INTRODUCTION

Rheumatoid Arthritis (RA) is a multi-system autoimmune disease which manifests mainly as symmetric poly-arthritis but can also involve other organ systems. RA has a worldwide distribution and affects around 1% of the adult population in Europe with almost same prevalence in the developing countries. RA untreated or un-responsive to therapy, can lead to significant disability and is associated with early mortality due to cardiovascular diseases. There have been major advances in the treatment of RA in the last few decades and the emphasis now is on early recognition and early treatment with Disease Modifying Anti-Rheumatic Drugs (DMARDs) targeting disease remission.

Treat-to-target approach was not much talked about until European League Against Rheumatism (EULAR) 2010 guidelines for treatment of RA with conventional DMARDs. Outcome measures of remission and low disease activity were defined as per DAS 28 score criteria. Patient response to treatment was also determined by EULAR response criteria.

Results: Out of 67 patients, 50 patients completed the 6 months study period, rest were lost to follow-up. All patients were started on Methotrexate and mean weekly dose at 6 months was 18.9 ± 3.8 mg. Remission was achieved in 17 (34%) and target of low disease activity was achieved in 29 (58%) of patients. EULAR good response was seen in 28 (56%), moderate response in 21 (42%) and no response to treatment in 1 (2%).

Conclusion: By applying treat-to-target approach in early RA, achievement of clinical remission or low disease activity with conventional DMARDs is a realistic goal in routine practice.


ORIGINAL ARTICLE

Treat-to-Target Approach in Daily Clinical Practice in Pakistani Patients with Early Rheumatoid Arthritis

Sumaira Farman, Nighat Mir Ahmad, Muhammad Ahmed Saeed, Kanwal Asad and Ghulam Shabbir

ABSTRACT

Objective: To determine the frequency of patients with early Rheumatoid Arthritis (RA) achieving disease remission and/or low disease activity after 6 months of treatment with conventional Disease Modifying Anti-Rheumatic Drugs (DMARDs) by using treat-to-target approach in routine clinical practice.

Study Design: Descriptive study.

Place and Duration of Study: Division of Rheumatology, Fatima Memorial Hospital (FMH), College of Medicine and Dentistry, Lahore, from March 2011 to February 2012.

Methodology: Patients with early RA defined as disease duration ≤ 1 year were enrolled by purposive sampling, diagnosed as per American College of Rheumatology (ACR) 1987 criteria. Treat-to-target approach was defined as per European League Against Rheumatism (EULAR) 2010 guidelines for treatment of RA with conventional DMARDs. Outcome measures of remission and low disease activity were defined as per DAS 28 score criteria. Patient response to treatment was also determined by EULAR response criteria.

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INTRODUCTION

Rheumatoid Arthritis (RA) is a multi-system autoimmune disease which manifests mainly as symmetric poly-arthritis but can also involve other organ systems. RA has a worldwide distribution and affects around 1% of the adult population in Europe with almost same prevalence in the developing countries. RA untreated or un-responsive to therapy, can lead to significant disability and is associated with early mortality due to cardiovascular diseases. There have been major advances in the treatment of RA in the last few decades and the emphasis now is on early recognition and early treatment with Disease Modifying Anti-Rheumatic Drugs (DMARDs) targeting disease remission. Treat-to-target approach was not much talked about until European League Against Rheumatism (EULAR) 2010 guidelines for the management of RA. Clinical remission in early RA has been an achievable target in many randomized controlled trials and an early remission or low disease activity is associated with much reduced radiographic damage and improved functional status. Different scores have been developed to measure disease activity and guide treatment decisions. One of the most commonly used measures is the Disease Activity Score 28 (DAS 28). It is a validated and reliable tool to assess disease activity based on 28 joint counts in clinical trials as well as in daily practice. It consists of tender and swollen joint counts, patient’s global assessment of disease activity on a visual analogue scale from 0 - 100 and the value of ESR or CRP.

Disease remission is now a realistic goal in a significant proportion of patients. A meta-analysis by Ma et al. showed that on an average 33% of the patients with early RA had achieved remission in studies utilizing DAS remission cut-points. A study from Netherlands conducted in daily practice showed that 31% of their patients achieved target of low disease activity as per DAS 28. Recent studies advocate early treatment with DMARDs as window of opportunity lies in first year of illness. This study applied the treat-to-target approach in our local patients with early RA in routine clinical practice as per standard of care guidelines developed by EULAR. The objective of this study was to determine the frequency of patients with early Rheumatoid Arthritis...
(RA) achieving disease remission and/or low disease activity after 6 months of treatment with conventional DMARDs by using treat-to-target approach in routine clinical practice.

**METHODOLOGY**

This prospective study was conducted in Division of Rheumatology, Fatima Memorial Hospital (FMH), College of Medicine and Dentistry, Lahore, from March 2011 to February 2012. The study was approved by institutional review board and informed consent was taken from all participants.

