immunologic disorders, renal disorders, cardiac disorders, respiratory disorder, gastrointestinal disorders and dermatologic disorders.

Infusion reactions: These are the most common and dangerous side effects of the RTX. In randomized controlled trials, 80% to 90% of patients receiving RTX had allergic or anaphylactic reactions (Kasi et al., 2012). Many reactions usually developed or appeared within 30 to 120 min after the first infusion and can differ in severity from mild to life-threatening. Fever, skin rash, chills, urticaria, hypotension, angioedema, ventricular fibrillation, shock, anaphylaxis, and death are all possible infusion reactions (Cohen et al., 2006, Coiffier et al., 1998).

Infections: Although studies have shown that RTX raises the risk of infectious complications within a year of treatment completion, most infections resolved or treated without significant consequences. Bacterial, viral, and fungal infections can all occur. John Cunningham virus infection, hepatitis B and C, herpes simplex, varicella-zoster, Cytomegalovirus, and West Nile virus are examples of new or reactivated viral infections (Avilés et al., 2009). Aksoy et al., 2007 found that, patients with lymphoma were most commonly infected with HBV (39.1%), cytomegalovirus (23.4%), varicella-zoster virus (9.4%), and others (28.1%). (Aksoy et al., 2007). Therefore, patients under RTX therapy supposed to HBV reactivation risk and older patients are more susceptible to emerging of severe infectious complications like pneumonia and colitis which may be fatal infections after RTX administration (Copelan et al., 2009).

Renal disorders: RTX monotherapy has been associated with acute kidney injury due to tumor lysis syndrome, especially in NHL (Taylor and Lindorfer, 2007). Within 24 hours of the first infusion, tumor lysis syndrome can cause hypocalcemia, hyperuricemia, hyperphosphatemia and acute renal failure. Renal toxicity has been observed in studies combining RTX and cisplatin.

Cardiovascular disorders: Different cardiovascular adverse effects have been reported including tachycardia, non-ischemic cardiomyopathy, peripheral edema, supraventricular arrhythmias, chest pain, severe hypertension and cardiac tamponade (Cheungpasitporn et al., 2017). Myocardial infarctions have also been documented (Keystone et al., 2007). In addition, RTX has occasionally been associated with fatal heart failure (either monotherapy or combination therapy), independent of pre-existing heart conditions or history of consecutive heart failure (Lenz et al., 2005, Keystone et al., 2007). Patients with a history of angina or arrhythmias necessarily need a cardiac monitoring during and after RTX therapy.

Respiratory disorder: Therapy with RTX induce different respiratory ill include upper respiratory tract infections, cough, rhinitis, bronchospasm, epistaxis, pulmonary toxicity and dyspnea. Moreover, status asthmaticus, diffuse alveolar hemorrhage, hypersensitivity pneumonitis, and bronchiolitis obliterans have been documented (Kasi et al., 2012). In a 2011 study, 5.3% of 418 patients who received RTX monotherapy established adverse pulmonary reactions (Kang et al., 2012).

Dermatologic /mucocutaneous disorders: Several dermatological disorders were reported with RTX treatment including skin rash, pruritis, alopecia, and life-threatening reactions like paraneoplastic pemphigus, toxic epidermal necrolysis and Stevens-Johnson syndrome (Scheinfeld, 2006). In a non-randomized study of 356 patients treated with RTX monotherapy for lymphomas, 37% developed urticaria, rash, and itching, while 2% of the study participants experienced serious cutaneous adverse effects (Gellrich et al., 2005).

Gastrointestinal disorders: Occurrence of abdominal pain in patients under RTX therapy ought thoroughly investigation for an acute abdomen. Patients treated with RTX for NHL had suffered 47 cases of bowel obstruction (nine deaths) and 37 cases of gastrointestinal perforation (four deaths) by the end of 2006 (Cornejo et al., 2009). A study reported an average onset of symptoms for 98 patients treated with combination chemotherapy containing RTX is approximately 6 days after the first dose as well as some serious gastrointestinal complications, including one fatality (Avilés et al., 2007).

Neurological disorders: Different neurological signs were reported in patients receiving RTX. A cerebrovascular infarction, epilepsy, convulsion, and serotonin syndrome were described in 465 patients treated with RTX for rheumatoid arthritis that was resistant to methotrexate (Emery et al., 2006). The incidence of fatal ischemic and hemorrhagic strokes is extremely rare (Cornejo et al., 2009). Other neurological signs include dizziness, anxiety, headache, insomnia and depression.

Pregnancy: RTX therapy during the third trimester of pregnancy can induce immunosuppression in the newborn. Since the long-term effects of RTX are unknown, it is recommended more investigation during treatment and for a year after the last dose (Cohen et al., 2006).

