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Economic impact of rheumatoid arthritis and cost effectiveness analysis of disease modifying antirheumatic drugs in the management of rheumatoid arthritis

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Abstract
Background: Patients with rheumatoid arthritis consume large proportion of their monthly and annual income due to continuous treatment, frequent hospital visits, laboratory monitoring after defined intervals and hence loss of employment due to disability and pain may be the outcome which leads to economic burden on individual, whole society and health care system. The study aims to evaluate the cost effectiveness of traditional disease modifying antirheumatic drugs used in the management of rheumatoid arthritis and the disease burden on affected population.
Materials and Methods: A retrospective, observational and questionnaire based study was designed to evaluate cost effectiveness of disease modifying antirheumatic drugs and disease burden on outpatients of a hospital of Lahore Pakistan during the period July-2017 to September-2017. Both male and female patients with 30-55 years age were included. Data was collected from prescriptions of 100 randomly selected patients and was analyzed using statistic mean and rheumakit Health Assessment Questionnaire-Disability Index (HAQ-DI) score calculator.
Results: The results showed that all the patients were on combination therapy of disease modifying antirheumatic drugs. Average cost per patient was found to be PKR 1484.1, PKR 660.33, PKR 1044.03, PKR 1734.03, and PKR 1594 for sulfasalazine + hydroxychloroquine, methotrexate + hydroxychloroquine, methotrexate + sulfasalazine, methotrexate + sulfasalazine + leflonamide and hydroxychloroquine + sulfasalazine + methotrexate respectively.
Conclusion: Methotrexate + Hydroxychloroquine combination was found to be cost effective. The average direct cost per patient per month was PKR 4611.87 and PKR 55,324.44 annualy (USD 850.426). Total increase in cost was approximately two times due to adverse effects of therapy.

Keywords: Rheumatoid arthritis, HAQ-DI, cost effectiveness, combination therapy, disease burden

Introduction
Rheumatoid arthritis (RA) causes chronic inflammation in membrane lining of joints resulting in progressive bone and cartilage erosion, joint destruction, deformity and disability [1]. It is an autoimmune disease. RA can be diagnosed clinically in which patient experiences morning stiffness for atleast 6 weeks, arthritis of 3 or more joints, abnormal serum rheumatoid factor and radiographically in which bone erosion shown by radiographs of hands and wrist [2].
Laboratory assessments include Rheumatoid factor, Erythrocyte sedimentation rate,C-reactive proteins, and anticyclic citrulinated peptide antibodies. Radiographic images detect irreversible joint damage. Initial laboratory evaluations include complete blood count, liver and renal functions [3]. RA has 1% worldwide prevalence [4]. About a decade earlier, the prevalence of RA in Southern Pakistan has been reported as 0.142%, whereas prevalence of RA in Northern Pakistan has been reported as 0.55% [5].
Treatment is non-pharmacological and pharmacological based on disease activity of patient. Non-pharmacological approach includes patient education, occupational support, physiotherapy program to improve joint mobility & muscle strength and surgical interventions like synovectomy & arthroplasty. Guidelines for treatment of RA has

developed by American College of Rheumatology and Europeon League against rheumatism[6]. Pharmacological approach includes non-steroidal anti-inflamatory drugs, disease modifying antirheumatic drugs (methotrexate, hydroxychloroquine, leflonamide, sulfasalazine) and biological agents (etanercept, infliximab, abatacept, adalimumab etc) [7].

Patients with RA consume large proportion of their monthly and annual income due to continuous treatment, frequent hospital visits, laboratory monitoring after defined intervals and may lead to loss of employment due to disability and pain resulting in economic burden on individual as well as on whole society and health care system [8]. In Sweden a study showed average cost per patient 49,650 SEK ($4,730) in 1999 [9].

Use of supplements, and other drugs to treat adverse effects of therapy also contribute a lot to total cost of drugs, therefore, cost must be considered in making decision for management of RA [10]. In Pakistan government funded hospitals for patients with RA are minimal [11].

In 2002, in Italy a study estimated that the socioeconomic cost of RA was 1600 million euros (1210 million for indirect social costs) [12].