Patients aged 18 - 65 years at baseline visit having active RA were enrolled from out-patient clinics of Division of Rheumatology, FMH, by purposive, non-probability sampling. They were diagnosed as having RA according to 1987 American College of Rheumatology Criteria (ACR). It was ascertained that all patients had disease duration less than one year at their initial visit, which was determined by the onset of symptoms compatible with diagnosis of RA and not from the date of diagnosis. Only those patients were enrolled who were either DMARD naive or had been on sub-optimal dosages of DMARDs (MTX < 15 mg/week, Leflunomide < 10 mg/day, Sulfasalazine < 2 gm/day) for less than 3 months. All patients had active RA based on DAS 28 score ≥ 3.2. Female patients of child bearing age who were not willing to use safe and effective contraception, pregnant or lactating females, those planning for pregnancy, male RA patients planning to father a child, currently active alcohol or any other drug abuse were excluded. Similarly, any known active malignancy, evidence of Hepatitis B or C infection on the basis of positive HBs Ag or Anti-HCV antibodies by ELISA, any evidence of active tuberculosis on chest X-ray, clinically significant Intestinal lung disease or active vasculitis secondary to RA or evidence of any significant cardiac, pulmonary, renal, neurological or psychiatric illness which, in the investigator's opinion could preclude patient's participation was considered as exclusion. Those who had been on dose of prednisone more than 10 mg at their enrollment visit or had more than one intra-articular injection of gluco-corticoids in the last 4 weeks, and patients previously known to have intolerance to MTX were also excluded. Concurrent treatment with any biological agent was not allowed. Presence of any of the overlap syndromes (Systemic Lupus Erythematosus (SLE)/ RA, RA / Polymyositis, RA/ Scleroderma) was also considered as an exclusion criteria.

Routine clinical practice was pre-defined as per EULAR guidelines for treatment of RA. All enrolled patients were followed after every 4 - 8 weeks for 6 months. Their disease activity was measured by DAS 28 score using DAS calculator at baseline and on each follow-up visit. Each patient was started on MTX 10 mg/week and the dose was increased by 2.5 - 5 mg on subsequent visits to an optimal dose of 15 - 25 mg/week as per EULAR guidelines for use of synthetic DMARDs. Hydroxychloroquine (HCQ) was used as a combination at the discretion of treating rheumatologist. If there was an inadequate response or intolerance to particular dose of MTX, then either Leflunomide (LEF) or Sulfasalazine was used alone or in combination with MTX. Optimal dosages of the DMARDs at 6 months visit were defined as Methotrexate (MTX) 15 - 25 mg/week, Leflunomide (LEF) 10 - 20 mg/day, Sulfasalazine (SS) 2 - 3 gm/day, Hydroxychloroquine (HCQ) 200 - 400 mg/day. Oral Prednisone in doses ≤ 10 mg was allowed in combination with other DMARDs if deemed necessary by the investigator. Prednisone was tapered as rapidly as possible in accordance with the clinical situation. Patients were allowed to continue NSAID on demand basis along with analgesics like acetaminophen. One intra-articular steroid injection during the 6 months period was allowed, if deemed necessary.

Outcome measures like remission was defined as DAS 28 score of ≤ 2.6 and target of low disease activity was defined as score of ≤ 3.2. EULAR response rates were calculated as per EULAR response criteria. It classifies individual patients as none, moderate, or good responders, dependent on the extent of change and the level of disease activity reached after a specified time period.

For statistical analysis, data retrieved from source documents was entered into an SPSS version 17. All the qualitative variables were presented as percentages and quantitative variables as means and standard deviations. Outcome variables were disease remission, low disease activity and EULAR response rates. Frequency and percentages were calculated for all the outcome variables. Effect modifiers like use of prednisone was addressed through data stratification. Repeated measure ANNOVA was applied to calculate p-values for efficacy variables following normality, like DAS 28 score. Friedman Test was applied for other efficacy variables not following normality, including Tender Joint Count (TJC), Swollen Joint Count (SJC), ESR, and patient's overall assessment of disease activity on Visual Analogue Scale (VAS) between baseline, 12 weeks and 24 weeks visits.

For comparison of numerical data between the group of patients in which prednisone was used concomitantly with DMARDs and the group in which DMARDs were used alone, t-test was applied. For comparison of categorical data, Chi-square test was used. P-value of ≤ 0.05 was considered as significant. Variables not following normality like tender and swollen joint counts, ESR and patient VAS, were presented as median and interquartiles range (IQR). For comparison of these variables between patients on prednisone and DMARDs vs. DMARDs alone, Mann Whitney U test was applied.
RESULTS
Out of the 67 patients, 50 patients completed 6 months study period, and the rest were lost to follow-up. There were 31 (62%) females. Mean age of patients was 39.5 ± 12.6 years. Mean disease duration was 7.6 ± 4.9 months. Rheumatoid factor was positive in 45 (90%) of patients. Data regarding Anti-Cyclic Citrullinated Peptide (Anti-CCP) status was available in 29 (58%) patients.