## METHODOLOGY:

### Design and Setting

A retrospective cross-sectional study was conducted from July 2020 to August 2021 at KSUMC, Riyadh, KSA. The patients included in the study had received RTX treatments deemed appropriate by their treating physicians. Patients included in the registry received different RTX regimens depending on their autoimmune or malignancy disease since RTX was prescribed off-label. In addition to receiving guidance on data collection, participating physicians were informed of the inclusion and exclusion criteria before patients were selected. In brief, Physicians or health care providers who had agreed to participate were asked to provide retrospective data on any patient with an autoimmune disease diagnosed prior to 31 August 2021 who had received RTX. Principal investigators at the KSUMC collected data retrospectively by using an Excel form for data collection. To eliminate any inconsistencies in data collection, the electronic Excel spreadsheets were designed to be available only to target population members with permits for access. A selection of 12 diagnoses could be entered. Other autoimmune diseases were classed as 'other autoimmune diseases' when they were not pre-defined. Data entry was open between the first of July 2020 and the end of August 2021.

### Data collection and ethical approval

The study involved 89 Saudi patients aged 18 to 90 years old. The patients enrolled on the register all had an autoimmune or malignancy diagnosis from their electronic files and if their response to previous standard of care was inadequate, they were excluded. To be eligible for RTX, RTX had to have begun on or after July 2020, with the last follow-up on or before 31 August 2021. The data was collected from the patient files. They were organized on Excel data collection sheets, and the following variables were examined: age, gender, height, body weight, BMI, smoking history, any history of allergy, comorbidity, other

medical history and finally indication for RTX. Electronic Excel data collection was based on the care provided by physicians and patient data were entered under a code number according to current standards, so participating patients' data could only be accessed by the physicians who entered the data via the data collection sheets. The study was initiated following ethical approval by the Institutional Review Board (IRB) of Riyadh Elm University (REU), Riyadh, approval no. "FPGRP/2021/591/487/461".

**Sample size and statistical analysis**

All eligible patients admitted to KSUMC between July 2020 to August 2021 will be recruited in this study. All patients who fulfill inclusion criteria were included in this study. Patients were excluded if they had fewer than three months of continuous RTX therapy before study. We used this criterion for patient selection rather than random assignment for complicated cases. Data analysis was carried out using the SPSS software, version 22 (IBM. Armonk, NY: IBM Corp). The data were analyzed to determine the prevalence of non-hematological side effects of RTX in KSUMC. Descriptive and inferential statistics were used to report the data. ANOVA testing for differences between departments and disease types was performed, as well as standard descriptive statistics (mean, median). Responses for individual diseases were analyzed using the chi-squared test and a row mean difference test to determine if there were differences in distribution patterns of response between diseases. Statistical significance was defined as a p-value less than 0.05.

**RESULTS:**

In this study, 89 Saudi patients were included with a diagnosis of an autoimmune condition or malignancies disease and treated with RTX. Patients with DLBCL (36.0%) were most likely to be diagnosed. Data related to the study characteristics for participant patients was recorded and analyzed (Table 2). The patients were 53 (59.6%) male and 36 (40.4%) females. The mean age of eligible patients was 53.4; however, they ranged from 18 to 90. Most of the participants were between the ages of 46 and 65 years. In addition, 48.3% of patients belonged to this age group. Patients aged 45 and less and those over 65 accounted for 28.1% and 23.6%, respectively. Patients were a mean weight, length and BMI of the patients were 73.2 kg, 163.2 cm and 26.4 respectively. The total study population had eight smokers (8.9%) and only three allergic patients (3.4%).

We have collected data as laboratory investigations for the study patients included ALT, AST, albumin, bilirubin, serum creatinine (SrCr) and creatinine clearance (CrCl). The range of ALT and AST was varied from 36 to 354 and 8 to 313 U/L. For ALT, the mean was 214±55.2 U/L and for AST, it was 181±36.4 U/L. The albumin and bilirubin ranges were varied from 17.23 to 48.52 g/dL and the mean was 38±34.3 g/dL. Furthermore, the range of bilirubin was varied from 4.79 to 174.21 mg/dL. However, the mean was 161±28.6 mg/dL respectively. CrCl and SrCr were the most important measured laboratory parameters. The range of SrCr was varied from 26 to 447 µmol/L, whereas the mean was 79.3 ±16.2 µmol/L. The range of CrCl varied from 8 to 177 mL/min, with a mean of 121.1 ±35.3mL/min (Table 2).

