**Title**

**Patient outcomes in Rheumatoid Arthritis on conventional DMARDs, in an Indian setting.**

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**Introduction**

Rheumatoid arthritis is a chronic inflammatory disease predominantly affecting synovial joints. It is now considered as the most common autoimmune disease affecting the joints with a worldwide prevalence of nearly 1%[1]. Clinically it is characterised by symmetric polyarthritis mainly involving the smaller joints of hands and feet. Patients also commonly experience morning stiffness lasting for 1 hour or more. As disease progresses, deformities also set in, in a number of patients. Extraarticular manifestations in the form of interstitial lung diseases, vasculitis are also seen is a number of patients as disease progresses.

However, with the advent of disease modifying anti rheumatic drugs and newer biological agents, patient outcomes have improved. We can now think of targeting remission in a disease that could be only symptomatically treated earlier . The treatment strategy for RA has seen a major change over the last few decades, with rheumatologists worldwide now favouring the hit early hit hard approach[2,3,4]. It is now widely accepted that early diagnosis with prompt and aggressive treatment with disease modifying anti rheumatic drugs (DMARDs) can lead to significantly better patient outcomes.[5,6].

The diagnostic criteria for rheumatoid arthritis have also seen major changes over the years. The American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) 2010 classification criteria for rheumatoid arthritis redefined its diagnostic scenario by focussing on the early stages of the disease[7]. As per ACR1987 criteria, patients diagnosed with rheumatoid arthritis already had advance disease. While as per the newer criteria, diagnosis is established in the early stages of the disease, thus promoting early intervention to target remissions and better patient outcomes.

However, there still remains a gap between disease onset and initiation of DMARDs in RA, particularly in the Indian setting. It is seen that majority of patients are correctly diagnosed within 2 years of disease onset irrespective of the category of medical practitioner who is approached by the patient[8]. What is lacking is immediate initiation of aggressive DMARD therapy and maintenance, which in turn results in poor outcomes. Its has been observed that only about 2/3rd patients with RA are prescribed with DMARDs in the 1st year of their disease while the remaining 1/3rd remain DMARD naive[9].

It becomes essential for the general practitioners to recognise the symptoms and refer to a rheumatologist so that therapy can be started as early as possible, to ensure better patient outcomes and longer remissions. Knowledge about the effects of delay in initiation of DMARDS as well as that of continuing DMARDS over a long term period, may motivate general practitioners to facilitate the same, by referring to a trained rheumatologist.

We therefore conducted an observational study that aimed at studying disease outcomes such as disease activity and presence of deformities in relation to a delay in initiating DMARD therapy after disease onset. We also aimed at studying the effect of duration of DMARD therapy on disease activity.

**Methodology**

This prospective observational study was conducted in the rheumatology outpatient department (OPD) of B.Y.L Nair Charitable Hospital, a tertiary care centre, in Mumbai. The study was approved by the institutional ethics committee.

Patients of RA diagnosed by ACR criteria(1987), above the age of 18 years and on a regular course of conventional DMARD therapy, that included weekly methotrexate singly or in combination with chloroquine/ hydroxychloroquine or sulphasalazine were included in the study. Newly diagnosed cases of RA and patients on DMARD therapy for a duration of less than 6 months were excluded from the study.

A written informed consent was taken from each patient. The study was conducted between March 2011- May 2011. Each patient’s history was noted and was clinically examined for tender and swollen joints. Relevant clinical information like age, sex, duration of therapy, treatment followed and the latest ESR by the Westergreen’s method were obtained by review of individual patient record. Duration of disease in terms of onset of appearance of symptoms, delay in initiation of therapy since onset of disease were enquired for. Patient’s general health on a visual analog scale was also recorded. DAS28 was calculated for each patient.

The MDHAQ was administered to each patient in a language they understood and their responses noted. Respective RAPID3 score was calculated by adding the physical function (FN), Pain (PN) and patient global status score (PTGL).

The data collected was analysed using the SPSS software and Graphpad Instat.

Patients were divided into 2 groups on the basis of delay in initiating DMARD therapy from onset of disease activity. One group with duration of <=2 years and second with duration of > 2 years and patient outcome in terms of presence or absence of deformities, and disease severity as recorded on DAS28 >5.1 and RAPID3>12, studied.

Patients were also divided into 2 groups on the basis of duration of DMARD therapy. One group with duration of <3 years and the second with that of >=3 years and the patient outcomes as mentioned above, studied.

**Results:**

Of the 81 patients included in the study, 70 were females and 11 were males, with a male to female ratio of 1: 6.36.

Of the 70 female patients, 54.3% showed haemoglobin levels of <=11g/dl while 45.7% showed haemoglobin levels of >11g/dl and of the 11 male patients, 5 (45.5%) showed hemoglobin levels of <=12g/dl and 6 (54.5%) showed haemoglobin levels of >12g/dl. Thirty eight of 81 patients showed the presence of various deformities like swan neck deformity, boutonnière deformity, wrist deviation.

