Research Paper

Treatment and Monitoring Costs in Rheumatoid Arthritis: Preliminary Results from an Indian Setting

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The aims of this study were to determine the total cost of drug treatment in patients of rheumatoid arthritis, to estimate the costs of management of gastrointestinal side effects of non-steroidal antiinflammatory drugs and to estimate the cost of monitoring the side-effects of disease modifying antirheumatic drugs. The original prescription of the patients was used to calculate the direct cost of treatment. For calculating the indirect cost, the patients were interviewed. The cost of monitoring the side-effects was also calculated from the patient records. The study was carried in out patient department of a government teaching hospital. A total of 96 patients were recruited in this study between August-November 2003. The average total cost of drug treatment was found to be Rs.999±76 per month. The average monthly direct cost of rheumatoid arthritis was estimated to be Rs. 623±31. The average indirect cost was found to be Rs.368±62 per month. The average iatrogenic cost factor value was found to be 1.78. The average monthly cost of monitoring side-effects in patients prescribed with disease modifying antirheumatic drugs was Rs. 57 per patient. The study provides preliminary results for costs of drug treatment and monitoring in patients suffering from rheumatoid arthritis.

In chronic illnesses, the outcomes are largely dependent upon the adherence to the drug therapy according to the prescribed regimen. In achieving this goal, the pharmacoeconomic evaluation plays a dominant role since the costs and stakes of therapy in a chronic disease are high. Such analysis of cost assumes more relevance when both direct and indirect as well as the social costs are high as in case of rheumatoid arthritis (RA)[1]. The patients suffering from RA fall into a clinical spectrum ranging from a slowly progressive to a rapidly progressive and aggressive course. And, the drug treatment of patients has witnessed a paradigm shift in the recent past.

The available evidence suggests that maximal success in pharmacotherapy of RA depends largely on early and aggressive medical therapy[2]. Further, it is also becoming increasingly clear that disease modifying antirheumatic drugs (DMARDs) should be introduced as soon as possible[3]. The rheumatologists have several drugs to choose from, either alone or in combination; each with different costs, monitoring protocols, and potential risks and benefits. The results of pharmacoeconomic analyses aid the rheumatologists while making the choice of drug(s) for the patient. It is not only the physicians' preference but also the patients' preference that should be kept into consideration while selecting a drug. It has been demonstrated[4] that the patients are more compliant to etodolac-SR once daily than the conventional dosage form. However, if the disease were effectively controlled early, there would be long-term benefits to be offset against the higher treatment cost[5,6]. It has been shown that if DMARDs are used since the onset of disease, it leads to improvement in disability index values[7]. Of late, leflunomide and tissue necrosis factor alpha antagonists have become available for the treatment of RA[8]. However, the high costs of these drugs limit their use in routine prescriptions[9].

The therapeutic benefits of non-steroidal antiinflammatory drugs (NSAIDs) are accompanied by gastrointestinal (GI) side-effects due to the inhibition of the constitutive cyclooxgenase-1 (COX-1) enzyme, with clinical manifestations that include gastritis, erosions, ulcers, hemorrhage, perforation, and even death[10]. This leads to an increase in iatrogenic cost of treatment[1,11-13]. There are very limited studies on costs of treatment in rheumatoid arthritis from this region of the country.

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This study, preliminary in nature, aimed to determine the total cost of drug treatment in case of patients of RA, to estimate the costs of management of gastrointestinal side-effects of NSAIDs and to estimate the cost of monitoring side-effects of DMARDs.

MATERIALS AND METHODS

The study was conducted at a government teaching hospital. The patients fulfilling the ACR 1987 criteria for RA[14], attending out patient rheumatology clinic at Government Medical College, Chandigarh, were enrolled. The patients who were freshly diagnosed of rheumatoid arthritis and who were presenting any co-morbid condition in the out patient department were excluded from the study. A total of 96 patients were recruited between August-November 2003. The patients with incomplete information about their medication and/or laboratory tests were excluded from analysis of the determination of the costs.