Table I: Patients and disease demography (n=50).

<table>
<thead>
<tr>
<th>Age in years (Mean ± SD)</th>
<th>39.5 ± 12.6 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female n (%)</td>
<td>31 (62%)</td>
</tr>
<tr>
<td>Disease duration in months (Mean ± SD)</td>
<td>7.6 ± 4.9</td>
</tr>
<tr>
<td>RA Factor positive n (%)</td>
<td>45 (90%)</td>
</tr>
<tr>
<td>Anti-CCP positive n (%)</td>
<td>26 (86.6%)</td>
</tr>
</tbody>
</table>

*(Anti-CCP) status was available in 29 (58%) patients.

Table II: Change in efficacy variables from baseline to 24 weeks (n=50).

<table>
<thead>
<tr>
<th>Efficacy variable</th>
<th>Baseline</th>
<th>12 weeks</th>
<th>24 weeks</th>
<th>p-value ***</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tender Joint Count Median (IQR)</td>
<td>8.0 (6.25)</td>
<td>4.0 (3.0)</td>
<td>2.0 (3.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Swollen Joint Count Median (IQR)</td>
<td>4.0 (3.0)</td>
<td>1.0 (2.3)</td>
<td>0 (1.0)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>ESR Median (IQR)</td>
<td>43.0 (35.7)</td>
<td>27 (20.8)</td>
<td>20.5 (22.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Pain VAS** Median (IQR)</td>
<td>77.5 (50)</td>
<td>40 (25)</td>
<td>20 (20)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>DAS 28*** Mean ± SD</td>
<td>5.9 ± 1.14</td>
<td>4.3 ± 0.86</td>
<td>3.2 ± 0.9</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

*Visual Analogue Scale. **Disease Activity Score on 28 Joints Count. ***Repeated measure ANOVA was applied to compare DAS 28 score from baseline to 12 and 24 weeks. Friedman Test was applied for all variables not following normally.

Table III: Comparison of patients demography, disease characteristics, baseline disease activity variables and frequency of target of low disease activity between patients on Prednisone and DMARDs vs. patients on DMARDs alone.

<table>
<thead>
<tr>
<th></th>
<th>Prednisone and DMARDs (n=21)</th>
<th>DMARDs alone (n=29)</th>
<th>p-value ****</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years (Mean ± SD)</td>
<td>41.9 ± 12.4</td>
<td>37.6 ± 12.5</td>
<td>0.233</td>
</tr>
<tr>
<td>Female n (%)</td>
<td>13 (61.9 %)</td>
<td>18 (62.1%)</td>
<td>0.991</td>
</tr>
<tr>
<td>Disease duration in months (Mean ± SD)</td>
<td>7.6 ± 3.2</td>
<td>6.7 ± 4.0</td>
<td>0.418</td>
</tr>
<tr>
<td>RA Factor positive n (%)</td>
<td>20 (95.2 %)</td>
<td>25 (86.2%)</td>
<td>0.293</td>
</tr>
<tr>
<td>Anti-CCP positive n (%)</td>
<td>9 (100 %)</td>
<td>17 (85)</td>
<td>0.220</td>
</tr>
<tr>
<td>Tender Joint Count Median (IQR)</td>
<td>09 (10)</td>
<td>07 (4.5)</td>
<td>0.278</td>
</tr>
<tr>
<td>Swollen Joint Count Median (IQR)</td>
<td>05 (3)</td>
<td>03 (3.0)</td>
<td>0.211</td>
</tr>
<tr>
<td>ESR Median (IQR)</td>
<td>45 (32.5)</td>
<td>40 (41.0)</td>
<td>0.883</td>
</tr>
<tr>
<td>Pain VAS Median (IQR)</td>
<td>100 (40)</td>
<td>70 (30)</td>
<td>0.016</td>
</tr>
<tr>
<td>DAS 28*** Median (IQR)</td>
<td>6.2 (1.5)</td>
<td>5.8 (1.0)</td>
<td>0.201</td>
</tr>
<tr>
<td>Target of low disease activity (%)</td>
<td>11 (52.4%)</td>
<td>18 (62.1%)</td>
<td>0.493</td>
</tr>
</tbody>
</table>

*(Anti-CCP) status was available in 29 (58%) patients. 9 in prednisone and DMARDs group and for 20 patients in DMARDs alone group. **Visual Analogue Scale. ***Disease Activity Score on 28 Joints Count. ****t-test was applied for comparison of means and Chi-square test or Fisher’s Exact test where applicable, for comparison of frequencies (%). Variables not following normality have been presented as Median and Interquartiles range (IQR) and for their comparison Mann Whitney-U test has been applied.