**Table 2: Demographic and clinical features of patients receiving RTX (n=89)**

| Variable | Outcome | Frequency | Percentage | Mean ±SD | Min-Max |
|---|---|---|---|---|---|
| Gender | Male<br>Female | 53<br>36 | 59.6%<br>40.4% | NR | NR |
| Age | ≤ 45 years<br>46-65 years<br>> 65 years | 25<br>43<br>21 | 28.1%<br>48.3 %<br>23.6 % | 53.4 ±55.6 | 18-90 |
| Weight, kg | ≤ 60 kg<br>61-80 kg<br>> 80 kg | 27<br>33<br>29 | 30.3%<br>37.1%<br>32.6% | 73.2 ±57.3 | 47-113 |
| Length (Cm) | ≤ 160<br>> 160 | 35<br>54 | 39.3%<br>60.7% | 163.2 ±24.7 | 141-183 |
| BMI | ≤ 25<br>> 25 | 30<br>59 | 33.7%<br>66.3% | 26.4 ±16.6 | 16.1-44.7 |
| Smoking | Smoking<br>Nonsmoking | 8<br>81 | 8.9%<br>91.0% | NR | NR |
| Allergy | Patient with allergy | 3 | 3.4% | NR | NR |
| Clinical investigations | ALT (U/L)<br>AST (U/L)<br>Albumin (g/dL)<br>Bilirubin (mg/dL)<br>SrCr (mmol/L)<br>CrCl (mL/min) | -<br>-<br>-<br>-<br>-<br>- | -<br>-<br>-<br>-<br>-<br>- | 214±55.2<br>181±36.4<br>38±34.3<br>161±28.6<br>79.3 ±16.2<br>121.1 ±35.3 | 36 - 354<br>8 - 313<br>17.23 - 48.52<br>4.79 - 174.21<br>26 - 447<br>8 - 177 |
| Dose (mg) | ≤ 500 mg<br>501-700 mg<br>> 700 mg | 8<br>58<br>23 | 9.0%<br>65.2%<br>25.8% | 762.5±26.1 | 375-1000mg |
| Duration | 3 – 6 months<br>7 – 9 months<br>1 year | 31<br>56<br>2 | 34.8%<br>62.9%<br>2.2% | NR | NR |

SD, standard deviation; NR, not reported.

In this study, the most common indications for RTX were DLBCL (36%), B cell lymphoma (20.2%), non-Hodgkin's lymphoma (NHL) (15.7%), chronic lymphocytic leukemia (CLL) (10.1%), and Hodgkin's lymphoma (7.9%). The mean dose of RTX received by the patients was 2,860 mg/patient over a median period of 240 days. The most common doses of RTX prescribed in our study were 550 mg, 750 mg, and 800 mg. However, the duration of treatment ranged from 1 to 12 cycles and the most common was 6 cycles (50.6%) followed by 3 and 4 cycles (14.6%) and (13.5%). Patients with NHL -associated T cell/histiocyte rich large B cell lymphoma, stage IV (bone, lung, liver, spleen) received the highest doses of RTX (mean dose/ patient 2,980 mg).

**Table 3: Diagnoses, patient number (%), rituximab doses and the number of cycles received by patients with various autoimmune diseases**

| Diagnosis | Patients No | Percentage | Mean (SD) RTX dose, mg | Treatment Cycles |
|---|---|---|---|---|
| DLBCL | 32 | 36.0 % | 786±24.2 | 1 – 8 |
| B cell lymphoma | 18 | 20.2 % | 752±55.6 | 2 – 6 |
| NHL | 14 | 15.7 % | 704±16.3 | 3 – 6 |
| Waldenstrom macroglobinemia | 1 | 1.1 % | 700 | 3 |
| CLL | 9 | 10.1 % | 772±36.1 | 4 – 6 |
| Systemic lupus erythematosus | 1 | 1.1 % | 880 | 4 |
| Tubular left breast | 1 | 1.1 % | 590 | 3 |
| Rheumatoid Arthritis | 1 | 1.1 % | 1000 | 2 |
| Splenomegaly | 1 | 1.1 % | 660 | 3 |
| Hodgkin's lymphoma | 7 | 7.9 % | 555±35.3 | 2 – 6 |
| Burkitt's lymphoma | 1 | 1.1 % | 740 | 3 |
| Chronic thrombocytopenic purpura | 2 | 2.2 % | 800 | 4 |
| Gastric MALT lymohoma | 1 | 1.1 % | 600 | 12 |

DLBCL, Diffuse large B-cell lymphoma; NHL, non-Hodgkin's lymphoma; CLL, chronic lymphocytic leukemia; SD, standard deviation.

