

Risk Factors for Infusion Reactions Associated With Rituximab Therapy

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Abstract

Background/Aim: Although rituximab is used to treat a range of diseases, the high frequency of rituximab-associated infusion reactions (IRs) poses a clinical challenge. This study aimed to identify pre-treatment risk factors associated with rituximab-induced IRs using retrospective patient data.

Patients and Methods: We retrospectively analyzed the medical records of patients treated with rituximab. Data were compared between patients with and without IRs.

Results: Among the variables assessed, an elevated C-reactive protein (CRP) level prior to rituximab administration was significantly associated with IR occurrence (odds ratio=2.591; 95% confidence interval=1.160-5.791; $p=0.020$).

Conclusion: Elevated pre-medication levels of CRP are a significant risk factor associated with the use of rituximab, thereby highlighting the need for close monitoring of patients receiving rituximab who present with elevated CRP levels prior to the initiation of therapy.

Keywords: Rituximab, infusion reactions, risk factor, C-reactive protein, clinical treatment.

Introduction

Rituximab is a chimeric murine/human anti-cluster of differentiation (CD)20 monoclonal antibody (1) that binds to CD20 antigens on the surface of B cells, thereby triggering complement-dependent and antibody-dependent cell-mediated cytotoxicity (2). It is an important drug for the treatment of B-cell lymphoma (3, 4), and has been used in cases of transplant rejection,

lupus nephritis with inadequate response to existing therapy, and immune thrombocytopenic purpura (5, 6). Infusion reactions (IRs) are among the most frequently observed side effects of rituximab medication (7). These include rashes, flushing, generalized pruritus, urticaria, nausea/vomiting, throat tightness, bronchospasms, dyspnea, hypoxia, wheezing, and, in severe cases, hypotension (8). Although appropriate management of IRs is essential for the safe administration of rituximab, details



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of the mechanisms underlying the development of these reactions following drug administration have yet to be sufficiently determined (9). Although pre-medication with acetaminophen, antihistamines, and corticosteroids has been established to prevent the development of rituximab-induced IRs, these can still occur in certain instances (10). At present, it is extremely difficult to predict the likelihood of an IR prior to the administration of rituximab, thereby highlighting the importance of identifying patients with a heightened susceptibility to IRs, so as to be able to take the necessary precautionary measures prior to the initiation of treatment. Currently, however, there are no simple techniques that can be applied to assess the risk of IR occurrence prior to rituximab therapy. Consequently, in this study, we investigated the risk factors for developing an IR-associated rituximab therapy based on a comprehensive retrospective analysis of available patient information.

Patients and Methods

Research patients and study contents. This study was based on the data of inpatients who were treated at the University of Tokyo Hospital between September 2012 and August 2014. Hospitalized patients who received their first dose of rituximab during the aforementioned period were selected. Age, sex, and laboratory values immediately before treatment initiation were extracted from patient information, and details of the diseases requiring rituximab administration were obtained from the patient medical records. Patient information was collected using the opt-out method.

For the purposes of analysis, we selected clinical laboratory data for the following parameters: blood urea nitrogen, creatinine (Cre), aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, albumin (Alb), C-reactive protein (CRP), sodium, potassium, chloride, white blood cells, red blood cells, hemoglobin, hematocrit, and platelets.

Determination of infusion-related reactions. The following symptoms were assessed to be associated with IRs:

anaphylaxis, shortness of breath, hypotension, swelling, rash, pruritus, urticaria, flushing, chest pain, myalgia, arthralgia, chills, headaches, or hypertension (11). Patients for whom any of the aforementioned symptoms were noted in their electronic medical records were considered to have experienced an IR.

Statistical analyses. For the two-group comparison between the IR and non-IR groups, we used Student's *t*-test to evaluate quantitative data, whereas Fisher's exact test was used to evaluate qualitative data. Multiple logistic regression (MLR) analysis was performed using factors with a *p*-value <0.05 in univariate analysis as explanatory variables and the presence or absence of IRs as the objective variable, with odds ratio (OR) and 95% confidence interval (CI) values being determined. On the basis of these analyses, we identified the risk factors for the development of IR following rituximab administration. In addition, we used receiver operating characteristic (ROC) curves to determine whether the two groups could be distinguished based on their CRP levels. Statistical analyses were performed using Bell Curve for Excel (Social Survey Research Information Co., Ltd, Shinjuku-ku, Tokyo, Japan) and R version 3.4.3 (R Development Core Team, Vienna, Austria), with the level of statistical significance being set at *p*<0.05.

Ethical approval. This study complied with the Ethical Guidelines for Life Sciences and Medical Research Involving Human Subjects, and the study protocol was approved by the Ethics Committee of the Faculty of Medicine at the University of Tokyo (approval number: 2529).

