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## Clinical efficacy and safety evaluation of adalimumab versus methotrexate in patients with early rheumatoid arthritis: Assessment of pathological parameters, joint damage and pain

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### Abstract

**Background:** Rheumatoid arthritis (RA) a chronic inflammatory condition that required long-term therapy, Current disease modifying drugs including methotrexate are have significant side effects on long-term use. Adalimumab is the first fully human, high-affinity, recombinant immunoglobulin G1 anti-TNF monoclonal antibody and recent studies are showing its clinical benefits in the treatment of RA.

**Objective:** To evaluate and compare the efficacy and safety profile of adalimumab versus methotrexate in the early-stage active RA patients.

**Methods:** Patients visiting to the outpatient department for their RA were considered to include in the study and written consent were obtained from them. Eligible patients were randomly divided into two groups to received adalimumab or methotrexate. Different parameters for efficacy were evaluated such as American College of Rheumatology 20% criteria (ACR20), radiographs, biochemical parameters, pains and swelling or tenderness in joints. All patients were closely monitored for any kind of adverse events.

**Results:** At 12 months period, more patients from the adalimumab treatment group met American College of Rheumatology 20% improvement criteria (79% and 67%, respectively). Similar difference was noticed for ACR 50 and ACR70 and also at 6-month time period. Adalimumab produced significant effects on ESR, CRP lever, joint counts (swollen and tender), pain and disease activity at 12 months, superior to methotrexate. Radiographic analysis showed that adalimumab reduced progression of joint damage as reflected in the changes in total sharp score, erosion score and joint space narrowing versus baseline. Adalimumab was not associated with any significant adverse event except injection site reaction.

**Conclusion:** Adalimumab as monotherapy was safe and was superior to methotrexate in reducing disease activity, preventing structural damage, and improving clinicopathological parameters over the period of 1 year in patients with early, aggressive RA.

**Keywords:** Rheumatoid arthritis (RA), pathological parameters, methotrexate, Rheumatology

### Introduction

Rheumatoid arthritis (RA) is the most common and chronic inflammatory arthritic condition. Worldwide 1% population is affected with RA with onset of disease is at any age with peaks between 30 and 50 years <sup>[1, 2]</sup>. Women, smokers, and individuals with a family history of the disease are most susceptible subjects for RA <sup>[3]</sup>. Most common symptoms of RA are swollen, tender joints, stiffness of joint stiffness (worse in the mornings and after inactivity), fatigue, fever and loss of appetite <sup>[4]</sup>. Disability is common and significant. Disease diagnosis is based on a combination of clinical and laboratory features which includes at least one joint with definite swelling without any other reasons, joint pain, elevated level of C-reactive protein, the presence of a rheumatoid factor or anti-citrullinated protein antibody and/or erythrocyte sedimentation rate <sup>[3]</sup>.

RA is therapeutically managed with early aggressive treatment with disease-modifying antirheumatic drugs (DMARD) including cyclosporine, cyclophosphamide, hydroxychloroquine, leflunomide, mycophenolate, sulfasalazine and methotrexate. These drugs showed efficacy in improving pain outcomes and preventing joint damage. These drugs are aimed to manage early arthritis, prevent clinical remission, in order to prevent

structural joint damage and long-term disability [5]. Among this methotrexate is the most commonly used DMARD due to its efficacy than any other agents per se and inexpensive. Like other DMARDs, methotrexate has side effects; it can cause rash and stomach upset, can be toxic to the liver or bone marrow and regular monitoring of blood cell count is essential for patients on methotrexate [6].

Due to considerable side effects, it is suggested that in patients with poor prognosis of disease, high disease activity and the presence of autoantibodies should be considered as candidates for the early introduction of biological therapies. Incorporating biological therapies into early treatment regimens has shown that remission of disease with inhibition of progressive joint destruction is an achievable treatment goal. Adalimumab is the first fully human, high-affinity, recombinant immunoglobulin G<sub>1</sub> (IgG<sub>1</sub>) anti-TNF monoclonal antibody [7]. Adalimumab in combination with methotrexate or standard antirheumatic therapies, or as monotherapy, is effective in the treatment of adults with active rheumatoid arthritis who have had an inadequate response to disease-modifying antirheumatic drugs. Adalimumab is also effective in the treatment of patients with moderately to severely active psoriatic arthritis, improving both joint and skin manifestations of the disease as well as disability due to joint damage [7]. The aim of this study was to investigate the early therapeutic introduction of adalimumab in patients with active RA not previously treated with MTX.