**Non-Hematological Side Effects of RTX**

In this study, infection was the most important factor observed. The overall infection rate during the study was 34.8% and the remaining had no documented infection during the course of treatment. Infected patients had glomerulonephritis (8 patients), hepatitis B infection (6 patients) and renal toxicity (5 patients). There were 11 bacterial infections, 6 viral (n = 6), and 1 fungal (n = 1) infections. During the first 6 months following RTX use, infections were most common, but they decreased after that ($\chi^2$ trend test, $P < .001$). In the study, only a few patients had more than one infection; four patients had two different infections. During the observation period of the study, only one infection was observed in most cases. Compared to the overall population, 3.6% of infections were mild, 12.1% were moderate, and 1.1% of patients had severe infections. In severe and mild cases, the most common bacterial infections were bacteremia, lower respiratory tract infections, upper respiratory tract infections, acute gastroenteritis, skin and soft tissue infections, and urinary tract infections. However, these patient groups were representing or identifying a disease-related higher risk for infections. Most clinically relevant infections occurred within six months after the first RTX infusion, according to the distribution of infections analysis (Figure 2). Overall, infection rates (ANOVA) were not significantly correlated to any diagnosis; however, a significant association was found between higher RTX doses and severe infection.

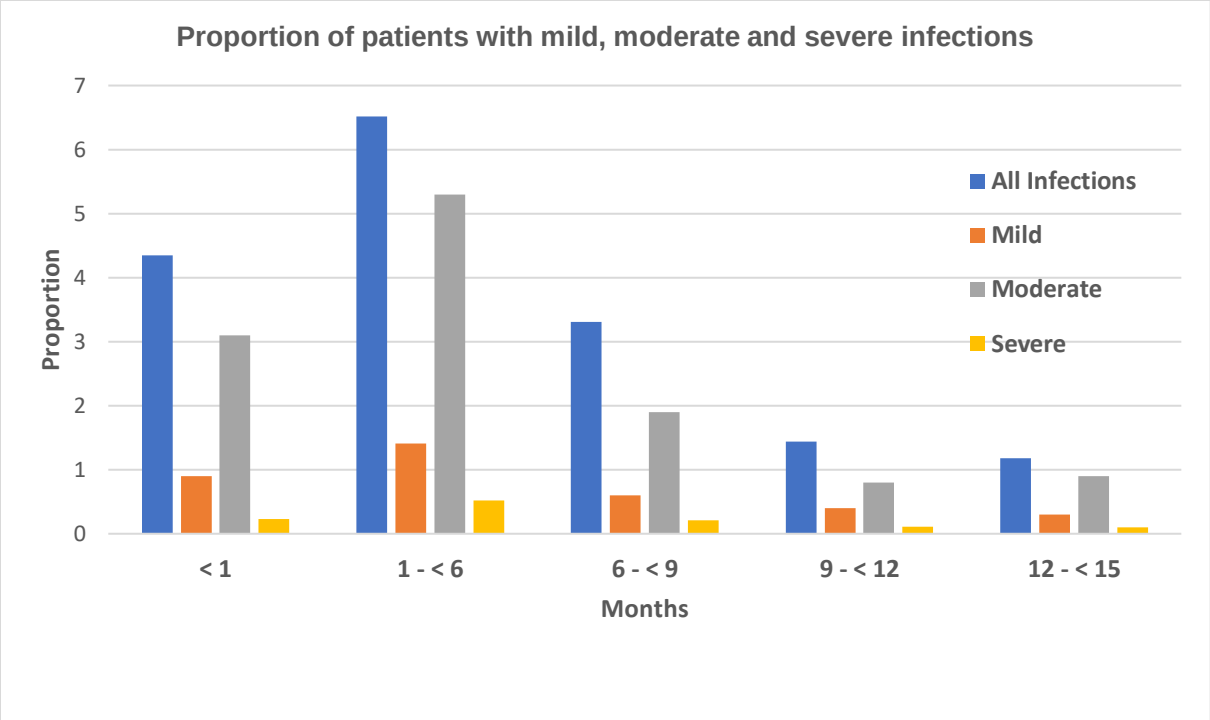


**Figure 2: Proportion of patients with mild, moderate, and severe infections associated with RTX.**

**Noninfectious Adverse Drug Events**

In this study, there have been no reports of death among the 89 patients treated with RTX. Moreover, there were more non-hematological adverse drug events occurring in patients receiving RTX (85.2%). These adverse drug events were including infusion-related reactions (defined as any adverse drug events reported during or within 24 hours of infusion) (24 patient), tumor lysis syndrome (14 patient), cardiovascular adverse reaction (16 patient), renal toxicity (5 patient), bowel obstruction and perforation (7 patient), hypertension (32 patient), dyslipidemia (14 patient), hypothyroidism (11 patient), kidney dysfunction (11 patient), heart failure (7 patient), diabetes mellitus (33 patient) and thrombosis (19 patient). Occasionally, patients experience more than one adverse effect during the study.

