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Original Article

Efficacy of JAK-JANUS Kinase Inhibitors as Mono Therapy and in Combination with Methotrexate in Active Rheumatoid Arthritis

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ABSTRACT

Objective: To compare the efficacyof Janus kinase inhibitors as mono therapy and in combination with methotrexate in patients with active rheumatoid arthritis.
Study Design: Quasi-experimental study.
Place and Duration of Study: Department of Medicine, Combined Military Hospital, Hospital Multan, Pakistan, from Nov 2022 to Oct 2023.
Methodology: A total of 1194 patients aging 18 years or above with active rheumatoid arthritis and taking Tofacitinab (5 mg twice daily) were included in this study. In Group-A patients were continued with oral Tofacitinab (5 mg twice daily) while patients in Group-B were added oral methotrexate (15–25 mg per week). The study's primary outcome was set as the number of patients achieving ACR50 at 6 months of the treatment. Secondary outcomes were the patients achieving ACR70, low disease activity (SDAI ≤11), remission (SDAI ≤3.3) and response of ≥0.22 in HAQ-D index at 6 months follow up.
Results: The Mean±SD of age in this study was 51.66±9.36 years. The female gender was 72.61% of total population while males were 27.39%. The results of the primary outcomes of the study show a statistically significant difference between Group-A and Group-B (39.20% Vs 44.72 respectively, p=0.05) proving the combination therapy to be more effective than monotherapy. Among secondary end points, significantly more patients achieved ACR 70 rate, SDAI ≤11 and SDAI ≤3.3 in Group-B compared to Group-A, however, no statistically significant difference was present regarding achieving ≥0.22 response at HAQ-D index.
Conclusion: The combination of a JAK inhibitor with methotrexate is more effective in the treatment of patients with active rheumatoid arthritis compared to JAK inhibitor monotherapy.

Keywords: Active rheumatoid arthritis, Combination treatment, Janus kinase inhibitors, Methotrexate, Monotherapy.

How to Cite This Article: *Wajid H, Rehman F, Rana ZH, Azam R, Batool S, Hashmi Z. Efficacy of JAK-JANUS Kinase Inhibitors as Mono Therapy and in Combination with Methotrexate in Active Rheumatoid Arthritis. Pak Armed Forces Med J 2024; 74(Suppl-2): S242-S246. DOI: https://doi.org/10.51253/pafmj.v74iSUPPL-2.11979*

INTRODUCTION

Rheumatoid Arthritis (RA), is marked by the swollen and painful joints and the course of disease eventually causes bone erosion and joint destruction. RA isa systemic autoimmune disease which has a detrimental effect on physical activity and lead to worsen the overall quality of life ofpatients.[1]

For the RA patients especially those with the raised disease activity, diagnosis at early stages and timely treatment are the key to good future prognosis. The biological disease-modifying anti-rheumatic drugs (DMARD) like infliximab and certolizumab have served as revolutionized therapeutic options over 2 decades. DMARDs are able to reduce inflammation, avert the structural damage and minimize the symptoms of RA. Now the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) suggest the conventional synthetic DMARD especially the methotrexate (MTX) as a first line treatment in patients diagnosed with early RA.[2]

A new generation of targeted synthetic DMARDS, named as Janus kinase (JAK) inhibitors is also revolutionizing the treatment of patients with RA. This class is recognized by international organizations as effective and tolerable treatment for RA.[3] JAK inhibitors are in fact the JAK/STAT pathway inhibitors. They also block the intracellular signals that are mediated by numerous proinflammatory cytokines and both these functions help to relieve RA.[4] In patients where synthetic DMARD are not effective, the treatment guidelines recommend to use either the JAK inhibitors or biological DMARDs.[5] JAK inhibitors are also a choice for those patients reported of inadequate response with biological DMARDs.[6]

The first JAK inhibitor approved by FDA was Tofacitinab (First generation JAK inhibitor with

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Received: 30 Mar 2024; revision received: 08 Nov 2024; accepted: 11 Nov 2024

JAK1/JAK3 selectivity).[7] Latter baricitinib (JAK1/JAK2 inhibitor), Upadacitinib (JAK1) and Filgotinib (JAK1) were introduced.[8] Results of trials on JAK inhibitors have shared the efficacy and safety of combination therapy of MTX with JAK inhibitors.[9] JAK inhibitors have a good tolerability and acceptability profile. Safety concerns mentioned regarding JAK inhibitors include herpes zoster while venous thromboembolism and malignancy are also mentioned as very rare incidences.[10]

This study was therefore planned to compare the efficacy of JAK inhibitors as mono therapy and JAK inhibitors in combination with MTX in patients with active RA. These results will help the physicians to decide whetherrecommending JAK inhibitors in mono therapy can provide similar efficacy that can allow its monotherapy in place of this combination in our local RA patients.