## Materials and methods

### Patients and inclusion criteria

Patients were recruited between January 2016 and September 2017 from 2 orthopaedic outpatient department. Eligible patients were aged 22-70 years with RA diagnosed according to the revised 1987 American College of Rheumatology (ACR) criteria [8]. Only patients considered in the study were suffering with RA for  $\geq 8$  weeks and  $\leq 4$  years. Another criterion was patients with active disease with a swollen joint count (10 joints) and tender or painful counts (12 joints) both  $\geq 8$  at screening, morning stiffness lasted at least 45 minutes, baseline CRP level of  $\geq 2.0$  mg/dl and an erythrocyte sedimentation rate  $>28$  mm/hour. We

have included only those patients who never get treatment with methotrexate.

### Study protocol

Patients were randomly assigned to receive 10 mg of adalimumab by subcutaneous injection twice weekly and 3 placebo tablets weekly or three 2.5-mg tablets of MTX weekly and twice-weekly subcutaneous injections of placebo. The initial 7.5-mg dose of MTX and its placebo was rapidly increased, to 8 tablets (20 mg) at week 8 if any joints were actively involved. All patients received folate supplementation (1 mg/day).

### Study end points

The American College of Rheumatology (ACR) core set of variables for each patient was collected. Disease activity was assessed according to ACR 20% improvement criteria and ACR 50% and ACR 70% improvement rates were calculated in an analogous manner (8). Radiographs of the hands, wrists, and feet were obtained at baseline and at 6, 12 months to evaluate the effect of treatment on erosions and joint space narrowing using the Sharp scoring method. In all patients, efficacy and safety has been evaluated every 3 months by measuring the disability index of the Health Assessment Questionnaire (HAQ) (10). Serum samples obtained at baseline and at months 6, 12 were tested for anti-etanercept antibodies by an enzyme-linked immunosorbent assay (ELISA).

The patients gave written informed consent before participation. The study was approved by the regional ethics committee. All the data was analyzed by standard statistical test using Graph-pad prism software.

## Results

### Demographics

The 180 patients diagnosed with RA, 171 patients were randomized to two groups. Adalimumab was given to 76 patients and methotrexate is administered in 95 patients. Out of 171 patients enrolled for 1<sup>st</sup> year, 165 patients continued the treatment for 1 year. The demographic characteristics of the patients who entered year 2 of the study were similar among groups (Table 1).

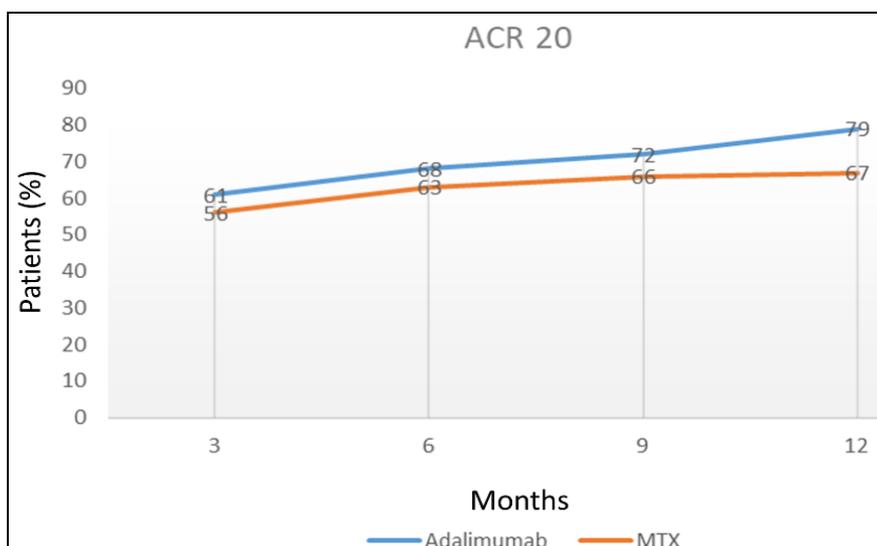
**Table 1:** Baseline demographic and disease characteristics (intent-to-treat population)

