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Original Research Article

Are acute infusion reactions after rituximab underreported?

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ABSTRACT

Background: Rigorous premarketing trials may fail to capture safety issues associated with new drugs. This is more likely to happen in case of biopharmaceuticals. We take the case of rituximab, and anti CD20 monoclonal antibody, which was the first monoclonal antibody to get approval. This open label observational study was done with the objective of estimating the incidence of acute infusion reaction associated with rituximab infusion.
Methods: The study population consisted of patients hospitalized for receiving rituximab, in day care centre(s) of a tertiary care hospital. Number and type of acute infusion reactions (AIR) were recorded on a case record form along with patient characteristics and medical history.
Results: A total of 50 infusions were observed and all infusions were followed by at least one AIR. Total 71 AIRs were recorded among these 50 infusions (1.4 AIR per infusion). Non-Hodgkin's lymphoma was the commonest indication for which patients were receiving rituximab. In a subset analysis, incidence of AIR was statistically lower in patients having received corticosteroids as premedication. However, brand of rituximab, gender of the patient and first or second cycle had no bearing on incidence of AIRs.
Conclusions: AIRs are more common in real time clinical settings than what is reported. There is a need to formulate appropriate risk management plan depending on post marketing clinical data. Use of corticosteroids as premedication may be one such strategy. New drugs, esp biopharmaceuticals, may have unidentified/under reported safety issues and there is a need to undertake focussed pharmacovigilance endeavours to unravel them.

Keywords: Acute infusion reactions, Biopharmaceuticals, Premedication, Pharmacovigilance, Rituximab, Similar biologics

INTRODUCTION

Every drug undergoes rigorous clinical trials before marketing approval but the process is not necessarily fool proof. Withdrawal of rofecoxib (within 5 years of approval), muraglitazar (after getting approval letter) and torcetrapib (taken off trials towards the end of approval process) are some recent examples.[1-3] These drugs were withdrawn because of safety issues which emerged late in the drug development process or after the drug had obtained approval. The uncertainties regarding efficacy and safety assume more significance in case of new biopharmaceuticals as the first generation is going off patent and similar biologics are not identical to the reference biopharmaceutical.[4-6] Possible minor variations may affect the efficacy and more importantly, safety of the similar biologic vis a vis reference biopharmaceutical.[7] Even periodic safety update reports (PSURs) may fail to cover all the facets of full scale clinical use and may suffer from reporting bias.

Due to aforementioned limitations of clinical trials and PSURs, there is a need to look beyond these regulatory activities so as to impart more prescience and clarity in the clinical application of newly approved drugs. Focusing pharmacovigilance activities towards newly approved drugs especially biopharmaceuticals and biosimilars, may be the way out.[8-10] We identified rituximab, a chimeric monoclonal antibody against CD20 on B cell surface and known to cause acute infusion reactions, for focused pharmacovigilance. It is the first therapeutic monoclonal antibody to receive approval,[11] is available in many generic versions and is used widely for a large number of oncological and immunological indications. The objective was to estimate the incidence of acute infusion reaction following administration of rituximab in real life settings. This study will provide limited data regarding the acute adverse effects (both anticipated and unanticipated) of rituximab.

METHODS

This was a prospective, cross-sectional, open-label, observational study. It was conducted in day care centres of Rheumatology, Medical oncology and Haematology of a tertiary care centre. The study was approved by Institutional Ethics Committee and all patients provided written informed consent. The study was conducted between September 2014 and January 2015.

Study population

Patients of either gender; hospitalized in day care centres of the study sites; receiving parentral rituximab as part of treatment for non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), rheumatoid arthritis (RA) and other conditions were included in the study. Patients less than 12 years and more than 65 years were excluded from the study.

Data collection

Patient demography, treatment and adverse event details and other relevant details were recorded in a case record form. Patients were observed for symptoms and signs of acute infusion reactions for 30 mins prior to start of infusion till 6 hours post-infusion. Any subjective complaints from the patients were also noted. In the event of an acute reaction, the infusion was to be stopped at the discretion of the treating physician only. WHO-UMC scale was used for causality assessment of adverse events as certain, probable, possible, unlikely, unclassified or unclassifiable. Rechallenge was not done as part of the study.