METHODOLOGY

This Quasi-experimental study was conducted at the department of Medicine, CMH Hospital Multan, Pakistan over a period of 1 year from 1st of November 2022 to 31st of October 2023. Sample size was calculated with following assumptions; Alpha= 5% (two sided), power= 80%, P1= 38%, p2=46%.[11]

Inclusion Criteria: Patients aging 18 years or above with active RA (as per defined by ACR and ELAR criteria) taking Tofacitinab (5 mg twice daily) were included.

Exclusion Criteria: Was set as patients with a history of hospital admission within last 6 months, infections during last two weeks, hepatitis (B or C), herpes zoster > 1 episode, laboratory abnormalities of clinical significance, inadequately treated tuberculosis or pregnancy.

Patients in Group-A continued with oral Tofacitinab (5 mg twice daily) while patients in Group-B were added oral MTX (15–25 mg per week) (Figure).

The primary outcome was set as the number of patients achieving ACR50 (ACR response rate of up to 50%) at 6 months of the treatment. Secondary outcomes were the number of patients achieving ACR70, number of patients achieving low disease activity assessed by simplified Disease Activity Index (SDAI≤11), number of patients achieving remission (SDAI≤3 ·3) and the number of patients achieving a response of ≥0.22 from the baseline at the Health Assessment Questionnaire-Disability Index (HAQ-DI) at 6 moth follow up visit.[12-14]

Laboratory investigations were done for the patients including CBC (complete blood count), ESR (erythrocyte sedimentation rate), CRP (C-reactive protein), rheumatoid factor, renal function and liver function tests at time of inclusion in the study, at 1 month and 6 month times. Follow up visits were planned at 1, 3 and 6 months after the start of treatment.

Written consent was obtained from the patients for the inclusion in the study. Permission for conducting study was taken from ethical committee of CMH Hospital Multan.

Data was analyzed using SPSS version 25. Quantitative variables were expressed in form of Mean±SD while qualitative variables were expressed in form of frequency and percentage. Study outcomes were compared between the 2 groups by applying Chi-square test where *p*-≤0.05 was considered statistically significant.

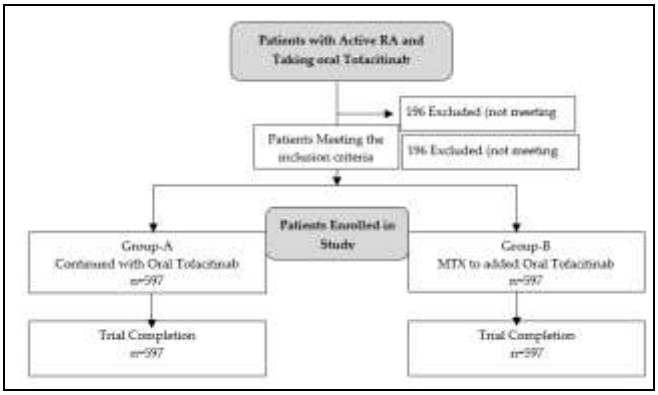

Figure: Patient Flow Diagram

RESULTS

The Mean±SD of age in this study was 51.66±9.36 years with age range of 32-71 years. The female gender was 72.61% of total population while males were 27.39%. The group wise demographic details, clinical assessment and laboratory investigations at the time of inclusion are given in Table-I.

The results of the primary outcomes of the study show a statistically significant difference between Group-A and Group-B. For secondary outcomes, statistically significant difference was present for all the outcomes except forachieving HAQ-D index ≥0.22 as shown in Table-II.

The data of adverse events showed more but with statistically non-significant difference in the incidences of adverse events in Group-B compared to Group-A as shown in Table-III.