A total of 30 patients had morning stiffness that lasted for more than 30 minutes with 66.7% of these retrospectively showing a delay in initiating DMARD therapy of more than 2 years indicating poor disease control. Off the 34 patients on DMARD therapy for more than 3 years only 8 complained of morning stiffness for more than 30 minutes suggesting that regular therapy provided better disease control.

As far as compliance to treatment and follow ups is concerned, 63 of 81(77.8%) showed good treatment compliance while the rest showed moderate to poor compliance and 60 of 81(74.1%) were regular in their follow ups while the rest were not.

**Effect of delay in initiating DMARD therapy from onset of disease:**

Patients were divided into 2 groups. Group 1 with a delay of less than or equal to 2 years and Group 2 with a delay of more than 2 years.

Thirty eight of 45 patients (84.4%) in whom treatment was delayed by more than 2 years after disease onset (group 2) recorded a severe disease activity of >5.1 on DAS28 (Table I). Similarly, severe disease activity using RAPID3 score of more than 12 was noted in a significant 77.8% patients from group 2(Table II). Also of importance is to note that a significant 62.2% of patients from group 2 showed presence of various deformities (Table III).

**The effect of duration of DMARD therapy on patient outcome:**

Patients were divided into 2 groups on the basis of duration of undergoing treatment. Group A with treatment duration of less than or equal to 3 years and Group B with treatment duration of more than 3 years.

Amongst the patients in group A, 76.6% (n=36/47) recorded severe disease activity on DAS28, 72.3% showed severe disease activity on RAPID3 and 48.9% (n=23/47) showed presence of deformities. (Table IV, V & VI)

52.9% (n=18/34) of patients from group B had their DAS28 scores less than 5.1 and the same number of patients also recored RAPID3 scores of <12. The observed differences being statistically significant (Table IV & V).

**Discussion:**

It has been observed that DMARDs are of particular benefit when the treatment is initiated as early as possible from the onset of disease symptoms, as has also been established by Furst DE et al[10].

However, it is commonly observed especially in India that there is a certain delay in initiating DMARD therapy from onset of disease activity. Multiple reasons point towards this delay, illiteracy of the population being catered, delay in seeking medical attention as a result of this illiteracy and unawareness, seeking care from general practitioners and people practising various other forms of medicine as a result of which establishing a diagnosis itself is delayed. It is however observed that irrespective of the type of medical faculty referred to, majority of the patients are diagnosed with rheumatoid arthritis within 2 years of disease onset as seen in a recent study conducted by Malviya and Gogia[8]. Irrespective of this fact, there is nearly always a delay noted in initiating DMARD therapy from onset of disease activity as is also seen in a study conducted by Crane et al[9] who concluded that nearly 1/3rd patients are not started on anti rheumatic drugs even after 1 year of disease onset and this statistic can be expected to be even more alarming in an Indian scenario.

An intensive approach using the DMARDs as soon as the patient is diagnosed with rheumatoid arthritis can improve patient quality of life and significantly reduce morbidities. In our study it has also been observed that 72.2% patients who started treatment within 2 years of onset of disease activity showed absence of any joint deformities, also 61.1% of patients who started DMARD therapy within 2 years of onset of disease activity had their DAS28 score less than 5.1,

This suggests that even when started on DMARDs within 2 years of disease onset, better deformity outcomes were seen in a majority of the patients. These findings match with similar results obtained in other studies as by Raza K,[11] who concluded that an earlier treatment was associated with higher rates of remissions.

Duration of treatment also affects the outcome and an aggressive use of DMARDs along with strict adherence to therapy for prolonged duration leads to better patient outcomes.

As seen in the present study, where 76.6% of patients, with treatment duration of less than 3 years recorded DAS28 scores more than 5.1 and a similar percent of patients showed RAPID3 scores of >12 indicating severe disease activity while 52.9% patients with a treatment duration of more than 3 years recorded a low disease activity (DAS28<5.1 & RAPID3 <12), the observed difference being statistically significant. These findings conform with those obtained in a study conducted by Ahsan T et al[12]. They suggested that patients have a higher chances of maintaining remissions as long as treatment integrity and compliance is maintained.

However, it is also observed in the present study that prolonged treatment with DMARDs has no significant effect on the presence of deformities as deformities that have once set in cannot be reversed as suggested by the 44.1% patients from our study who despite being on DMARDs for over 3 years still showed the presence of various deformities.

With the Indian scenario being slightly different from that abroad, it is the need of the hour to ensure a more stringent approach towards patient care in rheumatoid arthritis. It becomes essential that the diagnosis is made at first point of patient contact, which is most often the general practioner. A clear knowledge of the new ACR/EULAR diagnostic criteria 2010 can greatly help in the long run. The best approach would be to refer all cases of poly arthritis to a rheumatologist, at presentation itself. Immediate initiation of DMARD therapy with strict adherence and regular follow will significantly reduce morbidities and help achieve remissions.

It can thus be concluded that a systematic approach towards patient care needs to be practiced to obtain best patient outcomes. Significant effect on patient outcomes is noted as a result of delay in initiating DMARD therapy, with severe disease activity and presence of deformities. Early diagnosis and immediate initiation of aggressive DMARD therapy should be followed with regular treatment for longer durations.

