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Rituximab Utilization Evaluation with Focused on Available Evidence for Off-Labeled Indications

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ABSTRACT

Background: To investigate the on-labeled and off-labeled indications of rituximab according to available evidence and the cost benefit of using this expensive drug.

Methods: This retrospective cross-sectional study was conducted between August 2016 and August 2017 at a teaching hospital affiliated to Iran University of Medical Sciences, Tehran, Iran. Patients' demographic data and disease, indication for rituximab use, its dosage and treatment regimen and previous and concurrent treatments was assessed. The collected data were compared with the current criteria for the pattern of rituximab use. The last version of Lexicomp® acquired by Wolters Kluwer was used as the reference for on-labeled and off-labeled indications of the prescribed drug and its dosage. Level of evidences for applied indications and cost has also been evaluated.

Results: A total of 85 patients received rituximab during the study period. The most frequent reasons for rituximab prescription were: multiple sclerosis (50.6%), systemic sclerosis (10.6%), rheumatoid arthritis (7.05%) and Idiopathic inflammatory myopathies (4.70%). Rituximab was used in 8 (9.4%) cases according to on-labeled indications. There was level C evidence for rituximab use in off-labeled indications in 47 (55.3%) cases according to available evidences which accounts for the highest calculated cost.

Conclusion: Based on our results, rituximab was frequently administrated for off-labeled indications most of which are not supported by established levels of evidence. The total cost was higher for level C evidence indications of off labeled rituximab than for indications with a higher level of evidence (A and B). So, strong evidence is necessary for decision making regarding its effectiveness and its cost benefit.

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Introduction

Rituximab is a chimeric human/ murine monoclonal antibody, developed by genetic engineering, which can bind to the trans-membrane antigen CD20 on lymphocytes. It is approved by U.S. Food and Drug Administration (FDA) for the treatment of Non-Hodgkin's Lymphoma (NHL), Chronic Lymphocytic Leukemia (CLL), Rheumatoid Arthritis (RA), Granulomatosis with Polyangiitis (GPA) and Microscopic Polyangiitis (MPA) (1). However, the off-labeled use of rituximab in other conditions, in which B-cells and auto-antibodies are suggested to be involved in their pathogenesis, have increased during the past decade (1, 2).

In Iran, the legislation governing the off-labeled use of rituximab has changed since April 2015. Rituximab is now being prescribed for many other indications, rather than those approved by US FDA, according to physician prescription and insurance confirmation. However, it is preferred to preserve the off-labeled use of drugs for situations in which there are no appropriate response to conventional or newly developed therapies or there are no other approved alternative medications (2).

The easy availability and facilitated provision of many drugs without certain evidence of efficacy or toxicity leads to their over usage. All of these could be a matter of concern and a source of financial problems for hospital medical directors as far as there are insufficient or very limited data on the efficacy of such drugs (2, 3).

So far, due to lack of clear treatment guidelines regarding the dose schedule, combination therapy and follow up course of off-labeled uses of rituximab in addition to its high cost, some restrictions could be considered for its prescription. The aim of this study is to investigate the on-labeled and off-labeled indications of rituximab use, according to available evidence because of the high cost of this expensive drug and the evaluation of cost and benefit.

Table 1. Lexicomp Level of Evidence Definitions

A - Consistent evidence from well-performed randomized, controlled trials or overwhelming evidence of some other form (eg, results of the introduction of penicillin treatment) to support the off-label use. Further research is unlikely to change confidence in the estimate of benefit.
B - Evidence from randomized, controlled trials with important limitations (inconsistent results, methodological flaws, indirect or imprecise), or very strong evidence of some other research design. Further research (if performed) is likely to have an impact on confidence in the estimate of benefit and risk and may change the estimate.
C - Evidence from observational studies (eg, retrospective case series/reports providing a significant impact on patient care), unsystematic clinical experience, or from potentially flawed randomized, controlled trials (eg, when limited options exist for condition). Any estimate of effect is uncertain.
G - Use has been substantiated by inclusion in at least one evidence-based or consensus-based clinical practice guideline.

Methods

This retrospective cross-sectional study was conducted between August 2016 and August 2017 at Firoozgar hospital affiliated to Iran University of Medical Sciences, Tehran, Iran. The study protocol was approved by the local ethics committee (IR.IUMS.REC 1396.27529). In this period of time, patients who received rituximab were enrolled in this study. A retrospective assessment of medical records was performed to find patients information (demographic data) rituximab indication, dosage and previous and concurrent treatments.