Table-I: Demographics, clinical assessment and laboratory investigations n=1194

Demographics, clinical and laboratory characteristic		Group-A (n=597)	Group-B (n=597)
Age (Mean±SD) Years		51.52±9.45	51.8±9.28
Gender	Male n (%)	159 (26.63)	168 (28.14)
	Female n (%)	468 (73.37)	429 (71.86)
Duration of Disease (Mean±SD) Years		4.27±2.06	3.99±1.93
Use of Corticosteroids n(%)		321 (53.76)	334 (55.94)
Number of Tender Joints (Mean±SD)		16.89±2.19	17.09±2.06
Number of swollen Joints (Mean±SD)		13.89± 2.20	14.3±5.22
SDAI Score (Mean±SD)		42.04± 4.84	41.65± 4.55
CDAI Score (Mean±SD)		40.05±4.78	39.64±4.47
HAQ-D Index Score (Mean±SD)		1.64±0.26	1.55±0.26
hsCRP levels (Mean±SD) mg/lite		20.49±3.06	17.31±2.31
ESR (Mean±SD) mm/hour		48.83±2.59	48.30±1.85
Patients with +ve RA Factorn (%)		449 (75.20)	435 (72.86)

Table-II: Study outcomes among the two groups n=1194

Study outcomes	Group-A (n=597)	Group-B (n=597)	*p*-value
Primary outcomes			
Patients achieving ACR 50 n(%)	234 (39.20)	267(44.72)	0.05
Secondary outcomes			
Patients achieving ACR 70 n(%)	140(23.45)	170(28.47)	0.04
Patients achieving SDAI (≤11) n (%)	237(39.69)	278(46.56)	0.01
Patients achieving SDAI ≤3.3 n (%)	75(12.56)	99(16.58)	0.04
Patients achieving HAQ-D index ≥0.22 n(%)	418(70)	445(74.54)	0.08

Table-III: Incidences of adverse events n=1194

Adverse events	Group-A (n=597)	Group-B (n=597)	*p*-value
Treatment withdrawal due to adverse event (%)	19(3.18)	26 (4.35)	0.28
Serious infections n (%)	9 (1.5)	15 (2.51)	0.21
Serious or non-serious Herpes Zoster	5 (0.83)	9 (1.5)	0.28
Adverse Cardiovascular events	0	0	NaN
Any type of malignancy	1	0	0.31

DISCUSSION

A lot of work has been done previously regarding treatment options in patients with active RA, however fewer studies have focused on the efficacy of new generation of targeted synthetic DMARDS, JAK inhibitors.[13-15] The available data on comparison of the efficacy of JAK inhibitors as mono therapy and JAK inhibitors+MTXin active RApatients is even smaller.

Lee EB conducted a phase IIItrialcompared the efficacy of a JAK inhibitor (Tofacitinab) and MTX in RA patients. The primary end point was the percentage of patients who achieved ACR70 after 6 months of study while change in the severity score (indicating joint damage)) from the base line after 6 months was another primary end point. The results of this study showed an improvement of 25.5% and 37.7% in ACR 70 with tofacitinib 5mg and tofacitinib 10 mg respectively. These results were significantly better compared to 12% improvement observed in MTX group (p<0.001). The researchers concluded that monotherapy with tofacitinib was superior when compared to MTX in slowing down the course of structural damage to the joints and controlling signs and symptoms of RA and must be considered for these patients, however, while keeping adverse events in to account.[16]

Another phase III study evaluated the efficacy of monotherapy with a JAK inhibitor (baricitininb 4mg once a day), MTX monotherapy and combination of JAK inhibitor with MTX. The study proved that JAK inhibitor monotherapy was significantlybetter than MTX monotherapy in shape of better ACR 20 response after 6 months of treatment (77% Vs 62%, p=0.01). The comparison of MTX monotherapy and combination of JAK inhibitor with MTX showed only modest benefits (but with some increased risk profile) of combination therapy in shape of decreases inflammation and structural joint damage.[17]