The relationship between therapy effectiveness and its cost help in dividing resources efficiently as economic analysis show positive and negative outcome of intervention [13]. Cost effectiveness analysis is the most commonly used pharmacoeconomic method [14]. Direct cost includes expenses for visiting the hospital or doctor, cost of diagnostic or monitoring tests, cost of medicines, cost of radiologic examinations and cost of special aids. Indirect costs are due to lost productivity including absence from duties, sick leaves, early retirement etc. Intangible costs are defined as pain and suffering of a patient because of disease and include reduction in physical function, increased psychological distress and reduced social function [15].

Data on RA is minimal as compared to Western countries, factors contributing to unawareness of RA burden are shortage of rheumatologists and trained physicians to recognize disease [16].

In Thailand, an economic study of RA has shown that it incurred considerable expenditures for society. A cost effectiveness analysis (CEA) has indicated that methotrexate-based combination disease modifying antirheumatic drugs (DMARDs) are cost-effective in the treatment of RA [17].

The study aimed to evaluate the cost effectiveness of disease modifying antirheumatic drugs (DMARDs) used in the management of RA and to assess the disease burden on affected population.

Materials and methods

A retrospective, observational and questionnaire based study was conducted by randomly selecting 100 Patients during the period July 2017-September 2017 from rheumatology department of a hospital of Lahore Pakistan. Patients with RA, both male and female with 30-55 year age group were included. Patient with autoimmune diseases other than RA, hospitalised patients and patients on concurrent treatment with any biologic agent were not included.

Data collection form was designed covering the various aspects including patient profile, prescribing trend, adverse drug reactions, cost of treatment and laboratory findings. The Stanford Health Assessment Questionnaire-Disability Index was used to assess physical functions. Collected data was analyzed using statistic mean and Rheumakit HAQ-DI score calculator. The results were presented in the form of tables and graphs. Average cost effectiveness ratio was found by using the formula:

ACER=Net Cost/Health outcome

Results

Demographics of patients are depicted in Table-1. Results showed that RA was approximately two times more prevalent in females than males (64% Vs 36%). 23% of the patients were in the range of 30-40 years of age, 67% were in the range of 40-50 years of age, and 10% patients were above 50 years of age. 48% patients were treated from prolong period e.g, more than 1 year while 39% were on therapy from 7-12 months, and only 13% patients were on therapy from 1-6 months. Monthly income of 74% patients was PKR 10,000-30,000, while of 21% patients was PKR 30,000-50,000, and of only 5% patients was more than PKR 50,000.

Prescribing trend was combination therapy of disease modifying antirheumatic drugs (DMARDs) NSAIDs, Steroids, Supplements, and few analgesics. Figure-1 showed most commonly used combination was of hydroxychloroquine and methotrexate i.e; in 45% patients. 21% were on sulfasalazine and hydroxychloroquine, 18% were on methotrexate and sulfasalazine, 7% were on Methotrexate and sulfasalazine and leflonamide, 9% were on hydroxychloroquine, sulfasalazine and methotrexate.

Table-2 depicts that NSAIDs were prescribed for 35% patients, supplements, other drugs e.g, analgesics, anti-ulcer and steroids were prescribed for 100%, 29%, and 22% respectively.

Table-3 depicts that average cost per patient was found to be 1484.1PKR, 660.33PKR, 1044.03PKR, 1734.03PKR, 1594PKR for sulfasalazine + hydroxychloroquine, methotrexate + hydroxychloroquine, methotrexate + sulfasalazine, methotrexate + sulfasalazine + leflonamide and hydroxychloroquine + sulfasalazine + methotrexate respectively. Average cost of NSAIDs, steroids, supplements and other drugs per patient monthly was 263.6PKR, 298.5PKR, 782.57PKR, 514.07PKR respectively.

Figure-2 showed that 58% patients were suffering from nausea, other side effects like rash, myopathy, hypertension and retinopathy were observed in 2%, 38%, 1%, 3% patients respectively. Figure-3 showed components of direct cost. Average cost per month of drugs was PKR 2776.87, and of Laboratory monitoring was PKR 1785. Hospital charges were PKR 50, that remained same throughout the period.