For calculating the direct cost, the original prescription of patient was used. The direct cost of treatment included the amount charged by the hospital, cost of the drugs prescribed and the cost of the laboratory tests performed. The amount charged by the hospital was not included in this study because it is the one time charged cost while making the hospital card and the patient does not pay it on the follow up visits.

The calculation of the costs of drugs prescribed was performed using the current issue of Current Index of Medical Specialties (CIMS)[15]. In cases where generic drugs were prescribed, either the patient was interviewed regarding the specific drug being taken or in the absence of this information, the average cost of the drug was used. The cost of laboratory tests in the hospital varies depending upon the income of the patient (or the family). In this study, the costs charged to the middle income category (group B whose monthly income Rs. 1000-3000) patients were taken into the consideration for the calculation of the laboratory investigation expenses.

For calculating the indirect cost, the patients were interviewed. The indirect cost was the aggregate of the cost of travel to the hospital, the loss of work (income) on the day of the visit to the hospital, the loss of income of accompanying person to the hospital and the cost of household help in daily work, if required. The cost calculation was done at a single point assessment and the cost was calculated for the month. All the costs were represented as mean±standard error of the mean (along with other statistical parameters).

The cost of monitoring the side-effects of the NSAIDs was calculated using the ICF value. This value reflects an estimate of the additional costs associated with treating adverse events arising out of the treatment with NSAIDs. The ICF value is the ratio of the total daily cost of NSAID therapy (cost of NSAID plus cost of additional gastro-protective agent required such as proton pump inhibitor) to the daily cost of the NSAID only. Even if the gastro-protective agent was used for the prophylaxis, it was included in the ICF calculation. Further, the cost of monitoring side-effects of the DMARDs - like eye checkup with hydroxychloroquine treatment and complete blood count, liver function test, renal function test (with the use of methotrexate, sulphasalazine, leflunomide) was also calculated.

RESULTS AND DISCUSSION

Of the 93 patients in this study, over 75% of the patients were females. The prevalence of RA is known to be three times higher in females than the males. The age profile of the 93 patients reflected that approximately 60% patients were in the age group of 40-60 y (fig. 1). It was noted that almost half of the patients (48%) enrolled in the study had never been to the school. The number of graduate and post-graduate patients was very small and they comprised approximately only one-fifth of the total patient population of the study. Secondly, only a small fraction of patients (18%) had the facility of medical reimbursement (fig. 2). However, the reimbursement was not sufficient to cover the cost of therapy in 32% of the cases (fig. 2). This shows that a very large proportion of the patients depended on their own income source (or the family) for the treatment of RA. It was found that none of the patients had any kind of health insurance cover.

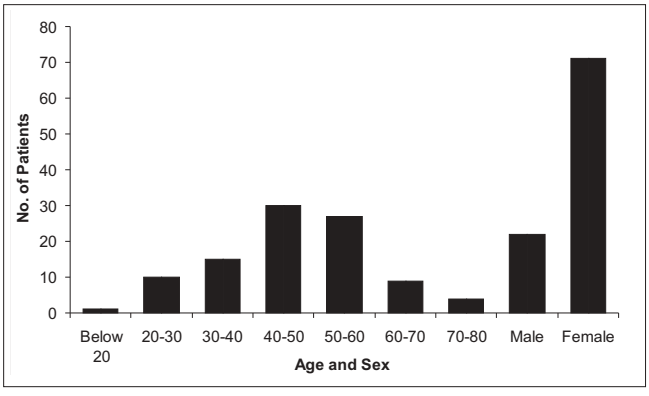

Fig. 1: Distribution of age and sex profile of patients

The determination of the total cost of treatment of RA (n= 93) revealed that the average total cost of treatment in RA was Rs.999±76 per month (mode Rs. 910). The distribution of the total cost was, however, not normal (fig. 3). The cost of treatment in RA depends upon various factors (like disease progression, the severity of the disease, the mode/distance of travel, the daily income of the patient and so on) and this may be the reason for the variations seen in the data on total cost. The total cost comprised direct and indirect costs. The average monthly direct cost was estimated to be Rs. 623±31 (mode Rs. 781). The average indirect cost was found to be Rs. 368±62 per month (fig. 3). The direct cost includes the costs of drugs for the month and laboratory tests performed in that particular month. It was estimated that average expenditure on drugs was Rs. 530±30 (mode Rs. 353) and average expenditure on laboratory tests was Rs. 90±0.18 (mode Rs. 115).