A total of 87 patients (97.8%) were received more than one infusion of RTX. In total, 50.6% of patients received six RTX infusions across all diagnoses, followed by 19.2% , 14.5% and 13.5% for five, four and three courses, respectively, with two patients receiving only one course (2.2%). Over 26% of patients receiving RTX treatment had infusion-related reactions during the study. The reactions associated with infusion occurred in 24 patients, typically after the first dose (5 patients [20.8%]). The majority of patients (19 [79.2%]) were able to complete the infusion and were received subsequent doses without a recurrence. Most of the infusion associated reactions were occurred in the first injection (Figure 3). Transient allergy symptoms, such as hypotension, respiratory distress, itchy skin and urticarial are usually resolve after pausing the infusion or giving oral antihistamines. If necessary, paracetamol was prescribed in addition to antihistamines and/or bronchodilators administered intramuscularly or intravenously. The infusion was stopped immediately in patients who experienced a severe reaction to their infusion. Upon the symptomatology returning to normal, the rate of infusion was reduced to half what precipitated the reaction.

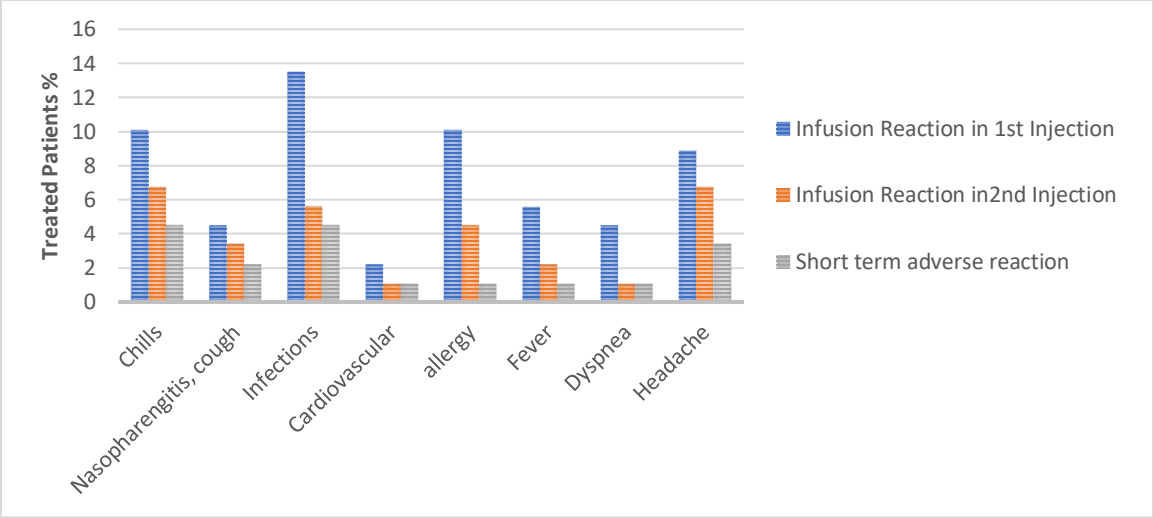


**Figure 3: Types of adverse reaction during the 1st, 2nd infusion and short term**

Tumor lysis syndrome cases were most frequently reported after repeated infusions in 14 (15.7%) of all patients. A cardiovascular adverse reaction was also reported in 17.9% of the study population. These include abnormal heart rhythms (11 patients [68.8%]), coronary artery disease (3 patients [18.8%]) and cardiomyopathy (1 patient [6.3%]). Additional adverse effects including renal toxicity (5,6%), bowel obstruction and perforation (7,9%), dyslipidemia (15,7%), hypothyroidism (12,4%), kidney dysfunction (12,3%), heart failure (7,9%), thrombosis (21.3%) were also observed. There were also 32 patients with hypertension (36.0%) and 33 patients with diabetes (37.1%) Table 4.

**Table 4. Drug-related adverse reactions**

| Adverse reaction | No. (%) |
|---|---|
| Infection (bacterial, viral and fungal) | 31 (34.8%) |
| Infusion-related reactions | 24 (26.9%) |
| Tumor lysis syndrome | 14 (15.7%) |
| Cardiovascular adverse reaction | 16 (18.7%) |
| Renal toxicity | 5 (5.6%) |
| Bowel obstruction and perforation | 7 (7.9%) |
| Hypothyroidism | 11 (12.4%) |
| Dyslipidemia | 14 (15.7%) |
| Kidney dysfunction | 11 (12.3%) |
| Heart failure | 7 (7.9%) |
| Hypertension | 32 (36%) |
| Diabetes mellitus | 33 (37.1%) |
| Thrombosis | 19 (21.3%) |

## DISCUSSION:

In this study, we assessed the prevalence of non-hematological side effects of RTX among Saudi patients with malignancies or autoimmune diseases at KSUMC, Riyadh, KSA. This study had a higher proportion of males compared to previous studies because of the higher prevalence of malignancy and autoimmune disease in females (Ngo et al., 2014). Maybe the small sample size contributed to this finding. The mean age was almost similar to other studies as well (Vidal et al., 2009).