Table-4 depicts Health Assessment Questionnaire Disability Index score, that was calculated using Rheumakit HAQ-DI score calculator for each patient. These values indicate patient health outcome after taking medicine for defined period.

Discussion

Economic resources in treating RA in cost effective manner are limited in Pakistan. The study highlighted cost effectiveness analysis of disease modifying antirheumatic drugs (DMARDs) and burden of RA in an urban population of Lahore Pakistan. RA was more prevalent in the patients of middle age. Prevalence of RA was found to be high in women as compared to men [5, 9]. Genetic (X-linked) factors

and hormonal changes (estrogen and progesterone level decrease with increasing age) are involved in high disease rate in women. Majority of the patients had been under treatment for more than one year, continuous treatment is required to stop progression and control of disease.

Laboratory tests were erythrocyte sedimentation rate, complete blood count, liver function test and renal function test, Anti-Cyclic citrullinated peptide antibodies and rheumatoid factor. Elevated levels of erythrocyte sedimentation rate are indicative of inflammation. X-RAY was also prescribed. Radiographic changes showed extent of bone and cartilage errosion. These tests were required to conduct after defined interval (different for different patients) depending on disease activity and duration of treatment.

Combination therapy of disease modifying antirheumatic drugs was used in all patients. Methotrexate + hydroxychloroquine combination was used in majority patients [17]. Other methotrexate based combinations were also used e.g; methotrexate + sufasalazine, methotrexate + sufasalazine + leflonamide according to disease activity and severity of disease. Unit cost of medicines was determined from hospital pharmacy as well as from retail pharmacy. Cost of medicines was almost same from both pharmacies.

This study reveals that average per month cost of methotrexate + sulfasalazine + leflonamide was higher than other combinations [10].

NSAIDs, steroids, supplements and other drugs e.g, analgesics, muscle relaxants, anti-ulcers were also prescribed. Only deltacotril steroid was prescribed. Naproxin, Meloxicam, Aceclofenac, Diclofenac Na were prescribed as NSAIDs.

Calcium supplements and gastroprotective agents were prescribed to prevent ADRs such as epigastric pain and steroid-associated osteoporosis. Folic acid was added to prevent methotrexate associated anemia. Nifedipine was prescribed for hypertensive patients. Tizanidine and orphenadrine was prescribed for myopathy. This study showed medicines to treat ADRs increase two times the total cost of treatment [16].

This study showed that average direct cost per patient, PKR 55,324.44 annualy ($ 850.426).

Average cost effectiveness ratio was determined for each combination therapy by using net cost per patient and mean HAQ-DI. Methotrexate based combinations e.g. methotrexate + hydroxychloroquine were more cost effective that is comparable to a study conducted in US and Canada [16, 19].