DISCUSSION
Treat-to-target approach has been the talk of time and is stressed in all latest recommendations. Despite of it, this approach has not been uniformly practiced and this is especially true for developing countries like ours. This study provided us an opportunity to determine the outcome of treat-to-target approach in our local patients with early disease. Although it is an observational study such longitudinal studies designed in daily practice setting, unlike clinical trials reflect real world scenarios.

Early intervention has long been advocated but it is still debatable as to what is the exact time frame of
therapeutic window of opportunity.\textsuperscript{10} It has been observed that many patients during this phase responded exceptionally well to conventional DMARDs even leading to sustained DMARDs free remission.\textsuperscript{13}

In this study, target of low disease activity was met in 58\% of patients and EULAR good and moderate responses were achieved in 56\% and 42\% of the patients respectively. In a study published from Peshawar, Pakistan conducted in daily practice setting in patients with established rheumatoid arthritis of 10.9 ± 3.42 years diseases duration, the EULAR good and moderate responses were only around 30.1\% and 38. 8\% respectively.\textsuperscript{14} This supplements the fact that in earlier course of disease, there lies a window of opportunity.

It is acknowledged that the definition of early RA is a bit arbitrary but this cohort was unique in the sense that patient’s disease duration was calculated on the basis of onset of symptoms compatible with RA and not from the day of diagnosis. One possible concern would be that some patients might have a self-limiting disease as spontaneous remission is not uncommon in early arthritis. But the mean disease duration in our patients was 7.6 ± 4.9 months. It is also worth mentioning that all patients were fulfilling the new EULAR/ACR 2010 criteria as well as 1987 ACR criteria. Patients had very active disease with baseline mean DAS 28 score of 6.1 ± 1.1. Additionally, 90\% of patients were RA factor positive and Anti-CCP Antibodies (ACCPA) were detectable in 86.6\% of the patients and both these disease parameters were proven markers of persistent and an aggressive disease.\textsuperscript{15} So it is less likely that these patients had self-limiting disease.

Remission was 34\% in this study compared to a similar study from Hong Kong.\textsuperscript{16} They used treat-to-target approach in their local patients with a follow-up of one year. But their mean baseline DAS 28 score was only 4.9 compared to 6.1 in this series. They also used MTX as an anchor drug but the mean dose in their study was only 13 mg while in our study it was 18.9 ± 3.8 mg and 18\% of patients were receiving 25 mg/week dose. This is reassuring as our cohort seems to have comparable response even after 6 months treatment and despite having high baseline DAS scores.

In this study, HCQ was combined with MTX in 40 (80\%) patients which have been the most preferred combination worldwide.\textsuperscript{17} As per latest recommendations patients with poor prognosis factors should receive combination of synthetic DMARDs. The authors also used 5 - 10 mg prednisone in about 42\% of the patients. Though the remission rates were almost similar in prednisone vs. non-prednisone groups, the former group of patients had significantly high overall assessment of their disease on Visual Analogue Scale (VAS) at baseline (p=0.01) suggesting that this is one of the factors for deciding clinician to start low dose prednisone along with the DMARDs to bridge the gap as maximum effect of DMARDs is appreciated in upto 3 months at least after their initiation. Recent studies have also shown that adding low dose prednisone in early RA has disease modifying function as it reduces joint erosions.\textsuperscript{18,19}

Regarding adverse events, MTX was very well tolerated in these patients. In few other observational studies done in Pakistani RA patients, MTX was well tolerated alone as well as in combination with other DMARDs.\textsuperscript{20}

Lately, a study has shown that aggressive therapy with combination of biologic and conventional DMARDs in patients with early mild to moderate arthritis results in similar outcome compared with conventional DMARDs alone.\textsuperscript{21} So it is imperative to optimize their use before considering biologics especially in developing countries where biologics are expensive and patients themselves have to bear the cost of medicines.

This study, being an open label short-term study, has few limitations as well. This has been a matter of debate whether the clinical remission achieved as per DAS 28 and ACR criteria is really a true remission. It has been seen in various studies that significant number of patients who have achieved clinical remission still have evidence of joint inflammation on MRI and ultrasound.\textsuperscript{22}

**CONCLUSION**

Clinical remission or low disease activity in early RA is a realistic goal as one-third of the patients in this study achieved remission and more than half at least achieved target of low disease activity. This study highlights that if RA is treated earlier in the course of disease as per treat-to-target approach, the chances of achieving the target of remission and low disease activity with conventional DMARDs are bright. In a developing country like ours, majority of patients cannot afford effective but expensive biologic therapies. Therefore, it is imperative that these patients should be treated aggressively with synthetic DMARDs as early as possible.

**REFERENCES**