Generally, in the present study most patients who received RTX had at least a partial response, and RTX was well tolerated across several autoimmune diseases. Clinical investigations have expressed some concerns about RTX, which is believed to increase the risk of adverse events and severe infections in patients with cancer and autoimmune conditions. From our study, it is therefore essential to understand the rate of infections associated with biologic drugs in order to ensure that treatments are both effective and safe over the long term.

In the present study we have reported that, the overall incidence of non-hematological adverse drug events (Table 4) occurring in patients receiving RTX (84.2%) as in a previous study in Italy (Covelli et al., 2010). Infusion-related reactions were higher (27%) with RTX during or following the first infusion. Most of these mild-to-moderate infusion-related reactions included pyrexia, flushing, nasopharyngitis, cough, hypertension, dyspnea, and dizziness, which diminished over time. During the first infusion, a greater proportion of patients received RTX treated patients (23%) suffering acute infusion reactions, such as fever, chills, pruritus, skin rash, cough, angioedema, rigors, throat tightness, sneezing, bronchospasm, with or without hypertension or hypotension more than (18%) in the previous study (Heelan et al., 2014).

From other investigators, we have observed the majority of patients in similar studies reported mild to moderate side effects, including chills, headaches, hypertension, itching, skin rash, shortness of breath and sore throat, especially during the first injection (Bar-Or et al., 2008; Hawker et al., 2009; Alldredge et al., 2018).

However, the possibility of patients experiencing an infusion-related reactions reduced with the 2nd infusion, as a result, patients receiving RTX experienced fewer acute infusion reactions (6.7%). Infusion reactions in one (1.1%) of the patients treated with RTX were classified as serious adverse effects (hypertension and anaphylaxis respectively), however, the majority of reactions were mild or moderate (Heelan et al., 2014).

In the present study patients with autoimmune diseases treated with RTX are at increased risk of symptoms such as moderate and serious infectious events (bacterial, viral and fungal), cardiovascular disease, renal toxicity, thrombosis, etc. Furthermore, this autoimmune condition requires a long duration of drug administration, which increases the risk of side effects. There is an almost two-fold greater risk in patients with cancer and autoimmune disease than in general population. Additionally, study have reported bacterial infections are a major cause of morbidity and mortality among patients with autoimmune diseases (Alldredge et al., 2018). The rapid depletion of normal B cells caused by RTX treatment can lead to infective complications as a result of a rapid loss of normal B cells. However, the levels of serum immunoglobulins do not increase following conventional treatment and are not consistently linked to increased infection rates (Lee et al., 2008).

During our retrospective study period, the infection rate was 34.8%. The main infection was bacterial and viral origin. This result was comparable with the previous studies on patients with hematological malignancies who received rituximab (Hainsworth et al., 2003; Lee et al., 2008; Aksoy et al., 2009; Vidal et al., 2009). A systematic review in lymphoma patients by Aksoy et al. in 2009 found significantly higher rates of infections among those who had received rituximab maintenance treatment. Similarly studies, a meta-analysis of randomized controlled trials found that patients in the maintenance rituximab arm had more infection-related adverse events than those in the observation arm (relative risk 1,99, 95% interquartile range 1,21–3,27). The effect was more pronounced when only grade 3 or 4 infection-related adverse events were included in the analysis (RR 2.90, 95% CI 1.24–6.76) (Vidal et al., 2009). As previously described, most patients treated with RTX developed some form of infection, most commonly nasopharyngitis and upper respiratory tract infection. This may be due to numerous confounding factors such as concurrent use of immunosuppressive agents, underlying medical conditions like cancer and diabetes mellitus which had made them more susceptible to life-threatening infections (Lucas et al., 2007).

The serious infection was reported in several studies with different percentage (Aksoy et al., 2009). Serious pneumonia infection was occurred in one patient with six courses of treatment during the study period. Further studies for microbial infection are required to determine the different species of infectious bacteria that need to be isolated and identified during the RTX treatment.
In the current study, all patients receiving RTX treatment were screened for hepatitis B virus. Patients who received

RTX follow-up therapy were found to have hepatitis B infection in 6.7% of cases. Different studies have reported the reactivation of hepatitis B after RTX follow-up therapy in patients with lymphoma (Sera et al., 2006; Ennishi et al., 2008, Dizdar et al., 2008). Sera et al. (2006) reported that a patient with chronic hepatitis that was negative for HBV surface antigen (HBsAg) and anti-HBV surface antibodies (anti-HBsAb) developed HBsAg-positive during RTX therapy. In HBsAg-positive patients, therefore, RTX-based therapy can cause serious HBV-related complications, even death (Pei et al., 2010). RTX must therefore be preceded by a baseline HBV screening. So, we were agreed with the above mentioned studies.