DMARDs contributed 47% of the proportion of the cost followed by the NSAIDs (36% contribution) and the folic acid supplements (prescribed only to the patients on methotrexate) was the last ranking category (fig. 4). Only 43 out of 93 patients, especially women over 50 yrs who were post-menopausal, were put on calcium supplements in order to avoid the chances of osteoporosis. This contributed to 10% of the total spending on the drugs. For a limited number of nine patients, supplements like glucosamine and iron were also prescribed depending on the individual requirement, and they contributed 4% to total cost. This is due to the fact that the drug acquisition cost is high for these drugs. Forty out of 93 patients were on steroids (43%) and majority of the patients were prescribed with prednisolone. A combination of DMARDs was prescribed to 13 patients, out of which 11 were on a two-drug combination and only 2 patients were on 3-drugs combination (Table 1). A very large number of patients were prescribed with the combination of hydroxychloroquine and methotrexate.

The rank order of indirect costs is represented in fig. 5. In the descending order of magnitude it was found to be travel> income of the accompanying person> amount spent on the hel *P*> income due to loss of work (60%, 16%, 14% and 10%, respectively).

The average amount of money spent on travel was

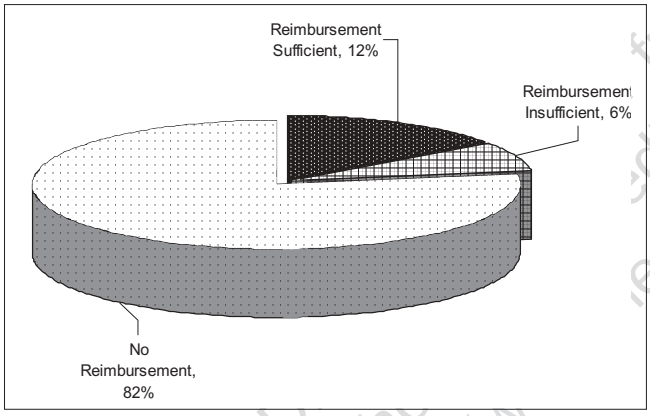

Fig. 2: Reimbursement availability and sufficiency

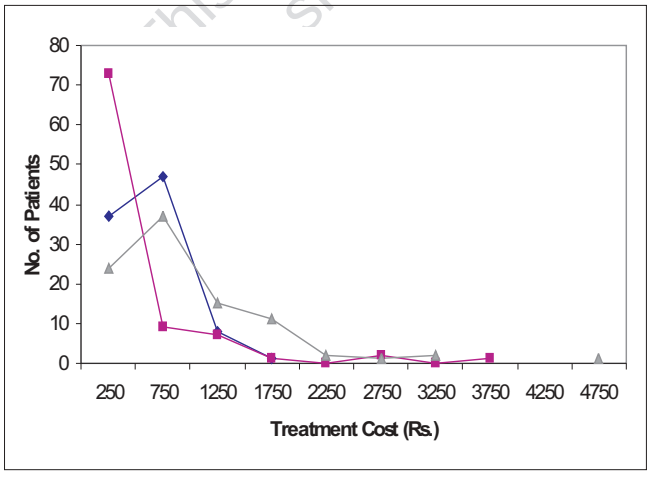

Fig. 3: Distribution of total, direct and indirect costs
Direct cost (-♦-), indirect cost (-▲-) and total cost (-■-)

