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Research Article

A Pharmacoepidemiologic Study on Rheumatoid Arthritis Patients Attending Outpatient Department at a Tertiary Care Hospital in Bangladesh

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Abstract

Background: The practice of multi-drug treatment among Rheumatoid Arthritis (RA) patients is very common. Unwanted adverse effects may occur due to Drug-Drug Interactions (DDI). Unfortunately, no data is currently available revealing the DDIs of RA patients in Bangladesh.

Objectives: This study was conducted to evaluate prescription pattern among the RA patients and to identify the DDI in the prescriptions.

Methods: The study was conducted from January to March 2017 with total 120 prescriptions obtained from the patients by regular visit at the outpatient department of Arthritis Clinic & Research Center, Dhaka Medical College Hospital, Bangladesh. Drug interactions in the prescriptions were determined by online drug interaction checker.

Results: Study revealed that RA was commonly seen in female patients (92.60%). An average number of drugs per prescription were 6.11±1.79. Only 36.67% prescriptions contained ≤ 5 drugs whereas 63.33% prescriptions contained more than 5 drugs. The overall drug usages revealed that Disease-modifying antirheumatic drugs (DMARDs) were most commonly used (31.81%). This study found that about 91.66% prescription had one or more potential DDIs whereas no potential interaction was observed in 8.34% prescriptions. Among 450 interactions, 60% interactions were between antirheumatic drugs and 40% interactions between antirheumatic and other drugs. The most frequently found DDIs were those with the methotrexate and prednisolone 14.23%.

Conclusions: Our study found potential DDIs in the prescriptions of RA patients. The government and the drug regulatory authority along with physicians should impose strict control over the prescribing pattern to reduce the unwanted drug interactions in the prescriptions.

Keywords: Drug-Drug Interactions; Disease-Modifying Antirheumatic Drugs; Prescriptions; Rheumatoid Arthritis; Survey Questionnaire

Introduction

Rheumatoid Arthritis (RA) is a systemic autoimmune disease which is characterized by chronic synovial joint inflammation and joint erosion [1]. Uncontrolled RA has an association with joint deformity and significant health-related expenses [2]. Approximately 1% of the population around the world is affected by RA. It can occur at any age [3]. But the age of onset is more common in the 4-5th decade. It is most commonly occurring in female than the male with the ratio of female to male is 3:1. Disability, morbidity, and mortality are the common features in patients suffering from RA [4].

Disease-Modifying Antirheumatic Drugs (DMARDs) are used to check disease activity, lessen joint erosions and improve quality of life of patients in RA [5]. To prevent structural damage, the 2012 American College of Rheumatology guidelines for the treatment of RA suggested the early use of DMARDs as monotherapy or as combination therapy in patients with RA depending upon severity [6]. These guidelines recommended the initiation of DMARDs in early RA of <6 months' duration as monotherapy for patients with low disease activity and as a combination of traditional DMARDs or addition of a TNFi or a non-TNF biologics or tofacitinib, rather than continuing DMARDs alone for moderate- or high-disease activity [6]. Moreover, the 2015 American College of Rheumatology guidelines for the treatment of RA advised the addition of short-term glucocorticoids at the lowest possible dose and the shortest possible duration if disease condition remains moderate despite the use of DMARDs, TNFi, non-TNF biologic therapy [7]. At present not much is known about the DMARD preferences of British rheumatologists. A survey conducted in the UK found that Sulphasalazine was the agent of the first choice for British rheumatologists, but nowadays methotrexate is widely considered as the standard against which other DMARDs should be compared [8]. Some very recent surveys, from North America, have shown that combinations of DMARDs are preferred in recent practice [9].

To decrease the pain and inflammation of joints non-steroidal anti-inflammatory drugs are used in case of RA [9]. With the addition of the anti-inflammatory effects, glucocorticoids in RA will retard the disease progression and joint damage. Glucocorticoids are mainly used to control the short term acute flare-ups while waiting for the DMARDs to act [10]. But prolonged use of glucocorticoids is linked with increased frequency of significant adverse drug reactions [11].

Adverse Drug Reactions (ADRs) and adverse drug events are the main consequence of drug interactions [12]. Drug interactions are described as a significant and extensively under-acknowledged source of the prescription errors [13]. As per a survey, the frequency and incidence of drug-drug interaction range from 3 to 5% in the patients taking a few drugs and it is around 20% in patients receiving many drugs [13]. The incidence and rate of occurrence of drug interactions are greater in patients receiving combinations of drugs or polypharmacy or suffered from co-morbidity of diseases such as RA, which require long-term and multi treatments and the risk of drug interaction will increase as they are treated with multi-therapies [12].