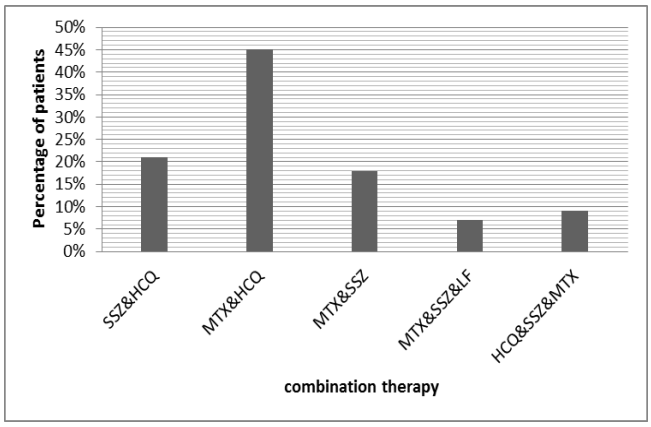

Fig 1: Combinations of disease modifying antirheumatic drugs

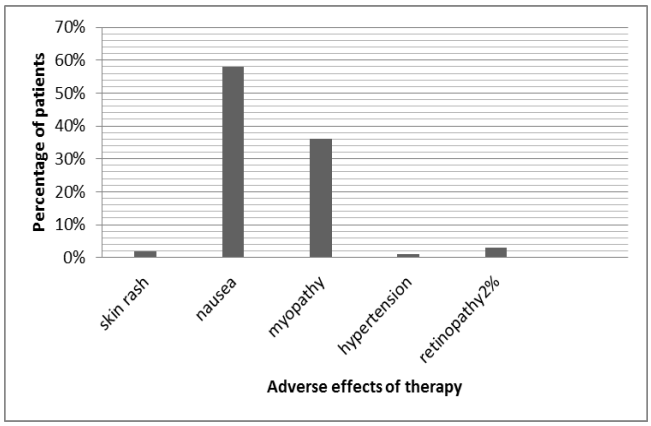

Fig 2: Adverse effects of Disease modifying antirheumatic drugs

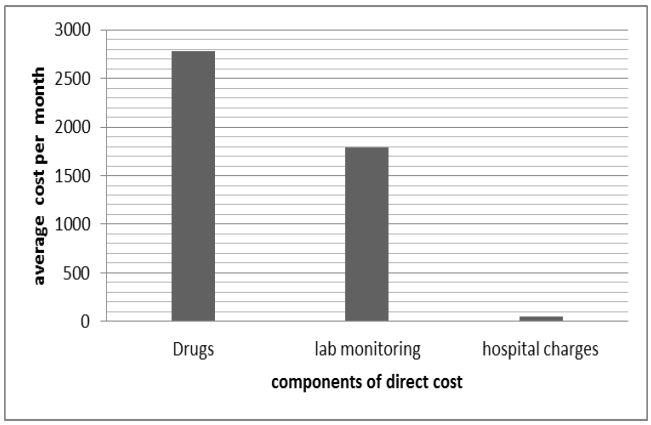

Fig 3: Components of direct cost per patient

Table 1: Demographic characteristics of patients

Parameters	Variables	Frequency (n=100)	Percentage
Age	30-40 years	23	23%
	40-50 years	67	67%
	Above 50 years	10	10%
Gender	Male	36	36%
	Female	64	64%
Duration of treatment	1-6 months	13	13%
	7-12 months	39	39%
	More than 12 months	48	48%
Monthly income	PKR 10000-30000	74	74%
	PKR 30000-50000	21	21%
	Above PKR 50000	5	5%

Table 2: Drugs used in rheumatic patients

Name of drugs	%age 0f patients
NSAIDs	35%
Steroids	22%
Suppliments	100 %
Other drugs i.e; anti-ulcers	29%

Note: NSAIDs= Non-steroidal antiinflammatory drugs

Table 3: Average cost per month of different combination therapies

Drugs	Cost PKR
SSZ and HCQ	1484.1
MTX and HCQ	660.33
MTX and SSZ	1044.03
MTX and SSZ and LF	1734.03
HCQ,SSZ and MTX	1594.23
NSAIDs	263.6
Supplements	782.57
Steroids	298.5
Other drugs	514.07

Note: SSZ= sulfasalazine, MTX= methotrexate, HCQ= hydroxychloroquine, LF= leflonamide

Table 4: Average cost effectiveness ratio of different combination therapies.

Combination therapy	Mean Direct cost per month (Rs)	Mean HAQ-DI	Average Cost Effectiveness Ratio (ACER)
SSZ and HCQ	1484.1	0.4905	3025.68
MTX and SSZ	1044.03	0.1319	7915.31
MTX,SSZ and LF	1734.03	0.2986	5807.2
MTX and HCQ	660.33	0.1305	5060
HCQ,SSZ and MTX	1594.23	0.3476	4586.4

Note: SSZ= sulfasalazine, MTX= methotrexate, HCQ= hydroxychloroquine, LF= leflonamide

Conclusion

The average direct cost per patient per month was PKR 4611.87 and PKR 55,324.44 annualy (USD 850.426). Methotrexate + hydroxychlroquine combination was found to cost effective as compared to methotrexate + sulfasalazine and sulfasalazine + hydroxychloroquine combination. Due to adverse effects of therapy total cost was increased two times.

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