Statistical analysis

Graph pad Instat was used for data analysis. The data is presented as descriptive, in the form of tables and graphs. Due to small sample size, non-parametric tests were used for comparison. A p value less than 0.05 was considered significant.

RESULTS

A total of 40 patients visited the study day care centres for receiving injection Rituximab. Out of these, 6 patients had received their first dose before study commencement. Of the remaining, 10 patients received first and second doses of rituximab during the study. A total of 50 infusion episodes were observed and recorded, out of which 34 were first and 16 were repeat infusions.

Out of these 50 infusions, 29 were for Non-Hodgkin's Lymphoma, 8 for Chronic Lymphocytic Leukemia and 4 for Rheumatoid Arthritis and 9 miscellaneous other indications. The brand of rituximab was guided by factors like cost, availability etc. Treating physician and/or study team exercised no influence on patient's choice. In these 50 infusions, a total of 71 acute infusion reactions (AIR) were observed out of which chills was most common and hypotension was least common. Some patients experienced more than one infusion reaction with an average of 1.4 AIR per infusion (Table 1).

Table 1: Distribution of observed acute infusion reactions in 50 infusions in 40 patients.

Reaction	Number
Chills	32
Rigors	18
Throat irritation	11
Fever	7
Rash	2
Hypotension	1
Total	71

Since NHL was the most common indication for which patients were administered rituximab, this subset was chosen for further analysis. A total of 29 infusions were given to NHL patients during which a total of 40 acute infusion reactions were experienced (1.4 AIR per infusion). Patients with other indications experienced 1.5 AIR per infusion. The rate of AIR observed did not vary with the brand of rituximab being used for NHL patients (P value - 0.6). Out of 29 infusions for NHL patients, 19 were first and 10 were repeat infusions and the frequency of AIR was 1.5 and 1.2 AIR/infusion respectively and they differed in types of AIR encountered (Fig 1). All the AIRs were classified as 'probable' as per WHO UMC criteria.

A total of 10 NHL patients received both the first and second infusion during the study duration. The rate of AIR during first and second infusion in same set of patients, were separately analyzed. It was lower the second time (1.4 AIR/infusion) as compared to the first time (1.6 AIR/infusion) (p value=0.53).

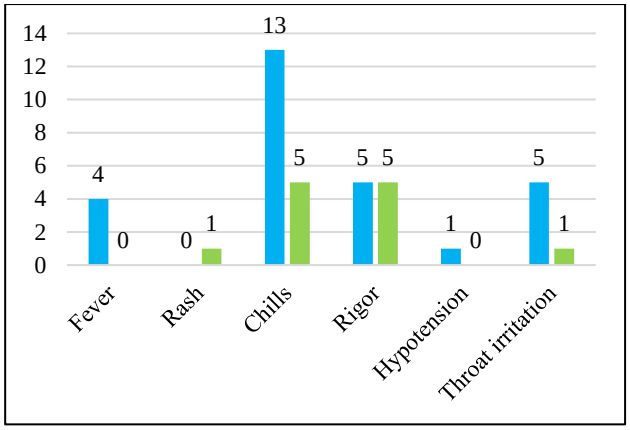

Figure 1: Acute infusion reactions in patients with Non-Hodgkin's lymphoma getting injection rituximab in first (blue) and repeat (green) infusions.

NHL patients were further analyzed depending on the type of premedication (received corticosteroids or not). The rate of AIR was significantly higher in patient who did not receive corticosteroids as premedication (1.71 vs 1.07 AIR per infusion respectively; p value=0.03). The type of AIR in these groups is depicted in Figure 2.