In polypharmacy, it is so important to find out the prevalence and rate of occurrence of drug interactions. As well, it is more significant to observe and detect agents that are the majority to produce unsafe and harmful interactions [14]. All the drugs used in the treatment of RA show significant interaction and hence it is very important that their use require regular monitoring for adverse reactions [15]. At present there are no data available regarding the current scenario of drug interaction occur in RA patient at Bangladesh. The present study is designed to estimate the prescribing pattern and the occurrence of adverse drug-drug interaction in patients with RA.

Methods

Study Design

This research work was carried out on 120 RA patients by inspecting their prescriptions from January 2017 to March 2017, through regular visit to the outpatient department at Dhaka Medical College (DMC) Hospital in Dhaka city, Bangladesh. This city was chosen because it is the most densely populated city in Bangladesh and one of the most populated cities in the world. Initially a pilot study was carried out with small number of patients using pre-designed questionnaires to set the variables of the study. After that necessary modification was done in the questionnaires as per as the objective of the study before conducting the final study.

Ethical Approval

Ethical clearance was obtained from the authority of DMC. Each and every patient was briefed about the purpose of the study prior to data collection and written informed consent was obtained from each of them. All followed procedure was in accordance with the ethical standards of Ministry of Health, Bangladesh.

Inclusion and Exclusion Criteria

The inclusion criteria for the respondents were both male and female suffering from established RA and receiving stable therapy for at least 3 months while those were suffering from other disease were excluded from this study. Patients who were not sufficiently co-operative to share their treatment profile and denied to handover their prescriptions were excluded. Patients suffering from severe general medical condition and patients having mental retardation and substance use disorder are also excluded. No doctors were informed about the study to avoid any kind of modification in their usual prescribing patterns.

Preparation of Questionnaire

The questionnaire was developed after a detailed review of relevant literature. In addition, some novel questions were developed in accordance with the study objectives. The questionnaire contained close-ended questions. The questionnaire consisted of questions on demographics of respondents (age, sex, year of study and religion), details about patient's disease, treatment details. The questionnaire was worded in English language and translated to Bangla languages.

Study of Drug Interaction

After collection of sufficient number of prescriptions, we attempted to determine possible DDI in the prescription of each

patient. For this purpose, we used online drug interaction checker namely "Drugs.com" (https://www.drugs.com/drug_interactions.php) and the results were analyzed. The drug interactions were categorized as severe, moderate and minor interactions. Major DDIs are highly clinically significant and these combinations should be avoided where the risk of the interaction compensates the benefit. In case of moderate DDIs, combinations should be avoided and these should be used only under special circumstances. Minor DDIs has minimal risk and an alternative drug may be considered

Statistical Analysis

The data was analyzed using Statistical Package for Social Science (SPSS) software (Version18) or Microsoft Excel for Windows and represented as mean ± Standard Deviation (SD). Descriptive statistics was used to compute the demographic characteristics of the study participants. Analysis of previous and current medications used by patients or suggested by physicians was done by frequency distribution using Microsoft Excel 2007.

Results

Demographic Characteristics of the Respondents

Table 1 shows the demographic profile of the study population. Out of 120 patients, the majority attending in the hospital were female (92.60%) with female to male ratio of 12.51:1 and the mean age of the patients was 39.57 ± 9.17 years. The study demonstrated that the age of 56.42% patients were below 40 years while 43.47% patients were found to be above 40 years of age. The total numbers of medications per prescription were of 3 to 12 including a mean of 6.11 ± 1.79. The study also showed that about 36.67% prescriptions contained ≤ 5 drugs whereas above half of the total prescriptions (55%) contained 6-10 drugs and another 8.33% prescriptions had more than 10 drugs [Table 1].

Variables	Values
Total number of prescription	120
Male	7.40%
Female	92.60%
Age range	24-94 years
Mean Age	39.57 ± 9.17 years
% of patients over 40 years	43.47%
% of patients below 40 years	56.42%
Total number of drugs	734
Number of drugs per prescription ± SD	6.11 ± 1.79
≤5	36.67% (n=44)
6-9	55% (n=66)
≥10	8.33% (n=10)

Table 1: Demographic profile of the study population.