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**Table I**

Delay in starting DMARD therapy and DAS28 score (N=81)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **DAS28** | **Delay in starting DMARD therapy** | | | | **Total** | |
| **<=2 Years(group1)** | | **>2 years(group2)** | |  | |
| **No.** | **%** | **No.** | **%** | **No.** | **%** |
| **<=5.1** | 22 | 61.1 | 7 | 15.6 | 29 | 35.8 |
| **>5.1** | 14 | 38.9 | 38 | 84.4 | 52 | 64.2 |
| **Total** | 36 | 100 | 45 | 100 | 81 | 100 |

X2 = 16.131, df = 1, p<0.0001, Highly significant (Graphpad Instat)

**Table II**

Delay in starting DMARD therapy and RAPID3 score (N=81)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **RAPID3** | **Delay in starting DMARD therapy** | | | | **Total** | |
| **<=2 Years(group1)** | | **>2 years(group2)** | |  | |
| **No.** | **%** | **No.** | **%** | **No.** | **%** |
| **<=12** | 21 | 58.3 | 10 | 22.2 | 31 | 38.3 |
| **>12** | 15 | 41.7 | 35 | 77.8 | 50 | 61.7 |
| **Total** | 36 | 100 | 45 | 100 | 81 | 100 |

X2 = 9.564, df = 1, p = 0.0012, considered very significant (Graphpad Instat)

**Table III**

Delay in starting DMARD therapy and presence deformity (N=81)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Deformity** | **Delay in starting DMARD therapy** | | | | **Total** | |
| **<=2 Years(group1)** | | **>2 years(group2)** | |  | |
| **No.** | **%** | **No.** | **%** | **No.** | **%** |
| **Present** | 10 | 27.8 | 28 | 62.2 | 38 | 46.9 |
| **Absent** | 26 | 72,2 | 17 | 37.8 | 43 | 53.1 |
| **Total** | 36 | 100 | 45 | 100 | 81 | 100 |

X2 = 8.195, df = 1, p = 0.0042, considered very significant (Graphpad Instat)

**Table IV**

Duration of DMARD therapy and DAS28 score (N=81)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **DAS28** | **Duration of DMARD therapy** | | | | **Total** | |
| **<=3 Years(groupA)** | | **>3 years(groupB)** | |  | |
| **No.** | **%** | **No.** | **%** | **No.** | **%** |
| **<=5.1** | 11 | 23.4 | 18 | 52.9 | 29 | 35.8 |
| **>5.1** | 36 | 76.6 | 16 | 47.1 | 52 | 64.2 |
| **Total** | 47 | 100 | 34 | 100 | 81 | 100 |

X2 = 6.258, df = 1, p = 0.0124, considered significant (Graphpad Instat)

**Table V**

Duration of DMARD therapy and RAPID3 score (N=81)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **RAPID3** | **Duration of DMARD therapy** | | | | **Total** | |
| **<=3 Years(groupA)** | | **>3 years(groupB)** | |  | |
| **No.** | **%** | **No.** | **%** | **No.** | **%** |
| **<=12** | 13 | 27.7 | 18 | 52.9 | 31 | 38.3 |
| **>12** | 34 | 72.3 | 16 | 47.1 | 50 | 61.7 |
| **Total** | 47 | 100 | 34 | 100 | 81 | 100 |

X2 = 4.371, df = 1, p = 0.038, considered significant (Graphpad Instat)

**Table VI**

Duration of DMARD therapy and presence of Deformity (N=81)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Deformity** | **Duration of DMARD therapy** | | | | **Total** | |
| **<3 Years** | | **>3 years** | |  | |
| **No.** | **%** | **No.** | **%** | **No.** | **%** |
| **Present** | 23 | 48.9 | 15 | 44.1 | 38 | 46.9 |
| **Absent** | 24 | 51.1 | 19 | 55.9 | 43 | 53.1 |
| **Total** | 47 | 100 | 34 | 100 | 81 | 100 |

X2 = 0.04133, df = 1, p = 0.8389, considered not significant (Graphpad Instat)

**Abstract:**

Treatment strategies and diagnostic criteria in rheumatoid arthritis (RA) have evolved over the decades. However, there still remains a gap between disease onset and initiation of DMARDs in RA, particularly in the Indian setting. It is essential for the general practitioners to recognise the symptoms and refer to a rheumatologist at the earliest for prompt initiation of treatment and better patient outcomes. We aimed at studying the effect of delay in initiating DMARD therapy and the duration of DMARD therapy on disease activity.

We assessed 81 cases of RA from the Rheumatology Clinic of B.Y.L Nair Charitable Hospital, Mumbai.

Severe disease activity was recorded in significant number patients with a delay in initiating DMARD therapy of >2years from disease onset. Also significant proportion of patients in this group of delayed DMARD initiation, showed presence of various deformities. Those with treatment duration greater than 3 years, had better disease control.

Hence, prompt referral of all cases of polyarthrits to a rheumatologist is important. Early diagnosis of RA with immediate initiation of DMARD therapy is essential. A strict adherence and regular follow-up will significantly reduce morbidities and help achieve remissions of RA.

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