Westhovens R compared JAK inhibitor montherapy, JAK inhibitorplus MTXcombination therapy andMTXmontherapy for efficacy as well as safety evaluation. Percentage of patients achieving ACR20 after 6 months of treatment was set asprimary end point. The results showed a comparable efficacy of Filgotinib 200 mg and MTX in ACR20 response rate. The efficacy of combination therapy showed an achievement of primary end points in 81% of the patients which was significantly better than MTX

monotherapy which was 71% (p<0.001). The safety and tolerable profile was comparable between the above 2 groups.[18]

Oral study, which was a double blind a phase 3b/4 study, compared the efficacy of Tofacitinib as montherapyversus Tofacitinib plus MTX in RA patients. Primary end point of the study was set as ACR 50 response at the 6 months follow up. The results showed that combinationwas significantly more effective (46%) than monotherapy (38%) as evaluated by the number of patients who achieved ACR 50 response.[14]

A review by Taylor *et al* was recently published to study a JAK1/JAK2 inhibitor Baricitinib for its efficacy in montherapy or in combination with MTX in patients with moderate to severe active RA. This review provided a summary of clinical data demonstrating that the benefit-risk balance presented in clinical trials of patients with RA treated with a JAK inhibitor (baricitinib) translates into efficacy in daily clinical practice with a low discontinuation rate.[19]

A recent meta-analysis published in 2022 focused on comparing the efficacy and safety profile of monotherapy of JAK inhibitors and combination of JAK inhibitors with MTX in patients with active RA. The analysis included 3 randomized controlled trials with 2290 patients having active RA as per the ACR criteria. The result of this meta-analysis showed a superior efficacy of combination therapy as assessed for achieving ACR20, ACR 50 and ACR 70 criteria after 6 months of treatment.The results also shared better efficacy of combination therapy for achieving low disease activity and high remission rate compared to monotherapy at 6 months and 1 year treatment times. There was, however, no difference in patients reported with response of ≥0.22 from the baseline at HAQ-D index at 6 months and 1 year follow up visits. The study results also mentioned higher risks of discontinuation due to adverse events in combination therapy group.[20]

The Mean±SD of age in our study was 51.66±9.36 years. The female gender was 72.61% of total population while males were 27.39%. The mean duration of disease in overall study population was 4.13±2.00 years.

The primary outcomes of our study showed a statistically significant difference between Group-A and Group-B in number of patients achieving ACR50 after 6 months of treatment (39.20% Vs 44.72 respectively, p=0.05) proving the combination therapy to be more effective than monotherapy in these patients with active RA. Among secondary end points, significantly more patientsin Group-B compared to Group-A achieved ACR 70 response rate (23.45% Vs 28.47%, p=0.04), low disease activity with SDAI ≤11 (39.69% Vs 46.56%, p=0.01) and higher remission SDAI ≤3.3 (12.56% Vs 16.58%, p=0.04). The study results, however, showed no statistically significant difference regarding achievement of ≥0.22 response at HAQ-D index in Group-B compared to Group-A (74.54% Vs 70% respectively, p=0.08). These results are in line with results shared by studies done previously with these treatment strategies in RA patients as discussed above.[14,18,19,20]

The number of adverse events reported was higher but statistically non-significant in combination therapy group as compared to montherapy group.

The study therefore demonstrate that combination therapy of JAK inhibitors and MTX provide a better treatment option in shape of achieving better ACR response rate, attaining low disease activity and achieving remission for patients with active RA compared to monotherapy with a JAK inhibitor while keeping in mind the side effects profile of this treatment regimen.

The major limitation of our study is the short follow up time for these patients. Future studies with follow up of longer duration regarding pharmacovigilance will help to provide more confidence to the physicians while recommending this combination.

ACKNOWLEDGMENT

The services of nursing staff of the department in recording and maintaining patients' data are acknowledged.

CONCLUSION

Combination of JAK inhibitor and methotrexate is more effective compared to JAK inhibitor monotherapy and can serve as a preferred treatment choice in treating patients with active rheumatoid arthritis.

Conflict of interest: None.

Authors' Contribution

Following authors have made substantial contributions to the manuscript as under:

HW & FR: Data acquisition, data analysis, critical review, approval of the final version to be published.

ZHR & RA: Study design, data interpretation, drafting the manuscript, critical review, approval of the final version to be published.

SB & ZH: Conception, data acquisition, drafting the manuscript, approval of the final version to be published.

Authors agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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