Prescription Pattern in RA

From the study of prescribed classes of drug pattern in Figure 1, it was observed that most commonly prescribed class drugs for the treatment of RA was modifying antirheumatic drugs (DMARDS) (31.81%). This was followed by vitamins and minerals (21.57%), antiulcer drugs (17.95%), corticosteroids (11.34%), NSAIDS (8.98%), anxiolytics (4.72%) and simple analgesic (3.15%). The use of opioid analgesic for the treatment of was very negligible (0.47%).

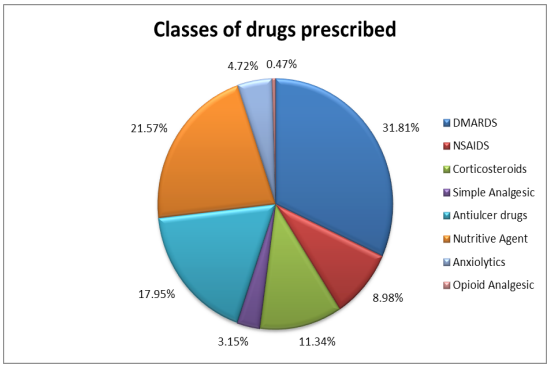

Figure 1: Most commonly prescribed classes of drugs for the treatment of RA.

Prescription analysis of the current study reported that the physicians used 2 different types of combined drug therapy for the treatment of RA; one containing 2 DMARDs and the later containing 3 DMARDs in summation with other drugs [Table 2]. About 49.16% of the total prescriptions were found containing the combination of 2 DMARDs with other drugs. In this category the combination of 2 DMARDs and 1 steroid was prescribed mostly (72.88%). The aggregation of methotrexate, hydroxychloroquine and prednisolone was most predominant (33.89%) in this subclass which pursued by the combination of methotrexate, leflunomide and prednisolone (13.56%); hydroxychloroquine, leflunomide and prednisolone (11.86%); and methotrexate, sulfasalazine and prednisolone (10.17%). The second highest percentage of in the category containing 2 DMARDs was observed for the combination of 2 DMARD with 1 NSAID (18.64%). Here the accumulation of methotrexate, sulfasalazine and indomethacin was mostly used (10.17%). Again, only 8.87% prescriptions were found to have the combination of drugs containing 2 DMARDs, 1 NSAID and 1 steroid [Table 2]. It is clear from [Table 2] that the combination therapy carrying 3 DMARDs with other drugs accounted for about 12.50% of the prescriptions. Among this category, 3 DMARDs (methotrexate, sulfasalazine and hydroxychlorquine) in coalescence with 1 steroid (prednisolone) was frequently used (11.86%). Another 6.78% of the prescriptions were seen for both

the combinations containing 3 DMARDs with 1 NSAID and 3 DMARDs with 1 steroid and 1 NSAID.

Combination therapy	Number of prescription (%)
Prescriptions with 2 DMARDs	59 (49.16%)
2 DMARD + 1 NSAID	11 (18.64%)
Methotrexate + sulfasalazine + indomethacin	6 (10.17%)
Methotrexate + hydroxychloroquine + naproxen	3 (5.08%)
Hydroxychloroquine + mycophenolate mofetil + Indomethacin	2 (3.39%)
2 DMARD + 1 steroid	43 (72.88%)
Methotrexate + hydroxychloroquine + prednisolone	20 (33.89%)
Methotrexate + sulfasalazine + prednisolone	6 (10.17%)
Methotrexate + leflunomide + prednisolone	8 (13.56%)
Hydroxychloroquine + leflunomide + Prednisolone	7 (11.86%)
Sulfasalazine + leflunomide + prednisolone	2 (3.39%)
2 DMARD + 1 NSAID + 1 steroid	5 (8.87%)
Methotrexate + hydroxychloroquine + Indomethacin+prednisolone	3 (5.08%)
Methotrexate + sulfasalazine + Indomethacin + Prednisolone	2 (3.39%)
Prescriptions with 3 DMARDs	15 (12.50%)
3 DMARD + 1 NSAID	
Methotrexate +sulfasalazine + hydroxychloroquine + naproxen	4 (6.78%)
3 DMARD + 1 steroid	
Methotrexate + sulfasalazine + hydroxychloroquine + prednisolone	7 (11.86%)
3 DMARD + 1 steroid + 1 NSAID	
Methotrexate + sulfasalazine + hydroxychloroquine + Prednisolone + naproxen	4(6.78%)
Disease-modifying antirheumatic drug (DMARDS); Nonsteroidal anti-inflammatory drugs (NSAIDs)	

Table 2: Combinations of drug classes used in the treatment of RA.