For evaluation of the utilization pattern, a list of rituximab recipients was provided for clinical pharmacist from the data bank of the pharmacy. The collected data were compared with the current criteria for the pattern of rituximab use. The last version of Lexicomp® acquired by Wolters Kluwer was used as the reference for on-labeled and off-labeled indications of the prescribed drug and its dosage (1). For conditions not mentioned in Lexicomp, a literature search was performed to collect available evidence. These conditions included multiple sclerosis (MS), systemic sclerosis (SSc), Idiopathic inflammatory myopathies (IIMs), sjogren's syndrome and acute disseminated encephalomyelitis (ADEM). The diagnosis of each disease was categorized according to the Lexicomp level of evidence definition (Table 1). Expert opinion was obtained by a group including clinical pharmacist, neurologist, rheumatologist, nephrologist, pulmonologist and the healthcare cost team members.

The cost of each rituximab vial was estimated based on the average price designated by the Ministry of Health of Iran at the time of the study. All costs are expressed in US dollars (1 US$ = 38000 Rials).

Data was entered from the mentioned application forms to SPSS® 20 Software for statistical analysis. The descriptive assessment is stated as mean ± standard deviations (SD) or median for numerical variables; number and percentages were expressed for nominal variables.

Results

A total of 85 patients received rituximab during the study period. Fifty two patients (61.2%) were female and 33 patients (38.8%) were male. The age of the patients ranged from 17 to 76 years with a mean age of 43.28 ±13.04 years and a median of 41 years. The neurology ward (61.2%) used rituximab more often than the other wards .The frequency of rituximab orders in other ward was as follow: rheumatology ward (28.2%), nephrology

ward (8.2%) and oncology ward (2.4%).

Rituximab was used for 15 different indications arranged in details in Table 2, 3. The most frequent reasons for the rituximab prescription were as follows: MS (50.6%) including relapsing-remitting MS (RRMS), primary progressive MS (PPMS), and secondary progressive MS (SPMS), systemic sclerosis (10.6%), rheumatoid arthritis (7.1%) and Idiopathic inflammatory myopathies (4.7%).

Table 2. Indications for on label and off label Rituximab use according to Lexicomp

Indications	On Label	Off Label	Off-Label Levels
RA	6 (7.05%)	-	-
Wegener's Granulomatosis	2 (2.35%)	-	-
Idiopathic membranous nephropathy (resistant)	-	4 (4.70%)	B
Lupus nephritis (refractory)	-	3 (3.52%)	B, G
ITP (refractory)	-	1 (1.17%)	C, G
TTP (acquired)	-	2(2.35%)	B
Neuromyelitis optica (relapse prevention)	-	3 (3.52%)	B
Myasthenia Gravis (refractory)	-	4 (4.70%)	B

RA: Rheumatoid Arthritis; ITP: Idiopathic thrombocytopenic purpura; TTP: Thrombotic thrombocytopenic purpura

Table 3. Other indications for off label Rituximab use

Indication	N (%)	Available Sources	Ref	Author's level of evidence according to Lexicomp definition
RRMS	4 (4.7%)	1 RCT (Phase II) 4 Open label studies (Phase I/ II) 3 Observational Study	8-14, 17	A
PPMS	6 (7.1%)	1 RCT (Phase II/ III) 1 Observational Study	15, 17	B
SPMS	33 (38.8%)	1 Case series 1 Observational Study	16, 17	C
SSc	9 (10.6%)	8 Open label studies 2 Case-Control Studies 6 Case Reports	20-34	C
IIMs	4 (4.7%)	1 RCT 4 Open label studies 24Case Series 19Case Reports	36	B
Sjogren›s syndrome	2 (2.3%)	4 RCT 14 Open label trial 5 Registry analyses	40-42	C
ADEM	2 (2.3%)	2 Case Reports	46-47	C

RCT: randomized, controlled trial; RRMS: relapsing- remitting MS (RRMS), PPMS: primary progressive MS; SPMS: secondary progressive MS; SSc: Systemic Sclerosis; IIM: idiopathic inflammatory myopathies; ADEM: acute disseminated encephalomyelitis

Rituximab was used in 8(9.4%) cases according to on-labeled indications. The levels of evidence for rituximab use in off-labeled indications were C in 47 (55.3%) of cases according to available evidences.

All patients received courses of pharmacological or/ and non-pharmacological interventions according to their medical records before rituximab. These prior treatments often included; one agent (12.9%), two

agents (56.5%), three agents (23.5%) and four or more (4.7%). Therapeutic interventions were commonly used included corticosteroids, interferon β-1a and interferon β-1b, fingolimod, glatiramer acetate, azathioprine, methotrexate, mycophenolate mofetil or mycophenolic acid, cyclophosphamide, hydroxychloroquine, intravenous immunoglobulin, and plasmapheresis

Out of 26 administrated rituximab cases (Table 2), 6 (23%) dose schedules were not concordance with recommended Lexicamp® dosing. However, a wide range of dosing methods and schedules were recorded for off-labeled conditions based on small studies and evidences. Some authorities allowed physicians to prescribe this agent according to their experience and patient's condition.