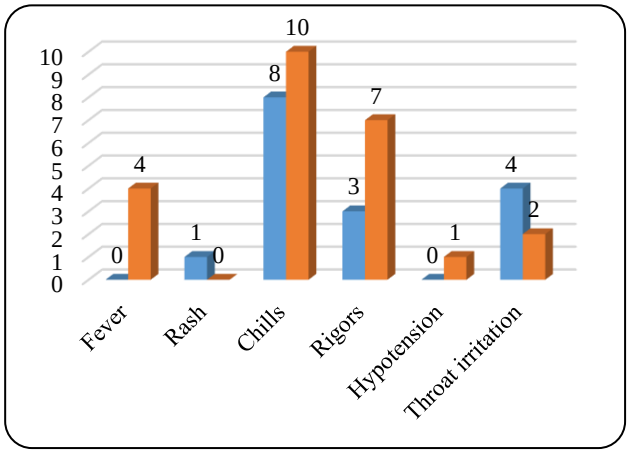

Figure 2: Types of infusion reactions in NHL patients who received corticosteroids (n=15, blue) and those who did not (n=14, orange).

Further analysis of AIR rates and the effect of gender was also done. All the patients of NHL receiving the same brand for the first dose were divided into 2 gender cohorts. There were a total of 23 such patients. Out of them, 17 were males and rest 6 were females. The rates of AIR in males and females were not statistically different (p value=0.7).

DISCUSSION

Biopharmaceuticals and similar biologics are being rapidly developed and increasingly used in practice. Pharmacodynamics, and especially toxicodynamics of a molecule, more so of complex molecules such as biopharmaceuticals, cannot be completely captured during limited controlled clinical trials. Biopharmaceuticals are immunogenic complex molecules which otherwise are known to lead to immunological adverse effects ranging from milder acute infusion reactions such as chills/ rigors, to severe anaphylactic reactions and non-immunological reactions such as tumor lysis syndrome.[12] Development of similar biologics and their distinct features as compared to the reference biopharmaceutical make it imperative that biopharmaceuticals and biosimilars are routinely and rigorously subjected to proactive pharmacovigilance even after they have been approved for marketing.[13]

This study was undertaken as a pilot study to execute focused pharmacovigilance in respect of rituximab, an anti CD20 monoclonal antibody indicated for Non-Hodgkin's Lymphoma, Rheumatoid arthritis, Chronic Lymphocytic leukemia, Wegener's Granulomatosis and Microscopic Polyangiitis.[14]

The overall rate of AIR observed in this study was more than 100% as all the patients experienced one or the other form of AIR. This is much more than the 50-77% mentioned in the package inserts of various brands.[15,16] The impact of various factor (such as disease condition, gender and brand used) on the occurrence of AIR is not completely known. There was no statistical difference between rates of AIR in NHL patient as compare to patient of other indication. To facilitate comparison among homogenous groups, a subset analysis of NHL patients was done. The brand used and gender of the patient were found to have no impact on the rate of AIR.

It is known that rate of AIR is likely to be less when rituximab injection is repeated in the same patient.[17] This was clearly brought out in this study as well. There are no clear guidelines regarding the premedication that is to be given to patients prior to rituximab. Premedication protocols depend on preference of the treating physician and differ between different settings. NHL patients were further sub divided into two groups on the basis of having received corticosteroid in premedication or not. The rate of AIR was significantly less in those patient who received corticosteroid as compared to those who did not. However, the type of background regime that the patient had been receiving for his illness was not taking into account and only the premedication given to the patient just prior to administration of rituximab was considered.

The present study clearly outlines the importance of focused pharmacovigilance as the spectrum of pharmacokinetics and dynamics may significantly differ in day to day clinical practice as compared to controlled clinical trial environment. Additionally, premedication protocols need to be evolved as the type of premedication used can affect the toxicodynamics of these molecules.

Since most of the results and observations emanate from post hoc analysis in this study, there is a need to validate these conclusions in more robust hypothesis testing

studies. Rituximab was chosen as an example of biopharmaceuticals, and going by what this study demonstrates, other recently approved biopharmaceuticals may require similar pharmacovigilance gaze. This study highlights the need to look beyond trial results, PSUR reports and other regulatory imperatives. There is a case for proactive pharmacovigilance of biopharmaceuticals and similar biologics in real time clinical use of these drugs, so as to further refine drug use and reassess benefit to risk ratio.

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