

## Anti-Inflammatory Drugs and Immunosuppressants in Rheumatological and Musculoskeletal Diseases

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### ABSTRACT

**Objective:** To determine drug compliance among patients with rheumatological and musculoskeletal diseases and to identify the reasons behind poor compliance.

**Study Design:** Cross-sectional study.

**Place and Duration of Study:** Department of Rheumatology Lady Reading Hospital, Peshawar Pakistan, from Aug 2020 to Feb 2021.

**Methodology:** All patients aged 16 to 70, of either gender with inflammatory rheumatic diseases who were prescribed conventional DMARDs for at least six months were included in the study.

**Results:** Two hundred and eighteen patients were included in the study. There were 59(27.1%) males and 159(72.9%) females with a mean age of 38.56±4.75years. There were 156 SPRA patients (71.5%), while SLE and SNIA accounted for 22(10.1%) and 17(7.8%) cases, respectively. Methotrexate was the most commonly prescribed medicine, 158(72.5%) while 90(41.3%) patients were prescribed Hydroxychloroquine and 43(19.7%) patients were prescribed Sulfasalazine. Regarding compliance, 112 (51.4%) patients were found to have good drug adherence. On the other hand, side effects and lack of awareness were found to be the most common cause of poor medication adherence.

**Conclusion:** We concluded that adherence to medication among patients with inflammatory rheumatic and musculoskeletal diseases is poor.

**Keywords:** Compliance, Methotrexate, Rheumatological and musculoskeletal diseases.

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### INTRODUCTION

Rheumatic and musculoskeletal diseases (RMDs) includes more than 100 different disorders, the commonly encountered RMDs by rheumatologists have inflammatory arthritides like rheumatoid Arthritis and seronegative arthropathies.<sup>1,2</sup> Other RMDs, like connective tissue diseases, are much less common and include conditions like Sjögren's syndrome, systemic lupus erythematosus, systemic sclerosis, and idiopathic inflammatory myositis.<sup>3,4</sup>

RMDs are huge health hazards around the world. In Europe alone, the RMDs affect around 30–40% of the general population.<sup>5</sup> Similarly, in the United States, a national survey found that approximately 24–40% of the indigenous population was affected by the RMDs. Similarly, Rheumatoid Arthritis (RA), one of the common RMDs, is believed to affect 1% of the population worldwide.<sup>6</sup>

Owing to their high morbidity and mortality, it is imperative to manage these conditions timely. The

medicines used for this purpose are primarily immunosuppressive or immune-modulating drugs.<sup>7</sup> These immunosuppressive medications include Methotrexate, Leflunomide, Sulfasalazine, Hydroxy-chloroquine, Azathioprine, and Mycophenolate mofetil.<sup>8,9</sup> Since these medicines suppress or modify the immune system, they are not without side effects. However, despite the risk of side effects, their administration is essential to keep the disease in remission and thus prevent the disease from permanently damaging the organs.

Despite the utmost importance of these medicines, compliance with these medicines at many times could be better. For example, in one study on RA, good adherence was found to be as low as 30%.<sup>10</sup> Therefore, our study aimed to determine drug compliance among our population and identify the reasons behind poor compliance.

### METHODOLOGY

The cross-sectional study was conducted at the Rheumatology Department of Lady Reading Hospital, Peshawar Pakistan, from August 2020 to February 2021. Ethical approval from the Hospital Ethical and

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Research Committee (ERC/IERB number=50/LRH/MTI) was taken. Non-probability consecutive sampling technique was used. The sample size was 218 using a 17.3% prevalence of RMDs,<sup>11</sup> with the help of WHO calculator for sample size determination.

**Inclusion Criteria:** All patients aged 16 to 70, of either gender with inflammatory rheumatic diseases who were prescribed conventional DMARDs for at least six months were included in the study.

**Exclusion Criteria:** All patients with inflammatory rheumatic diseases with significant steroid exposure (taking 7.5mg of prednisone per day for more than three months), patients on biological DMARDs, patients in critical conditions and patients with ankylosing spondylitis were excluded from the study.

All patients meeting the inclusion criteria were recruited in the study for data collection. Informed written consent was taken from the patients. All patients were worked up with detailed history and clinical examination, and all the information was recorded on a predesigned proforma. The conditions considered as inflammatory rheumatic and musculoskeletal disease i.e., Seropositive Rheumatoid Arthritis (SPRA); Seronegative inflammatory Arthritis (SNIA); Systemic Lupus Erythematosus (SLE); Systemic Sclerosis; Mixed connective tissue diseases; Polymyositis; Dermatomyositis; IgG4-Related Disease were included in the study.