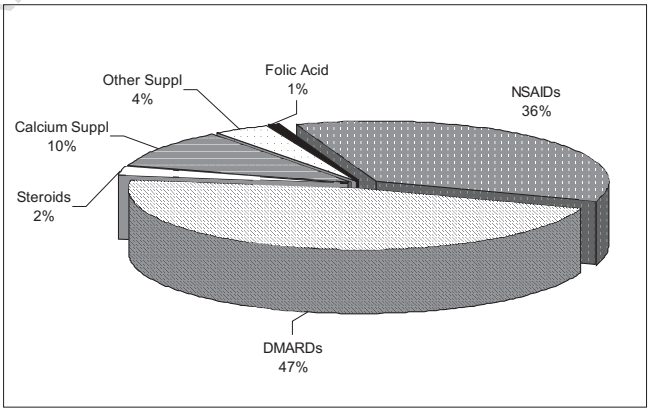

Fig. 4: Distribution of costs of drugs based on drug category

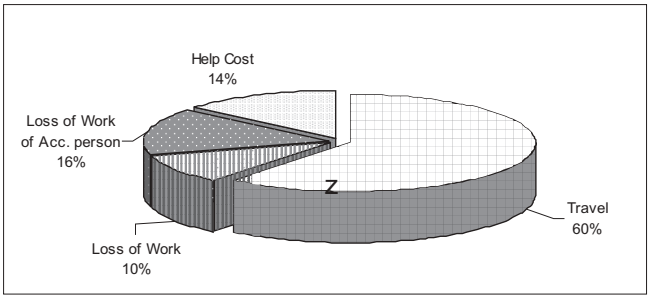

Fig. 5: Distribution of indirect cost

TABLE 1: DISTRIBUTION OF COMBINATION OF DMARDS PRESCRIBED

Combination of DMARDs	No. of patients
Hydroxychloroquine + Methotrexate	5
Sulphasalazine + Methotrexate	3
Sulphasalazine + Hydroxychloroquine	1
Chloroquine+ Methotrexate	1
Leflunomide + Hydroxychloroquine	1
Sulphasalazine + Hydroxychloroquine+ Methotrexate	1
Sulphasalazine + Chloroquine + Methotrexate	1

Rs.239±54. The relatively large variation in amount spent on travel can be attributed to the fact that the distance traveled and mode of travel varies between the patients. Out of 93 patients, only 12 patients were employed. Further, approximately 78% of the patients were females and 60% of the total population falls in the age group of 40-60 y. With less than one fifth of patients having reimbursement facility, the economic burden of treating RA lied on their family. The loss of the income of the patient depended on the type of job of the patient and it ranged between Rs. 60- Rs.1200. Similarly, the loss of income of accompanying person also depends on type of job and varied between Rs. 30-1000. Only 6 patients required household help and amount spent varied from Rs. 500-1000. It is expected because either people usually live in joint families or belong to lower income group and hence, cannot afford a helping aid.

The results showed that 32 patients were prescribed with nonselective COX-2 inhibitors and 51 were prescribed selective COX-2 inhibitors and only very few (3 of 93) patients were prescribed combination of non selective and selective COX inhibitors. Further, it was also found only 10 patients required the prescription of GI protective agents such as proton pump inhibitor or the H-2 receptor blockers. Out of these 10 patients, 2 were prescribed a combination of nonselective and selective COX-2 inhibitor, 5 were on selective COX-2 inhibitors, 2 were on nonselective COX-2 inhibitors and one was receiving any other NSAIDs.

Accordingly, ICF value determination was performed for the limited data of ten patients only. The average ICF value was found to be 1.78 (range 1.22-4.08). This value of ICF indicates that though moderate, yet there is an extra burden of managing the GI side effects. Further, the GI protective agents were prescribed only on the basis of complaints of GI disturbances by the patients. Since no laboratory tests, such as endoscopy, were performed, the subjectivity gets a role to play. Therefore, the drugs used to manage the GI side effects were prescribed without any clinical investigation. Finally, it was also noted that none of the patients required hospitalization due to GI side effects.