	Adalimumab (n = 76)	MTX (n = 95)
Age (Years)	57.3 (6.8)	53.4 (8.2)
Women (%)	52	61
Disease duration (Years)	9.4	10.3
Use of DMARDs (mean)	7.2	6.2
Erosive disease (%)	78.2	83.1
Rheumatoid factor Positive (%)	81.2	85.3

### ACR responses

The improvement in arthritis (as measured by ACR criteria) seen through the study period. Although, adalimumab was numerically superior to MTX, both agents continued to be effective in reducing disease activity (Figure 3). At the end of 12 months, significantly more patients in the adalimumab group (79%) than in the MTX group (67%) had an ACR20 response ( $P < 0.05$ ). At other timepoints also percent patients

with ACR20 are more from the adalimumab group, however this difference is not statistically significant. ACR50 response rates at 12 months were 51% in adalimumab verses 45% in methotrexate group. Similarly, ACR70 rates were 32% and 28% respectively in Adalimumab and methotrexate ( $P > 0.05$ ). Similar results were observed at initial timepoints i.e. 3, 6 and 9 months (Figure 1).



**Disease activity and biochemical parameters**

Tables 2 shows the adjusted changes in disease activity versus baseline after 12 month of drug treatments. The improvements were consistently superior in the adalimumab

therapy group compared with the methotrexate group 12 months. Significant effects on ESR, CRP lever, joint counts (swollen and tender), pain and disease activity score were observed in both groups at 12 months.

**Table 2:** Clinical variables at baseline and changes from baseline to 12 months assessments

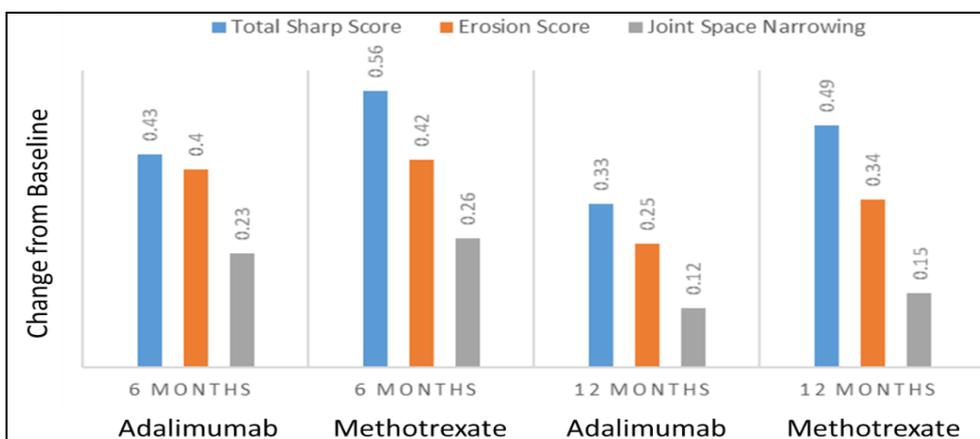
Parameters	Adalimumab (n = 76)			MTX (n = 95)		
	Baseline	12 months	P Value	Baseline	12 months	P Value
ESR	34.7	3.2	<0.01	32.1	6.5	<0.01
CRP	28.2	4.3	<0.01	25.3	10.4	<0.05
Swollen joints count	9.4	2.1	<0.01	7.1	4.3	<0.05
tender joints count	11.5	2.6	<0.01	10.3	6.2	<0.01
Visual analogue scale (Pain)	52.4	11.4	<0.05	53.9	21.1	<0.05
Disease activity score	5.7	1.4	<0.05	5.2	3.2	<0.05

ESR, erythrocyte suspension rate, CRP, C-reactive protein.