The duration of rituximab therapy or number of courses may also be significant. The duration of rituximab treatment, the reduction in IgM levels after rituximab therapy, and G-CSF administration were all associated with an infection risk in our study, according to a retrospective study of hematology patients (Kanbayashi et al., 2009). A retrospective study of hematology patients receiving rituximab found that duration of treatment, reduction of IgM after rituximab therapy, and G-CSF administration were related to infection risk. In our study, the rate of adverse events was highest during the 1st course, declined during the 2nd course, and remained stable at the end of the study.

## CONCLUSION:

This study is primarily concerned with Saudi patient safety. Globally, RTX is well tolerated in the short-term (single treatment) or in the medium-term. In conclusion our study found simple clinical prognostic factors to predict side effects of RTX treatment. Infection was found to be the most important adverse RTX therapy. The most frequent infections were bacterial and viral. Patients who received RTX follow-up therapy were found to be infected with hepatitis B. Therefore, baseline screening for HBV is mandatory prior to starting RTX.

**Recommendation:**

Bacterial and viral infections have been found to be the most common adverse reaction associated with RTX therapy. Following RTX follow-up therapy, all patients were found to have hepatitis B. Therefore, baseline HBV testing is necessary before starting RTX. Further investigation is needed to determine the prevalence of non-hematological side effects of Rituximab in Saudi Arabia.

**Limitation:**

In this study, there were several limitations: first, rituximab regimens variable according to the department and type of disease. Second, this study has different parameters which can bias study results towards different adverse drug reaction for the tested RTX. Other limitations of this study can be attributed to its observational design. There has been a recent emphasis on the importance of patient's registries in autoimmune, cancer and rare diseases, since they permit the collection of detailed case studies with standardised information and improve understanding of RTX adverse effects. The duration of exposure to rituximab was relatively short (one years), which limited precision for safety analyses.

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It is my honor and great pleasure to thank my second home Riyadh Elm University for providing me with the opportunity to study the specialty of my dreams and for enhancing the academic environment with all facilities to excel and succeed. Heartfelt thanks and appreciation for all the efforts and guidance of the faculty members who taught us the professional knowledge and skills I will never forget all the great support. Thanks, and gratitude goes to all the administrative staff and all the great people of the auxiliary services working day and night at the university for their continuous efforts to facilitate our needs and making the academic environment as comfortable as ever possible.

Best Wishes,
MOHAMMAD HADI ALMOTARED

**ABBREVIATIONS**

| | |
|---|---|
| ALT | Alanine aminotransferase |
| AST | Aspartate aminotransferase |
| CLL | Chronic lymphocytic leukemia |
| CrCl | Creatinine clearance |
| DLBCL | Diffuse large B-cell lymphoma |
| GPA | Granulomatosis with polyangiitis |
| KSUMC | King Saud University Medical City |
| McAbs | Monoclonal antibodies |
| MP | Microscopic polyangiitis |
| MS | Multiple sclerosis |
| NHL | Non-Hodgkin's lymphoma |
| PV | pemphigus vulgaris |
| RA | Rheumatoid arthritis |
| RTX | Rituximab |
| SrCr | Serum creatinine |
| IRB | Institutional Review Board |

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## APPENDICES
## ETHICAL APPROVAL LETTER

**Approval Letter by the Institutional Review Board of Riyadh Elm University**

Dear Mohammed Hadi Almutared

The research proposal submitted to the Research Center by you titled "'Study the Prevalence of Non- Hematological Side Effects of Rituximab in Riyadh, Saudi Arabia." with a registration number FPGRP/2021/591/487 has been reviewed by the Institutional Review Board (IRB) of Riyadh ElmUniversity (REU).

The IRB observed that you have complied with the ethical requirements of the IRB at Riyadh Elm University. Therefore, your research proposal has been approved with the IRB approval number "FPGRP/2021/591/487/461".

This approval is valid for one year starting 08-Jun-2021. If you require more time for your study, please submit a continuation request to the IRB through the research center portal. In case of any changes in thestudy protocol, adverse events or termination of the study, please report it to the IRB immediately. Also, note that the IRB might audit your research records at any time.