Data were analyzed using Statistical Package for Social Sciences (SPSS) version 26. The mean±standard deviation was calculated for continuous variables like the age of the patients. Frequency and percentages were calculated for qualitative variables like gender, compliance status, and reasons for poor compliance. The chi-square test was applied, and the *p*-value of <0.05 was considered statistically significant. Furthermore, we used the Odds Ratio to determine the extent to which patient compliance would vary in response to an increase or decrease in the number of medications.

**RESULTS**

A total of 218 patients were studied. There were 59(27.1%) males and 159(72.9%) females in our study population. The age of the patients ranged from 16 to 71 years, with mean±SD as 38.56±14.75 Years. SPRA constituted the most number of patients with 156 patients (71.5%), while SLE and SNIA accounted for 22 (10.1%) and 17(7.8%) cases, respectively. Methotrexate was the most commonly prescribed medicine 158 (72.5%) while 90(41.3%) patients were prescribed

Hydroxychloroquine and 43(19.7%) patients were prescribed Sulphasalazine (Table-I).

**Table-I: Baseline Characteristics of Patients (n=218)**

Characteristics	n(%)
Age ( Mean±SD)	38.56±14.75
Males	59(27.1%)
Females	159(72.9%)
<b>Diagnosis</b>	
Seropositive rheumtoidArthritis	156(71.5%)
Systemic lupus erythematosus	22(10.1%)
Seronegative inflammatory arthritis	17(7.8%)
Scleroderma	11(5.0%)
Dermatomyositis	4(1.8%)
Others	8(3.67%)
<b>Medications Used</b>	
Methotrexate	158(72.5%)
Hydroxychloroquine	90(41.3%)
Sulfasalazine	43(19.7%)
Leflunomide	20(9.2%)
Azathioprine	10(4.6%)
MycophenolateMofetil	8(3.7%)

**Table-II: Reasons for Poor Compliance (n=218)**

Reasons	n (%)
Good Compliance	112(51.4%)
Poor compliance	106(48.6%)
<b>Reason for poor compliance</b>	
Side effects	39(36.7%)
Lack of awareness	34(32%)
Forgetfulness	12(11.5%)
Unavailability	12(11.5%)
Cost	4(3.8%)
Others	7(6.6%)
Total	218(100.0)

Regarding compliance, 112(51.4%) patients were found to have good drug adherence, while 106(48.6%) were found to be non-adherent to medication. Adverse effects (36.12%)and lack of awareness (31.48%) were the most common cause of poor medication adherence (Table-II). There were 82(51.6%) male and female patients had good compliance, respectively (Table-III).

**Table-III: Association of Compliance with Gender and Diagnosis of Disease (n=218)**

Gender	Compliance		<i>p</i> -value
	Poor (n=106)	Good (n=112)	
Male	29(49.1%)	30(50.9%)	0.50
Female	77(48.4%)	82(51.6%)	
<b>Diagnosis of Disease</b>			
SPRA	81(57.1%)	75(42.9%)	0.55
Sclerderma	5(45.4%)	6(54.6%)	
SNIA	8(47.1%)	9(52.9%)	
SLE	7(46.6%)	15(53.4%)	
Dermatomyositis	2(50.0%)	2(50.0%)	
Others	4(36.3%)	7(63.7%)	

Among medications, poor compliance was most associated with Methotrexate 82(51.9%), while at least with Hydroxychloroquine 38(42.2%). In comparison, poor compliance was observed in 60(40.6%), 47(55.3%) and 68(59.65%) patients taking single, two or three drugs, respectively, with a  $p$ -value of 0.02, indicating that our findings with regards to the association of poor compliance with the increase in the number of drugs were statistically significant (Table-IV).