In our study we have also analyzed different types of combined drug therapy of DMARDs and the results are represented in [Table 3]. From the table it can be seen that methotrexate (32.50%) was the most frequently prescribed DMARD while sulfasalazine was used in 5.83% of the prescriptions as a monotherapy. The pattern of two DMARD combinations showed that methotrexate and hydroxychloroquine (21.67%), sulfasalazine and methotrexate (11.67%), leflunomide and methotrexate (6.66%), leflunomide and hydroxychloroquine (5.83%) were most commonly used. The combination of hydroxychloroquine with mycophenolate mofetil and leflunomide with sulfasalazine were used only in 1.67% of prescriptions respectively [Table 3].

DMARD therapy	Number of prescription (%)
Monotherapy with single DMARD	
Methotrexate	39 (32.50%)
Sulfasalazine	7 (5.83%)
Two DMARD therapy	
Methotrexate and hydroxychloroquine	26 (21.67%)
Sulfasalazine and hydroxychloroquine	2 (1.67%)
Sulfasalazine and methotrexate	14 (11.67%)
Leflunomide and hydroxychloroquine	7 (5.83%)
Leflunomide and methotrexate	8 (6.66%)
Leflunomide and salfasalazine	2 (1.67%)
Three DMARD therapy	
Methotrexate, hydroxychloroquine and sulfasalazine	15 (12.50%)
Disease-Modifying Antirheumatic Drug (DMARDS)	

Table 3: Pattern of combined therapy of DMARDs used in the treatment of RA.

This present research work also estimated the individual therapeutic class of drugs prescribed for the treatment of RA patients. The [Table 4] depicted that 8 different therapeutic classes of drugs were prescribed of which DMARDs were the predominant and it was prescribed for about 202 times in the 120 prescriptions. Methotrexate was the mostly (48.02%) prescribed drug within all DMARDs pursued by hydroxychloroquine (26.24%) and leflunomide (15.84%). Corticosteroids remained as the 2nd individual therapeutic class of drug used by the physicians (72 times) for the treatment of RA and prednisolone (93.05%) was the major generic drug prescribed in this class. Next to corticosteroids; NSAIDs were used for about 57 times in the investigated prescriptions where indomethacin, naproxen and diclofenac were used as 45.61%, 36.85% and 17.54% respectively. The data calculation reflects that about 4.72% (30 times) of the patients received anxiolytics drugs where amitriptyline 50 % was most commonly used in comparison to alprazolam (26.70%), bromazepam (10%), nortriptyline (4.26%) and fluphenazine (3.34%). A total of 3.15% (20 times prescribed) was simple analgesic where acetaminophen and caffeine combination 75% were most frequently used followed by acetaminophen 25% [Table 4].

Different therapeutic drugs other than the antirheumatic drugs were also prescribed for the treatment of co-existing diseases in some patients. Among these patients, 17.95% patients received antiulcer drugs where proton pump inhibitors (PPIs) were the drug of choice over H_2 receptor blockers (97.37% vs 2.63%). It was observed that large number patients (21.57%) were treated with vitamins and minerals and this individual therapeutic class of drug was prescribed for about 137 times. Within this class folic acid (70.80%) was predominant over others followed by calcium and vitamin D3 combination (23.36%), carbonyl iron (2.92%), zinc (1.46%) and vitamin C (1.46%).

Drug class (Times prescribed in total)	Number	
	Total (n)	Prescription rate (%)
DMARDS (n=202)		
Methotrexate	97	48.02
Sulfasalazine	32	15.84
Hydrochloroquine sulfate	53	26.24
Leflunomide	16	7.92
Mycophenolate mofetil	2	0.99
Tofacitinib	2	0.99
NSAIDS (n=57)		
Indomethacin	26	45.61
Neproxen	21	36.85
Diclofenac	10	17.54
Corticosteriods (n=72)		
Prednisolone	67	93.05
Deflazacort	2	2.78
Methylprednisolone	3	4.17
Vitamins and minerals (n=137)		
Folic acid	97	70.8
Calcium + Vitamin D3	32	23.36
Carbonyl iron	4	2.92
Zinc	2	1.46
Vitamin C	2	1.46
Simple Analgesic (n=20)		
Acetaminophen + Caffain	15	75
Acetaminophen	5	25
Opioid Analgesic (n=3)		
Tramadol	3	100
Anxiolytics (n=30)		
Alprazolam	8	26.7
Bromazepam	3	10
Fluphenazine	1	3.34
Amitriptyline	15	50
Nortriptyline	3	10
Antiulcer drugs (n=114)		
Proton pump inhibitor	111	97.37
H_2 receptor blocker	3	2.63
Disease-Modifying Antirheumatic Drug (Dmards); Nonsteroidal Anti-Inflammatory Drugs (NSAIDs)		

Table 4: Individual therapeutic class of drug prescribed for RA patients.