Results

Characteristics of patients with IRs. Table I summarizes the IR status of patients following an initial administration of rituximab based on age, sex, and clinical laboratory values extracted from patient medical records. During the study period, rituximab was administered to 81 patients, among

Table I. Univariate analysis of patient characteristics and clinical laboratory values in the infusion and non-infusion reactions groups.

	Infusion reactions (N=26)	Non-infusion reactions (N=53)	p-Value
Age (years)	62.5±13.8	64.3±13.7	0.569
Sex			
Males (n)	17	30	0.478
Females (n)	9	23	
BUN (mg/dl)	15.3±7.5	14.8±6.4	0.722
Cre (mg/dl)	0.97±0.79	0.74±0.21	0.048
AST (U/l)	22±12	23±11	0.537
ALT (U/l)	29±25	27±21	0.718
LDH (U/l)	276±232	245±98	0.407
Alb (g/dl)	3.5±0.6	3.7±0.4	0.047
CRP (mg/dl)	1.10±1.42	0.33±0.51	<0.001
Na (mmol/l)	139±3	139±3	0.517
K (mmol/l)	4.3±0.4	4.2±0.3	0.260
Cl (mmol/l)	104±2	105±4	0.639
WBC (×10 ³ /μl)	5.0±1.9	5.9±2.6	0.131
RBC (×10 ⁴ /μl)	388±69	397±60	0.563
Hb (g/dl)	11.6±2.3	12.3±1.8	0.148
PLT (×10 ⁴ /μl)	21.4±10.1	24.7±8.6	0.130
Hct (%)	35.0±6.6	37.1±5.0	0.124

Age and clinical laboratory values are expressed as the means±standard deviation. BUN: Blood urea nitrogen; Cre: creatinine; AST: aspartate aminotransferase; ALT: alanine aminotransferase; LDH: lactate dehydrogenase; Alb: albumin; CRP: C-reactive protein; Na: sodium; K: potassium; Cl: chloride; WBC: white blood cells; RBC: red blood cells; Hb: hemoglobin; PLT: platelets; Hct: hematocrit.

whom, two were excluded on the basis of the fact they had fever prior to administration and, consequently, drug-induced IRs could not be reliably determined. Among the remaining 79 patients, IRs were found to have occurred in 26 patients. No significant associations were observed between IRs and age or sex. Moreover, no particular disease trend was observed, as all 26 patients reporting an IR presented with B-cell lymphoma.

Risk factors associated with IR development. Univariate analysis used to identify factors associated with the development of IRs based on clinical laboratory data extracted from patient medical records (Table I) revealed significant differences between the two patient groups ($p<0.05$) with respect to the levels of Cre, Alb, and CRP levels. Subsequent MLR analysis (Table II), enabled us to

Table II. Factors influencing infusion reactions based on multiple logistic regression analysis.

	Coefficient (Estimate)	Odds ratio	95%CI	p-Value
Intercept	-1.342	0.261	0.002-29.235	0.577
Cre (mg/dl)	0.782	2.185	0.471-10.133	0.318
Alb (g/dl)	-0.159	0.856	0.261-2.800	0.797
CRP (mg/dl)	0.952	2.591	1.160-5.791	0.020

95%CI: 95% confidence interval; Cre: creatinine; Alb: albumin; CRP: C-reactive protein.

identify an elevated level CRP prior to rituximab treatment (OR=2.591; 95%CI=1.160-5.791; $p=0.020$) as a potential risk factor for IR development, which was substantiated by subsequent ROC analysis, which revealed that CRP levels prior to rituximab administration were a reliable predictor of IR occurrence. The area under the curve was 0.704, and the optimal cutoff value for CRP was 0.28 mg/dl, with a sensitivity of 65.4% and specificity of 71.7%.

Discussion

We established that it is possible to assess a patient's risk of developing IRs at the pre-administration stage by using laboratory data widely used in clinical practice in this study. Our findings are consistent with those reported in a previous multifaceted review of laboratory data, which revealed that CRP levels tended to increase prior to the onset of IRs (Table I). Although CRP is well established as an acute-phase protein that serves as a biomarker of inflammation (12), the detailed mechanisms whereby elevated CRP levels contribute to the development of IR have yet to be ascertained. However, despite this gap in our understanding, the involvement of complement pathway activation has been suggested (13). The levels of complement activation have been established to be correlated with the severity of IRs (14), and there is evidence to indicate that CRP activates the complement pathway (15). Moreover, we have previously found that elevated levels of CRP prior to the administration of infliximab may constitute a risk factor for the occurrence

of IRs (16). Consequently, we hypothesize that elevated levels of CRP may be indicative of conditions deemed favorable for the onset of rituximab-induced IRs.