**Table-IV: Association of Compliance with Common Drugs and Number of Drugs (n=218)**

Drugs	Compliance		$p$ -value
	Poor (n=106)	Good (n=112)	
<b>Methotrexate</b>			
Yes	82(51.9%)	76(48.1%)	0.78
No	24(40.0%)	36(60.0%)	
<b>Sulfasalazine</b>			
Yes	19(44.1%)	24(55.9%)	0.30
No	87(49.7%)	88(50.3%)	
<b>Hydroxychloroquine</b>			
Yes	38(42.2%)	52(57.8%)	0.70
No	68(53.1%)	60(46.9%)	
<b>Azathioprine</b>			
Yes	2(20.0%)	8(80.0%)	0.60
No	104(50.0%)	104(50.0%)	
<b>Number of Drugs Prescribed</b>			
Single drug	46(40.3%)	68(59.7%)	0.02
2 drugs	47(55.3%)	35(44.7%)	
3 drugs	13(59.0%)	9(41.0%)	

## DISCUSSION

We studied patients' adherence to their disease-specific therapy and found that a very high percentage, (48.6%) of the patients, were non-compliant. First, we observed that side effects and the lack of awareness regarding continuous medicine intake were the most common cause of poor compliance. Secondly, we observed poor compliance irrespective of age, gender, or diagnosis. Finally, we observed that drug type affected compliance, and most patients were non-compliant with methotrexate.

An extensive literature review showed that no study had been performed that looked into the compliance of all RMD patients with medications. Most studies have been centred on one disease entity, such as RA or SLE. In one such study conducted in Korea,<sup>12</sup> medication non-adherence was found in 54.1%, similar to our results, i.e., 57.04%. However, these figures are much higher than those reported in the UK.<sup>13</sup>

Xie *et al.*<sup>14</sup> reported that there also exists a high prevalence of non-adherence to medication in SLE

patients. They studied 140 patients in Sichuan, China and observed that 75% of patients were non-compliant with their treatment. According to them, low education, rural residency, lack of awareness, adverse effects, and dissatisfaction with treatment were the primary reason for poor compliance. In contrast, Chehab *et al.*<sup>15</sup> reported a 37.3% prevalence of poor adherence to treatment among SLE patients. In our study group, 46.66% of SLE patients were non-compliant.

The cause of poor adherence among patients with RMDs might be multifactorial. This was also reported by Ubaka *et al.*<sup>16</sup> In this study, side effects were the most common cause of poor adherence, and steps should be taken to minimize the side effects of the drugs. Similarly, lack of awareness among the patients was found to be the 2nd most common reason for poor adherence.

We observed that among all RMDs, poor compliance was highest among the SPRA patients (57.04%). However, Pombo *et al.* reported that in Rheumatoid Arthritis patients, compliance to medications ranges from 30% to 80%, with higher compliance among patients who are on biologics.<sup>17</sup> Similar observations were reported by Maringo *et al.*<sup>18</sup>

Regarding drugs, we observed that the lowest compliance was seen with methotrexate (51.9%). The most common reason for discontinuing this drug was side effects, accounting for 39%. Indeed, according to the literature, 40% of patients on methotrexate developed adverse effects only.<sup>19</sup> The negative effects of methotrexate can be reduced by prescribing 5–10mg of oral folic acids, switching from oral methotrexate to a subcutaneous route or by splitting the dose of methotrexate.<sup>20</sup>

In this study, we observed that compliance became poor as the number of drugs increased from single to multiple, and this finding was statistically significant ( $p=0.02$ ). Moreover, we found that most patients prescribed Azathioprine were more compliant than the rest of the study group. One reason for this may be because, in our study, Azathioprine was mainly prescribed to SLE patients, most of whom have more severe diseases, which may make them more compliant with the drug.

We observed that lack of awareness among patients was found to be one of the most important causes, and this factor can be easily addressed by proper counselling of the patients. Thus our findings need to be notified to the health care officials so that recommendations are made to improve adherence.

### LIMITATIONS OF STUDY

Our study had limitations. Firstly, our study sample mostly included SPRA patients, while all the other RMDs were fewer in number. This is because rheumatoid Arthritis is far more common RMD compared to others; hence, our study represented the actual prevalence of the disease in our area. Secondly, we did not consider the disease activity while observing compliance. One reason for this was that in many diseases like SLE, complement levels and anti-ds DNA levels are part of the disease activity score while being expensive cannot be afforded by most patients. Nevertheless, poor adherence leads to high disease activity and hence would introduce bias.

### CONCLUSION

We concluded that adherence to medication among patients with inflammatory rheumatic and musculoskeletal diseases is poor. This is particularly of concern since poor compliance can lead to organ-threatening or life-threatening complications and can thus affect the quality of life.

**Conflict of Interest:** None.

### Author's Contribution

Following authors have made substantial contributions to the manuscript as under:

SHM & TD: Conception, study design, drafting the manuscript, approval of the final version to be published.

SA & RK: Data acquisition, data analysis, data interpretation, critical review, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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