Drug-Drug Interactions

The number of potential drug interactions per prescription was determined which were listed in [Table 5]. We found that within the 120 prescriptions about 91.66% had one or more potential DDIs whereas no potential interaction was observed in 8.34% prescriptions. The frequency of one, two, three, four and

five, six or more drug interaction was 7.23%, 13.64%, 16.36%, 22.72%, 20% and 16.36% respectively.

Pattern of DDIs	Frequency (%)
No potential drug interaction	10 (8.34)
Single or multi drug interaction	110 (91.66)
1	8 (7.23)
2	15 (13.64)
3	18 (16.36)
4	25 (22.72)
5	22 (20)
≥6	18 (16.36)

Table 5: Pattern of DDIs in the prescription of RA patients.

We also identified the most frequent potential DDIs from different drug combinations. In the present research, a total of 450 drug-drug interaction were found out of 120 patients where major 45.33% (n = 204), moderate 41.78% (n = 188) and minor 12.89% (n = 58) shown in [Table 6]. The most frequently encountered severe DDIs were those with the methotrexate and esomeprazole (10.22%) followed by methotrexate and omeprazole (8.89%), methotrexate and Indomethacin (5.56%), prednisolone and leflunomide (5.10%), methotrexate and naproxen (3.55%). The combination of methotrexate and prednisolone (14.23%) was found to be the commonly occurred moderate type of drug interaction found in our study. The second moderate DDI was found for the combination of methotrexate and sulfasalazine (6.22%) pursued by the combination of acetaminophen and methotrexate (4%), naproxen and omeprazole (4%) and methotrexate and caffeine (3.55%).

Drug Interactions	Number of interactions	Percentage (%)
Major interactions	**204**	**45.33**
Methotrexate+Esomeprazole	46	10.22
Methotrexate+Omeprazole	40	8.89
Methotrexate+Indomethacin	25	5.56
Prednisolone+Leflunomide	23	5.1
Naproxen+Methotrexate	16	3.55
Methotrexate+Leflunomide	14	3.11
Methotrexate+Diclofenac	9	2
Methotrexate+Rabeprazole	7	1.55
Hydroxychloroquine+Leflunomide	7	1.55
Methotrexate+Pantoprazole	3	0.66
Methylprednisolone+Leflunomid	2	0.45
Diclofenac+Leflunomide	2	0.45
Sulfasalazine+Leflunomide	2	0.45
Naproxen+Leflunomide	2	0.45
Methotrexate+Tofacitinib	2	0.45
Clopidogrel+Esomeprazol	2	0.45
Clopidogrel+Omeprazole	2	0.45
Moderate interactions	**188**	**41.78**
Methotrexate+Prednisolone	64	14.23
Methotrexate+Sulfasalazine	28	6.22
Acetaminophen+Methotrexate	18	4
Neproxen+Omeprazole	18	4
Methotrexate+Caffeine	16	3.55
Indomethacin+Prednisolone	10	2.22
Naproxen+Sulfasalazine	9	2
Calcium carbonate+Hydroxychloroquine	8	1.78
Naproxen+Prednisolone	7	1.55
Indomethacin+Sulfasalazine	4	0.89
Sulfasalazine+Diclofenac	4	0.89
Prednisolone+Diclofenac	1	0.22
Omiprazole+Mycophenolate mofetil	1	0.22
Minor interactions	**58**	**12.89**
Methotrexate+Hydroxychloroquine	33	7.33
Folic acid+Sulfasalazine	25	5.56

Table 6: Details of potential drug-drug interaction.

The final focus of our study was the analysis of the interaction between anti-rheumatoid drugs itself and the interaction between anti-rheumatoid drugs and other drugs. The study results are depicted in figure 2 from which it is clear that about 60% interactions encountered between anti-rheumatoid drugs itself while other 40% interaction was found to be present between anti-rheumatoid drugs and other drugs.