The commonly used DMARDs were methotrexate, sulphasalazine, leflunomide and hydroxychloroquine. The average monthly cost of monitoring side-effects in patients prescribed with DMARDs was computed as Rs. 57±5.24 per patient (range 0-230). It is interesting to note that methotrexate has the highest cost of monitoring while the drug acquisition cost is least among all the DMARDs. The most expensive drug, on the basis of acquisition cost, among DMARDs was found to be leflunomide.

This study has made a preliminary attempt to estimate the total cost of drug treatment, the costs of management of gastrointestinal side effects of NSAIDs and the side effects of DMARDs in chronic patients of RA. The results are based upon the data obtained from 93 patients. The average total cost of treatment of RA was found to be Rs.999±76 per month, which is very close to the mode of the data. The monthly direct cost was found to be Rs. 623±31**.** In this case, however, the mode (Rs. 781) is larger than the average of Rs. 623; this reflects positive skew in the direct cost data. The monthly direct cost ranged from as low as Rs. 35/- to as high as Rs. 1356/-. Further, the average monthly indirect cost was calculated to be Rs. 368±62. However, in this case the mode is 20, which is much lower than average indirect monthly cost.

It is important to note that the costs, in a chronic disease like RA, are usually reported as the annual costs because the intensity of symptoms varies between different seasons. However, since this study is preliminary in nature it will be unreasonable to make comments on the annual costs based on this data. Yet, for the purpose of obtaining raw annual estimates, the extrapolation of the monthly data reveals that the total annual cost of treatment of RA is close to Rs .12,000/-, the direct cost Rs. 7,500/- and the approximate indirect cost is Rs. 4,400/-. Such representation of annual data facilitates better comparison with the results of the other researchers.

The results of a US-based study, on patients with early as well as prolonged RA, reported the average annual direct cost of treatment to be US$ 6,000[16]. The patient inclusion criteria are in concurrence with the one used in the current study. Further, the average annual direct cost - generated from 2,32,825 RA patients in UK- was found to be to be GBP 2,597 only[17]. There is a huge difference between the costs of treatment in India and these two

countries. The results of another Dutch study demonstrated the direct costs of treatment of patients with early RA (0-6 yrs) to be Dfl 11,500[18]. Finally, the annual total cost of treatment of RA in Canada was found to be CAN $2162 per patient[1].

A simplistic comparison of the results of the above studies is not possible because the categories of cost included and methods used differ markedly. For instance, in the study performed in Netherlands[18], the direct cost included the cost of health care workers, days in care facilities, medications, monitoring for side effects, alternative medicines used and also the adaptations devices required by the patients. But in the current study -performed in a public hospital- the cost of health care professionals, the cost of alternative medicines and the cost of adaptation devices used was not included. Such differences could be easily identified while comparing the studies head to head. Including these will bulge the extrapolated annual costs of the present study.

The chronic nature of RA has led some investigators to continue their studies for a much longer period of time i.e. beyond a year. The results obtained from 1,156 patients followed for as long as 15 yrs showed US $8,500 as the total medical costs. Nearly 70% of this amount was directly related to treatment of the disease. Hospital admissions accounted for over half of this in spite of the fact that less than one-tenth of the study group was hospitalized in any given year. The drugs accounted for a quarter of the direct cost, with cost of DMARDs compromising 75% out of that quarter spent as direct cost expense[19]. Further, in the present study 47% of the total amount spent on drugs was on the DMARDs. The second largest group of drugs used was analgesics - contributing 35% to the total spending on drugs. It was also observed that the cost of drugs was not uniformly distributed throughout the patient population but rather was highly skewed towards those patients with the worst functional status[20]. The functional status of individual is known to be the most consistent and strongest determinant of cost. The results of this study demonstrate a significant association between deformity in the patient and direct cost (P=0.001). A similar skewing of costs towards those with greater disability has also been noted in other cost studies of RA[18,21,22].