**Radiographic results**

Radiographic progression was significantly less in the adalimumab group compared with the MTX group (Figure 2). Post-6 months of drug treatment, the mean change from baseline in total sharp score was 0.43 units in adalimumab group versus 0.56 units in the methotrexate group (P<0.05). Similar trend was noticed at 12 months of treatment (0.33 vs 0.49). Mean changes in erosion score were 0.4 and 0.42

units, respectively in adalimumab and methotrexate group (P<0.05) at 6 months. At 12 months erosion score was 0.25 in adalimumab vs 0.34 in methotrexate group. Adalimumab also reduced joint space narrowing. It has changed 0.23 units from baseline at 6 months and 0.12 at 12 months in adalimumab versus 0.26 at 6 months and 0.15 at 12 months in methotrexate group.



**Fig 2:** Progression of joint damage from baseline to 6 months and 12 months

**Safety**

The most common adverse event in both adalimumab were injection site reactions similar to previous studies. On the

other hand, in methotrexate receiving patients showed nausea, alopecia and mouth ulcers.

## Discussion

Our study suggests a greater effectiveness of Adalimumab versus methotrexate immunotherapy in patients with established early-stage rheumatoid arthritis. The clinical response, improvement in the biochemical parameters and inhibition of structural damage observed with adalimumab or methotrexate monotherapy found sustained for 12 months in patients with early, active RA. However, consistent superior effect in adalimumab treatment group was observed across all the clinical symptoms as well as biochemical markers and radiographic changes for 12 months of treatment. MTX-naïve patients with recent onset rheumatoid arthritis showed improvement with adalimumab treatment. This is the first study to compare the safety and efficacy of methotrexate monotherapy with those of a biologic drug, adalimumab.

In the present study we found that both adalimumab and methotrexate are effective as monotherapy for the treatment of early RA. For the observation period of 12 months, we have consistently noticed relative advantages of adalimumab over methotrexate. Within the first few months of the study, a difference in clinical response between patients receiving adalimumab and those receiving methotrexate was observed. Adalimumab receiving patients were showing more prominent clinical benefits after treatment starts than the methotrexate group. We observed some significant effects as early as 2 months with adalimumab receiving patients. However, in the methotrexate receiving group first clinical benefits was noticed at 4 months of treatment. This difference was thought to be associated with the more rapid onset of action of adalimumab compared with MTX. Clinical response at for 1 year remained substantial from methotrexate group as compared to adalimumab group, although, patients from both groups showed clinical benefits. Compared with MTX, patient's adalimumab had a significantly greater clinical response at 1 year as measured by ACR20. Previously, similar benefits with etanercept were found against methotrexate [9]. Importantly, the proportions of patients achieving high-hurdle end points, including those with 20%, 50% and 70% improvement in their disease symptoms (ACR20, ACR50 and ACR70) were significantly greater with adalimumab.

Effect of adalimumab on biochemical parameters such as SER and CRP level was significant. Both these parameters were significantly improved at 12 months as compared to baseline level. Similar results were obtained with methotrexate, however outcomes with adalimumab were superior. Similarly, adalimumab was more effective in reversing number of swollen and tender joints. These patients also significantly improved the pain behavior and disease activity score. Heiberg *et al.*, 2006 also reported similar results with adalimumab in the RA patients [10]. They have reported the effect upto 6 months of treatment. In the present study results at 6 months timepoint is similar this their observations and additional provided clinical outcomes for extended period of treatment (12 months) [10].

We have evaluated the radiographic changes in the joints of hands, wrist and knees and evaluated total sharp score, erosion score and joint space narrowing. Both adalimumab and methotrexate were effective for inhibiting radiographic progression. However, significant benefits were noticed for adalimumab group. Proportion of patients without progression in total Sharp score, erosion score, and joint

space narrowing score were more adalimumab group than methotrexate one.

The most common adverse event in both adalimumab were injection site reactions similar to previous studies. On the other hand, in methotrexate receiving patients showed nausea, alopecia, and mouth ulcers. Pneumonitis was also observed in this group. Considering overall safety profile, adalimumab was found safer for long-term treatment regimen.

## Conclusion

In summary, adalimumab and methotrexate both showed excellent clinical profiles for initial treatment of patients with active, erosive RA. Adalimumab was superior in reducing swollen/tender joints, improving ESR and CRP level, pain and overall disease score along with preventing further damage to joints. In addition, adverse events were more manageable with adalimumab than methotrexate for longer period of treatment.

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