Nevertheless, although our findings in this study provided evidence to indicate that elevated levels of CRP prior to rituximab administration are a potential risk factor for the development of an IR, it is difficult to uniformly assess the risk of IR occurrence in all patients. Biopharmaceuticals are known to elicit the production of anti-drug antibodies (ADA) following administration, and it has been established that antibodies raised against infliximab are responsible for the high risk of developing acute IRs (17). The production of ADA has also been reported in response to rituximab therapy, and may likewise be involved in the occurrence of IRs (18). Consequently, combining an assessment of degree of inflammation immediately prior to rituximab administration with an assessment of ADA post-administration may facilitate a more accurate and quantitative prediction of the risk of developing an IR.

Recently, the effects of bepotastine and diphenhydramine, antihistamines used as pre-medication to prevent rituximab-induced IRs, were compared, and the results showed that bepotastine was more effective at suppressing IRs than diphenhydramine (19). In addition to its antihistamine effect, bepotastine stabilizes mast cell function, inhibits eosinophil infiltration, and inhibits interleukin (IL)-5 production which causes eosinophil migration to peripheral blood (19). These physiological effects may be involved in the occurrence of rituximab-induced IRs.

However, despite these important insights, the limitations of this study should be acknowledged. Notably, the study was limited by the small number of cases assessed, its retrospective design, and low power owing to its single-site nature. Furthermore, for the purposes of our data analysis, we considered only the initial dose of rituximab administered to the study participants. Moreover, patient variables that were not included in the present study may have been risk factors for the onset of IRs following rituximab treatment. Consequently, the findings of this study should be validated in prospective studies that exclude these risk factors.

Conclusion

On the basis of the finding of this study, we identified CRP as a risk factor associated with the development of IRs in patients receiving rituximab therapy. These findings provide a theoretical basis for targeting CRP for the development of therapeutic strategies to alleviate rituximab-induced IRs. In addition, our observations highlight the importance of the post-administration monitoring of patients with elevated levels of CRP prior to therapy initiation to ensure the timely management of any potential IRs.

Conflicts of Interest

The Authors have no conflicts of interest to declare in relation to this study.

Authors' Contributions

Conceptualization, T.A; investigation, T.A; writing - original draft preparation, T.A; writing - review and editing, H.S. All Authors have read and agreed to the published version of the manuscript.

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Artificial Intelligence (AI) Disclosure

No artificial intelligence (AI) tools, including large language models or machine learning software, were used in the preparation, analysis, or presentation of this manuscript.

References

- 1 Pérez-Callejo D, González-Rincón J, Sánchez A, Provencio M, Sánchez-Beato M: Action and resistance of monoclonal CD20 antibodies therapy in B-cell Non-Hodgkin lymphomas. *Cancer Treat Rev* 41(8): 680-689, 2015. DOI: 10.1016/j.ctrv.2015.05.007