Totally 204 vials of rituximab were used during this study. The cost of each vial of rituximab was $ 570.23, resulting in an overall cost of $ 116,327. The median cost per patient was $ 1283.0175. The most cost expenditure was for indications such as idiopathic inflammatory myopathies, with a median treatment charge of $ 1710.69 and PPMS with a median treatment charge of $ 1425.57; the least were RRMS and lupus nephritis with a median treatment charge of $ 1425.57 and 1710.69, respectively.

The total cost was higher for level C evidence indications of off labeled rituximab ($ 61, 584.84) than for indications with a higher level of evidence (A and B) ($42,767.25).

In addition, 32 cases out of 85 patients were admitted just to receive rituximab at any time, with the mean hospitalization of 4 days; the total budgets for their rituximab treatment including drug and hospitalization expenses were $ 531,113.5.

Discussion

The findings of this study showed that evaluation of rituximab utilization is very important due to diversities in consumption patterns among physicians. However, the results of this study, like other studies, indicated that the off labeled uses of rituximab are noticeably growing in hospital wards (2-6). This concern could rise from the opinion of possible involvement of humoral immunity in the pathogenesis of various diseases (5). The results of our study showed that rituximab was used with higher frequency for neurologic problems means as compared to other conditions. Evidence-based strategies are still needed to be defined for using rituximab in treatment of these diseases.

In our study, more than 50 percent of utilized rituximab was prescribed for the treatment of multiple sclerosis. Multiple Sclerosis (MS) is a chronic inflammatory and degenerative disease characterized by demyelization and axonal damage of central nervous system. It can present in three forms: Relapsing-Remitting Multiple Sclerosis (RRMS), Secondary-Progressive Multiple Sclerosis (SPMS) or Primary-Progressive Multiple Sclerosis (PPMS) (7). B cells and humoral immunity has shown to have a substantial role in the pathogenesis of MS in multiple studies, therefore therapies targeting B cells have been considered to have promising results in the treatment of MS in the past few years (7). The efficacy of rituximab for RRMS has been suggested in some studies (8-14, 17). Two smaller open-labeled phase I/II trials showed good results regarding the tolerability and substantial reduction in gadolinium-enhanced lesions in RRMS (8, 9). In an earliest randomized trial performed on 104 adult patients with RRMS, intravenous rituximab (1000 mg) was given on days 1 and 15 and their brain MRI were re-evaluated at week 24, which showed significant reduction in both total and new gadolinium-enhanced lesions as compared to placebo (10). In addition, the proportion of patients who experienced clinical relapse by week 24 was significantly reduced. In another observational study, rituximab or fingolimod were substituted for natalizumab in 256 patients with stable RRMS due to JC virus antibody positivity. The rituximab group experienced lower rates of clinically evident relapse, adverse events, and treatment cessation as compared to the fingolimod group (11).

An open-label multicenter phase II trial was performed on 75 patients with clinically stable RRMS for evaluation of safety and efficacy in reducing inflammation, in which the first-line injectable treatments were switched to rituximab. Rituximab has shown to have an almost equal or even superior effect in reducing inflammation in RRMS, proved by MRI and CSF-NFL, during the first year after treatment shift (12). Likewise, the overall treatment satisfaction rate (scale range: 1–7), significantly improved from a mean of 4.8, with injectable therapies, to a mean of 6.3 after 1 year of rituximab treatment, which remained constant for 2 years. There was no significant alteration in scores for the patient-perceived impact of disease, fatigue or disease progression (13). In a comparative study, a total of 461 patients from the Swedish MS registry in the rituximab arm and 922 patients from the IFN-β/GA arm in RRMS were compared (14). The results were indicative of a substantial reduction in Annualized Relapse Rate (ARR) associated with rituximab use. In addition, rituximab was associated with an 87% decrease in the relapse rate and a discontinuation rate reduction by 85% as compared to IFN-β/GA. When examined at 12 and 24 months, Expanded Disability Status Scale (EDSS) was significantly regressed from baseline in the rituximab group. In contrast, the OLYMPUS trial which is a phase II/III trial, enrolled 439 patients with PPMS and followed them for 96 weeks, failed to show any reduction in disease progression during follow up period (15). However, when considering the patients younger than 50 years or regarding the Gadolinium-enhanced lesions at baseline, a significant effect was detected (15).