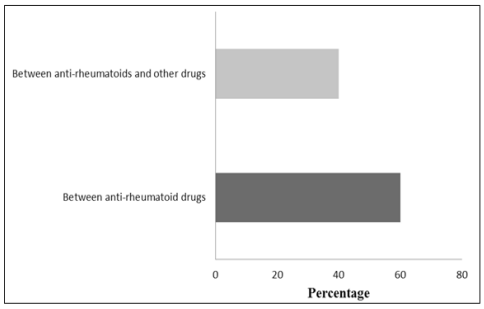

Figure 2: Percentage of drug interaction between anti-rheumatoid drugs itself and between anti-rheumatoids and other drugs.

Discussion

Analysis of drug utilization pattern in different diseases is important to identify the rational or irrational drug therapy in clinical practices. It helps to describe the underlying problem and provide corrective interventions. The present study showed that the majority of patients for the treatment of RA were of female and the age of onset was middle. RA is a chronic inflammatory and autoimmune disease that is predominant in female (about 2.5 times higher) compared to male [2]. This predominance in female is due to the reasons like influence of hormonal factors and X linked genes involved in the pathogenesis of RA [1].

The study of drug number per prescription reflects that the physicians prefer the combination of several drugs for the treatment of the patients. In our study, the average the number of drugs per prescription was found to be 6.1, which is more than the WHO recommendations [16]. It has been recommended that the limit of number of drugs prescribed per prescription should be two and that justification for prescribing more than two drugs would be required because of the increased risk of drug interactions. The increase in the number of drugs per prescription also increases the cost of prescription and patients may not purchase or take the prescribed drugs. This non-adherence to the therapy can deteriorate the said condition, prolonging the treatment duration. The present study observed that no drugs were prescribed by their generic name [16,17].

This study suggests that single DMARD was used in only 31.81% of patients and combination of two or three DMARD were used in 68.19% of patients. This may be due to the severity of the disease. The combination of DMARD was used when the disease was uncontrolled. According to the ACR 2015 guidelines to treat RA recommend that regardless of the disease activity level, DMARD monotherapy should be started initially for treating the patients [7].

Methotrexate (32.5%) is the drug of the first choice prescribed as monotherapy followed by sulfasalazine (5.83%). Approximately 12.5% patients were on DMARDs with 3 drugs. These included methotrexate, sulfasalazine, and hydroxychloroquine. In a study, it was seen that DMARDs with 2 drugs were commonly preferred [18]. Another study by Sukhpreet et al. also found that combination of 2 DMARDs was commonly prescribed [17]. A study by Shini et al. reported that majority of the patients were on single DMARD [18]. The variation in the number of DMARDs prescribed might be due to the varied severity of disease encountered in different hospital settings. Along with DMARD, highly use of corticosteroids and NSAIDs were found in this study. Furthermore, omeprazole, esomeprazole and calcium supplement are widely used to manage the adverse drug reactions like epigastric pain and steroid-associated osteoporosis. Anemia associated with methotrexate was prevented by adding folic acid (70.80%).

The drug-drug interaction was reported in 91.66% prescription. However, most of drug-drug interactions were major in nature. The most common drug-drug interaction was reported when methotrexate was given with steroids. Beside this, a large number of drug-drug interaction occurred due to the usage of omeprazole and esomeprazole along with methotrexate. The occurrence of the interaction of antirheumatic drugs with RA drugs was 60% and other drugs were 40%.

It is seen from the study that a large proportion of the RA patients are at high risk of experiencing drug interactions. To reduce the incidences of drug interactions it is very important that not only for physicians but also for pharmacist to recognize potential drug to drug interactions. Physicians should study the patient history about anything unusual in the patient which may be attributed to use of drugs before prescribing any medications. Pharmacists, more than physicians, should have to be aware of the changes in patient symptoms and unusual reactions that can be related to enhanced drug effects and interactions. Furthermore, polypharmacy needs to be reduced as much as possible.

Conclusions

Our study concludes that the practice of combined use of drugs in the treatment of RA in Bangladesh is very high. This polypharmacy may increase the degree of potential drug-drug interactions. The government and the drug regulatory authority should impose strict control over the prescribing pattern of the physician and should take sufficient initiative to develop awareness among the patients regarding the appropriate use of medication which will reduce the unwanted interactions in the prescriptions. As the study was conducted in a selected hospital with a small number of sample sizes, it may require further study with a large number of population in several hospitals of the country to represent the actual scenario of RA and pattern of prescription used for their management.

Conflict of Interest

The authors declare that they have no conflict of interest.

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