- 2 Cohen MD, Keystone E: Rituximab for rheumatoid arthritis. *Rheumatol Ther* 2(2): 99-111, 2015. DOI: 10.1007/s40744-015-0016-9
- 3 Karakatsanis SJ, Bouzani M, Symeonidis A, Angelopoulou MK, Papageorgiou SG, Michail M, Gainaru G, Kourti G, Sachanas S, Kalpadakis C, Katodritou E, Leonidopoulou T, Kotsianidis I, Hatzimichael E, Kotsopoulou M, Dimou M, Variamis E, Boutsis D, Kanellias N, Dimopoulou MN, Michali E, Karianakis G, Tsirkinidis P, Vadikolia C, Poziopoulos C, Pigaditou A, Vrakidou E, Economopoulos T, Kyriazopoulou L, Siakantaris MP, Kyrtsonis MC, Anargyrou K, Papaioannou M, Hatjiharissi E, Vervessou E, Tsirogianni M, Palassopoulou M, Stefanoudaki E, Zikos P, Tsirigotis P, Tsourouflis G, Assimakopoulou T, Verrou E, Papadaki H, Lampropoulou P, Dimopoulos MA, Pappa V, Konstantopoulos K, Karmiris T, Roussou P, Panayiotidis P, Pangalis GA, Vassilakopoulos TP, Hellenic Cooperative Lymphoma Group: Real-life experience with rituximab-CHOP every 21 or 14 days in primary mediastinal large B-cell lymphoma. *In Vivo* 36(3): 1302-1315, 2022. DOI: 10.21873/in vivo.12831
- 4 Prouet P, Giri S, Wiedower E, Fintel A, Yaghmour G, Lamb EP, Deneve J, Fleming M, Dickson P, Chandler JC, Martin MG: Addition of rituximab to chemotherapy reduced the rate of surgery for gastric-DLBCL without increasing early mortality. *Anticancer Res* 37(2): 813-818, 2017. DOI: 10.21873/anticancer.11382
- 5 Nakada T, Arihiro S, Gunji T, Ogasawara Y, Kato M, Kato T, Ikegami M, Yano S, Hokari A, Saruta M: A rare case of Epstein-Barr virus-positive diffuse large B-cell lymphoma, not otherwise specified, in a patient with ulcerative colitis. *Clin J Gastroenterol* 16(4): 543-549, 2023. DOI: 10.1007/s12328-023-01811-z
- 6 Berghen N, Vulsteke JB, Westhovens R, Lenaerts J, De Langhe E: Rituximab in systemic autoimmune rheumatic diseases: indications and practical use. *Acta Clin Belg* 74(4): 272-279, 2019. DOI: 10.1080/17843286.2018.1521904
- 7 Shaygannejad V, Fayyazi E, Badihian S, Mirmosayyeb O, Manouchehri N, Ashtari F, Asgari N: Long-term tolerability, safety and efficacy of rituximab in neuromyelitis optica spectrum disorder: a prospective study. *J Neurol* 266(3): 642-650, 2019. DOI: 10.1007/s00415-019-09180-9
- 8 Levin AS, Otani IM, Lax T, Hochberg E, Banerji A: Reactions to rituximab in an outpatient infusion center: a 5-year review. *J Allergy Clin Immunol Pract* 5(1): 107-113.e1, 2017. DOI: 10.1016/j.jaip.2016.06.022
- 9 Hayama T, Miura K, Uchiike A, Nakagawa M, Tsutsumi D, Sakagami M, Yoshida Y, Takei M: A clinical prediction model for infusion-related reactions to rituximab in patients with B cell lymphomas. *Int J Clin Pharm* 39(2): 380-385, 2017. DOI: 10.1007/s11096-017-0429-3
- 10 Öztürk E, Özyiğit LP, Öztürk AB, Akay MO, Çetiner M, Ferhanoglu B: Rituximab desensitization in three patients with severe rituximab allergy. *Curr Probl Cancer* 41(5): 349-354, 2017. DOI: 10.1016/j.cuprob.2017.07.003
- 11 Rusch C, Wood M, Kennedy AG, Tompkins BJ, Frasca JD: Rapid infusion of infliximab biosimilars and the incidence and severity of infusion-related reactions in patients with inflammatory bowel disease. *J Clin Pharm Ther* 47(11): 1851-1857, 2022. DOI: 10.1111/jcpt.13779
- 12 Shrivastava AK, Singh HV, Raizada A, Singh SK: C-reactive protein, inflammation and coronary heart disease. *Egypt Heart J* 67(2): 89-97, 2015. DOI: 10.1016/j.ehj.2014.11.005
- 13 van der Kolk LE, Grillo-López AJ, Baars JW, Hack CE, van Oers MH: Complement activation plays a key role in the side-effects of rituximab treatment. *Br J Haematol* 115(4): 807-811, 2001. DOI: 10.1046/j.1365-2141.2001.03166.x
- 14 Paul F, Cartron G: Infusion-related reactions to rituximab: frequency, mechanisms and predictors. *Expert Rev Clin Immunol* 15(4): 383-389, 2019. DOI: 10.1080/1744666X.2019.1562905
- 15 Noone DP, Isendoorn MME, Hamers SMWR, Keizer ME, Wulffelé J, van der Velden TT, Dijkstra DJ, Trouw LA, Filippov DV, Sharp TH: Structural basis for surface activation of the classical complement cascade by the short pentraxin C-reactive protein. *Proc Natl Acad Sci USA* 121(37): e2404542121, 2024. DOI: 10.1073/pnas.2404542121
- 16 Amemiya T, Suzuki H: Risk factors for infliximab-induced infusion reactions based on a retrospective study of medical information. *Int J Clin Pharmacol Ther* 62(07): 307-310, 2024. DOI: 10.5414/CP204568
- 17 O'Meara S, Nanda KS, Moss AC: Antibodies to infliximab and risk of infusion reactions in patients with inflammatory bowel disease: a systematic review and meta-analysis. *Inflamm Bowel Dis* 20(1): 1-6, 2014. DOI: 10.1097/01.MIB.0000436951.80898.6d
- 18 Vultaggio A, Matucci A, Nencini F, Pratesi S, Parronchi P, Rossi O, Romagnani S, Maggi E: Anti-infliximab IgE and non-IgE antibodies and induction of infusion-related severe anaphylactic reactions. *Allergy* 65(5): 657-661, 2010. DOI: 10.1111/j.1398-9995.2009.02280.x
- 19 Hori T, Yamamoto K, Nakagawa T, Nakagawa R, Okayama M, Sudou T, Hamasaki M, Yasuda M, Kobayashi S, Nakamura F, Yagi H, Kitahiro Y, Ikushima S, Yano I: Comparative inhibitory effects of bepotastine and diphenhydramine on rituximab-induced infusion reactions. *Int J Hematol*, 2025. DOI: 10.1007/s12185-025-03990-6