In this study, a very limited number of patients were prescribed with the COX-1 inhibitors; and of them, very few patients reported GI adverse effects. Of the 93 patients in this study, only 10 were prescribed with the GI protective agents (either proton pump inhibitors or the H-2 receptor blockers). The epidemiological evidence suggests that NSAIDs increase the risk for lower and upper GI clinical events. However, the COX-2 selective inhibitors decrease the upper GI clinical events but the effect(s) on lower GI event have not been determined. The results from an earlier study, involving 8076 RA patients, demonstrate that serious lower GI events were 54% lower with the use of the selective COX-2 inhibitor (rofecoxib) compared to naproxen[23]. Another study noted that the daily average cost of therapy with rofecoxib in incident cases was € 1.88 which was 7.4% lower than that of NSAIDs (€ 2.03), and in prevalent cases it was € 1.87, 28.1% higher than that of NSAIDs (€ 1.46)[24]. The cost due to GI adverse effects amounts to 2-8 times the cost of the original NSAID therapy[10].

The iatrogenic cost factor (ICF) for NSAIDs gives an estimate of the additional costs associated with treating adverse events. The results from UK[25] showed the ICF ranging from 1.97-8.41, depending on the GI endpoints. Likewise, the results from Quebec[26] confirmed ICF to lie between 1.59-7.49, depending on the patient's risk by age. The results of Pouvourville and co-workers[27] showed that the ICF ranged from 1.36-2.12, depending on the NSAID taken. However, the co-prescription with GI protective agents was not included. The average ICF value, in the present study, was found to be 1.78 (range 1.22-4.08). The GI protective agents were prescribed on the basis of patients' complaints of GI disturbances; however, no laboratory tests were performed. In this study, the drugs were prescribed on the clinical judgment of the physician. It was largely due to the reason that none of the patients presented with a complication requiring a clinical investigation or has to be hospitalized due to GI side effects.

In this study, leflunomide (prescribed only to 11 patients) was found to be most expensive drug as per the acquisition costs. The conventional drugs, like gold and pencillamine, were not prescribed frequently; none of the patients was prescribed gold and only one patient was prescribed with pencillamine. Prashker and Meenan[28] considered the total cost of drug to be composed of 3 components viz., the actual cost of drug, the cost of monitoring patients for potential side effects of the drug and the cost of treating the side-effects when they occur. They noted that the cost of monitoring and treating side effects contributed to over 60% of the total cost of all medications except injectable gold. When the total costs were compared, it was found that while oral gold was the

cheapest the injectable gold was the most expensive. Further, they reported methotrexate to be the most expensive drug in terms of monitoring costs. The results of the present study demonstrate that Methotrexate was the cheapest drug in terms of acquisition; however, it is the most expensive drug in terms of monitoring the side effects since regular (every 4 weeks) liver function test, renal function tests and complete blood count are required.

In the present study, the cost of treatment was determined for patients (n=93) suffering from Rheumatoid Arthritis. The average total cost of treatment was found to be Rs. 999±76 per month. The average monthly direct cost of RA was determined as Rs. 623±31; and the average monthly indirect cost was found to be Rs. 368±62 per patient. The average ICF value was found to be 1.78. Finally, the average monthly cost of monitoring the side effects in patients prescribed with DMARDs was calculated as Rs. 57±5.24 per patient. These costs reflect the burden of disease in Rheumatoid Arthritis patients and in lack of insurance cover the patients has to bear these costs themselves. These costs, however, are exclusive of the cost of folic acid supplement prescribed to the patients on methotrexate.

These preliminary data on the cost of treatment of rheumatoid arthritis is an initiating point for such pharmacoeconomic analysis by the pharmacy professionals. The authors expect a larger participation of pharmacists in conducting such studies. Such results will strengthen the clinical decisions taken by the rheumatologists in the Indian setting and generate our own data instead of banking on the western results and trends.

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