We wish you a successful project.
Best Regards,
Sincerely yours

Dr. Omar Alkadhi BDS,MSc. Chairman,
Institutional Review BoardRiyadh Elm
University

Name of Chief Investigator: Mohammed Hadi Almutared Name(s) of
Co Investigator: Mohammed Hadi Almutared, Dr.Saeed Al-qahtani, ,
Name(s) of Co Supervisor: Dr. Tanveer Khan

**دراسة انتشار الآثار الجانبية غير الدموية للريتوكسيماب في الرياض، المملكة العربية السعودية**

**الملخص**

**المقدمة:** تم استخدام علاج ريتوكسيماب للأورام الخبيثة الدموية وأمراض المناعة الذاتية لفترة طويلة، وقد تم توثيق فعاليته وسلامته جيدًا. على الرغم من النتائج المتضاربة من التجارب السريرية فيما يتعلق بالارتباط بين ريتوكسيماب والالتهابات، فقد تم الإبلاغ مؤخرًا عن زيادة حالات العدوى بين المرضى الذين يتلقون ريتوكسيماب للأورام اللمفاوية. حتى الآن، لم تكن هناك أي تجربة إكلينيكية تربط ريتوكسيماب بآثار جانبية غير دموية مختلفة.

**الأهداف:** التحقيق في مدى انتشار الآثار الجانبية غير الدموية في المرضى ومرضى العيادات الخارجية الذين يتلقون علاج ريتوكسيماب في المملكة العربية السعودية.

**الطرق:** أجريت دراسة مقطعية بأثر رجعي من يوليو 2020 إلى أغسطس 2021 في المدينة الطبية بجامعة الملك سعود ، الرياض، المملكة العربية السعودية. تم تضمين جميع المرضى المتعاقبين الذين حضروا للمدينة الطبية في الفترة من يوليو 2020 إلى أغسطس 2021 والذين تمت إحالتهم بمرض المناعة الذاتية أو السرطان فى هذه الدراسة. تم استخدام الإحصاء الوصفى والاستنتاجى للإبلاغ عن البيانات.

**النتائج:** تم وصف ريتوكسيماب بشكل شائع لأنواع مختلفة من السرطان وأمراض المناعة الذاتية. تم تقييم التفاعل الضار غير الدموي لمدة تصل إلى عام واحد في المرضى الذين عولجوا بريتوكسيماب .كانت المؤشرات الأكثر شيوعًا للريتوكسيماب هي36) DLBCL ٪ (، سرطان الغدد الليمفاوية B (20.2٪ (، ليمفوما اللاهودجكين15.7) (NHL) ٪ (، ابيضاض الدم الليمفاوي المزمن (10.1٪) ، وسرطان الغدد الليمفاوية هودجكين (7.9٪). تم إجراء تحليل للارتباط بين ريتوكسيماب والعدوى بين مرضى الأورام الخبيثة الدموية واضطرابات المناعة الذاتية. كان الحدث الضار الأكثر شيوعًا هو العدوى والتفاعلات المرتبطة بالتسريب. لوحظ خلال الدراسة أن معدل الإصابة 34.8٪، والمرضى المصابون بالتهاب كبيبات الكلى (9٪) وعدوى التهاب الكبد B (6.7٪ ( وتسمم كلوي (5.6٪). أظهرت نتائج الدراسة أن ريتوكسيماب كان جيد التحمل بعد دورة واحدة أو أكثر. لم تؤد الدورات المتعددة إلى زيادة الإصابات الخطيرة.

**الخلاصة:** تشير البيانات الواردة من هذه الدراسة إلى أن ريتوكسيماب شائع الاستخدام لأمراض المناعة الذاتية والسرطانات ذات الآثار المفيدة المحتملة. على الرغم من أن ريتوكسيماب يحتوي على مجموعة واسعة من الآثار الجانبية غير الدموية، إلا أن علاجه جيد التحمل لأمراض السرطان و المناعة الذاتية. لتوضيح العلاقة بين ريتوكسيماب والعدوى، هناك حاجة إلى مزيد من البحث.
**كلمات البحث:** ريتوكسيماب ، غير دموي ، مناعة ذاتية ، عدوى ، ليمفوما هودجكين.

**دراسة انتشار الآثار الجانبية غير الدموية لدواء الريتوكسيماب في الرياض، المملكة العربية السعودية**

**بحث ماجستير العلوم في الصيدلة السريرية بواسطة:**
**محمد هادي داوود ال مطارد**
**طالب الدراسات العليا في الصيدلة السريرية**

تم التسليم استيفاء جزئياً لمتطلبات درجة ماجستير العلوم في الصيدلة السريرية لعمادة الدراسات العليا بجامعة رياض العلم، الرياض، المملكة العربية السعودية

**المشرف : الدكتور سعيد القحطاني**
أستاذ مشارك، كلية الصيدلة، جامعة الملك سعود، الرياض، المملكة العربية السعودية
**المشرف المشارك : الدكتور تنفير خان**
أستاذ مشارك، كلية الصيدلة، جامعة رياض العلم، الرياض، المملكة العربية السعودية

تم مناقشة الرسالة والموافقة عليها يوم الثلاثاء 7 ديسمبر 2021
الموافق 3 / 5 / 1443 هـ