An observational study of three SPMS patients who were treated with rituximab for at least 15 months showed that EDSS score was stabilized in all patients after a

dramatic increase over the previous years (16). Finally, a retrospective observational report of 822 Swedish patients with MS, including 557 RRMS, 67 PPMS and 198 SPMS who were treated with intravenous rituximab (500 or 1000 mg every 6 to 12 months) for a mean duration of 22 months showed that patients with RRMS had a low mean annual relapse rate (0.04) during rituximab treatment and their median disability status remained unchanged. Patients with PPMS had a low mean annual relapse rate (0.015) during rituximab therapy and their median disability status increased. Patients with SPMS had a low mean annualized relapse rate (0.038) and their median disability status increased. Infections were the most common non infusion-related adverse event of rituximab (17).

According to available studies, rituximab might be an effective treatment option in patients with RRMS and possibly in a subset of PPMS patients, but due to licensing issues the study was not further conducted for the treatment of MS (18, 19). These results suggest that although several research has been carried out, decision making regarding the use of rituximab in MS based on available evidence is difficult at this moment. Particularly most patients, who received rituximab in our study for the treatment of MS, were suffering from SPMS for which there are limited available studies.

Systemic sclerosis (SSc) is a connective tissue disorder with a chronic and almost frequently progressive course. Although there are few studies suggesting that rituximab could improve skin and articular involvements, and possibly, the pulmonary fibrosis in (SSc), most of these studies are case reports or open labeled (20-34). Update of European League against Rheumatism (EULAR) recommendations emphasizes on several drugs, including new promising therapies that might be helpful in the management of patients with SSc but could not be included in these evidence-based recommendations due to insufficient data at present (35).

There are some evidence that rituximab might be beneficial in treatment of patients with resistant idiopathic inflammatory myopathies (36). Idiopathic inflammatory myopathies (IIMs) are a group of acquired, systemic diseases of skeletal muscle, which includes adult Polymyositis (PM) and Dermatomyositis (DM), Juvenile DM (JDM) and PM (JPM), Anti-Synthetase Syndrome (ASS) and Inclusion Body Myositis (IBM) (36, 37).

B cells play a critical role in the initiation and progression of the immune response and suggested to be involved in the pathogenesis of myositis. Considering the likelihood of pathogenic role of B cells in myositis, rituximab has shown to take part in the treatment of myositis in several studies (36-39). Based on current evidence rituximab may play a role in the management of patients with resistant myositis.

The use of rituximab as a treatment option for sjogren's syndrome, has been extensively studied (40-42). The findings of all studies which were either case reports, randomized trials or open labeled have been variable (40-44). Similarly, Sjogren's syndrome Foundation clinical practice guidelines (CPGs) recommendations are weak for the use of rituximab in sicca symptoms and modest for other systemic symptoms of this disease (45). Rituximab is among the most expensive drugs with a high cost which has been used in treatment of patients in our study, similar to reports of other studies (2-6). Cost is usually a subject of debate in the perspective of off-labeled drug use, due to limited case based evidence and uncertainty of the cost–benefit rate. Therefore controversy exists in the off-labeled prescription of many drugs. For the advantage of healthcare managers, physicians and patients' demands and also reliable decision-making is necessary. Basically the patients who receive standard disease modifying medications but failed to get proper response or are unable to improve their conditions, have poor prognosis. Hence many physicians believe that the use of these drugs may be justified. Healthcare managers are not usually interested in restoring the treatment cost while there is little scientific evidence supporting their use (48). When a drug costly is considered for an off-labeled indication, careful selection of cases and assessments of the clinical outcome should be considered. On the other hand, the precise designation of adequate dose schedules is one of the important issues in the efficacy and safety of off-labeled prescription of any drug. Determining the lowest effective dose in various settings could possibly reduce probable adverse events, affects long-term safety and markedly decrease the economic burden applied by that costly drug. Therefore it necessitates performing appropriate clinical trials to assess the efficacy and safety of rituximab in off-labeled indications, although there might be challenges in performing investment trials in rare diseases. Meanwhile, sometimes it seems judicious to consider a probable more effective drug regardless of inadequate evidence on its efficacy, particularly in conditions unresponsive to other treatments. In the absence of randomized clinical trials, it seems rational to rely on the results of prospective registries of patients treated in these conditions or refer to observational studies that evaluate outcomes or review other studies and define the level of evidence according to available data (2).

This study has few of limitations. First, it is a retrospective observational study and we were unable to evaluate outcomes and safety issues. Furthermore, we did not have access to information of cancer cases, as these patients provide rituximab personally from defined centers which is not registered by hospital pharmacy system.

In conclusion, according to our study, rituximab is frequently prescribed for off-labeled indications, while many of them are not supported by established levels of evidence. In the absence of strong evidence and taking into

account that clinical trials can be difficult to conduct in some diseases, the decision making about its effectiveness in these conditions is difficult. In addition, it can lead to increased healthcare costs. Finally, this type of research is needed to understand the utilization pattern of costly drugs in various centers and may provide useful information to improve prescribing decisions in clinical practice.

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