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A COMPARATIVE, TWO ARM, RANDOMIZED, DOUBLE BLIND, PARALLEL GROUP, MULTICENTRIC, NON-INFERIOR CLINICAL STUDY TO EVALUATE EFFICACY, SAFETY AND TOLERABILITY OF IGURATIMOD TABLETS 25 MG AS AN ADD ON THERAPY OVER METHOTREXATE TABLETS 15 MG VS. METHOTREXATE TABLETS 25 MG FOR THE TREATMENT OF PATIENTS WITH ACTIVE RHEUMATOID ARTHRITIS

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ABSTRACT

Background: This study was designed to evaluate the efficacy, safety and tolerability of Iguratimod Tablets 25 mg for the treatment of patients with active rheumatoid arthritis. The objectives of this study were percentage of patients meeting ACR20, ACR50, ACR70 response criteria, mean reduction in DAS28 and HAQ score. **Method:** This was randomized, double-blind, study conducted in nine centers across India. The study was conducted in male or female subjects of the age 18 to 65 years. A total of 243 subjects were randomized in study. The treatment period was 28 week with follow-up on week 4, 8, 12, 18 and week 24 from the start of treatment. **Results:** At the end of study, 100% patients achieved ACR20, 73.45% patients achieved ACR50 and 19.47% patients achieved ACR70 criteria in Iguratimod group vs. 97.39% patients achieved ACR20, 61.74% patients achieved ACR50 and 10.43% patients achieved ACR70 criteria in Methotrexate group. The mean change in DAS28 at the end of study was -2.22 vs -2.0 in Iguratimod and Methotrexate group respectively. The mean change in HAQ score at the end of study was -0.91 vs -0.77 in Iguratimod and Methotrexate group respectively. There were 61 clinical adverse events reported in 45 subjects. No adverse event led to SAE. **Conclusion:** The add on therapy of Iguratimod Tablets 25 mg to Methotrexate Tablets 15 mg is statistically equivalent in achieving the ACR20, ACR50 and ACR70 criteria and statistically superior to mean reduction in DAS28 and HAQ score as compared to Methotrexate Tablets 25 mg.

INTRODUCTION

Rheumatoid arthritis (RA) is chronic systemic inflammatory and autoimmune disease of unknown etiology that primarily targets synovial tissue and is characterized by an activation of T lymphocyte, an increase in interleukin and tumor necrosis factor, and severe chronic inflammation of the joints, resulting in erosion and destruction of cartilage, bone, and tendon.[1,2] It is relatively common, with a prevalence of slightly less than 1% in adults all over the world.[1] Prevalence of moderate and severe disability in adults aging over 60 (in millions) due to rheumatoid arthritis by leading health condition associated with disability is 1.7 in high-income countries and 3.7 in low- and middle-income countries in 2012.[3] Years lost due to disability (YLD) per 100 000 adults aging over 60 due to rheumatoid arthritis is the 11th in the world in 2012.[3] Current treatments for RA emphasize the early use of traditional disease-modifying antirheumatic drugs (DMARDs), such as methotrexate (MTX), salazosulfapyridine (SASP), leflunomide, and cyclophosphamide to minimize or prevent joint damage.

The recent treatment goal for rheumatoid arthritis (RA) is to achieve remission.[4] According to the 2016 European League against Rheumatism (EULAR) recommendations for the management of RA[5], the initial treatment strategy involves therapy with methotrexate (MTX) (a conventional synthetic disease-modifying antirheumatic drug [csDMARD]) in combination with short-term glucocorticoids. The aim of this initial strategy is to achieve >50% improvement within 3 months and target attainment within 6 months.

MTX is considered the "anchor drug" for RA.[3] Although adequate responses to MTX monotherapy or combinations with other non-biologic DMARDs are seen in approximately two-thirds of patients with RA,[6] a substantial proportion of patients with RA cannot tolerate MTX because of the high risk of complications. Thus, there is a need for csDMARDs that can be easily administered (e.g., taken orally), and that are safe and effective for both monotherapy and combination therapy with MTX Iguratimod (IGU) is a csDMARD developed in Japan for the treatment of RA. In vitro studies found that IGU has an anti-inflammatory role by inhibiting tumor necrosis factor (TNF), interleukin (IL)-1β, IL-6, IL-8, and monocyte chemotactic protein-1 production.[7,8,9] Furthermore, its antirheumatic action is attributed to inducing a decrease of serum immunoglobulin (Ig)G, IgM, and IgA, and inhibiting the transcription factor nuclear factor-kappa B in human monocytic cells following stimulation with lipopolysaccharide or TNF. Non-clinical studies of this compound revealed that inhibition of the production of immunoglobulins and various inflammatory cytokines mainly contributes to its improvement effect on various arthritis models in animals. In addition, Iguratimod was found to possess anabolic effect on bone metabolism, through both stimulations of osteoblastic differentiation and inhibition of osteoclast genesis. Regarding a more detailed mechanism of its action, the suppression of nuclear factor kappa B (NF-kB) activation without blocking NF-kB inhibitor (IkBa) degradation has been indicated. Thus, Iguratimod Tablets will be a useful DMARD with novel properties and good clinical response. The present study was carried out to evaluate efficacy and safety of Iguratimod as an add on therapy to Methotrexate Vs Methotrexate alone.

MATERIALS AND METHODOLOGY

Study design

This study was "A Comparative, Randomized, Double Blind, Multicentric, Non-inferior, Active Controlled, Parallel Group, Two Arm, and Phase III Clinical Trial to Evaluate the Efficacy, Safety and Tolerability of Iguratimod Tablets vs. Methotrexate Tablets in Patients with Active Rheumatoid Arthritis."

A total of 256 subjects were screened and 243 subjects were randomized by computer generated randomization program to either of the study arm in 1:1 proportion. The total subjects randomized/enrolled were 124 in Iguratimod Tablets plus Methotrexate Tablets arm and 119 in Methotrexate Tablets arm. This report includes data of 243 subjects of 18 to 65 years of age (both inclusive). All the sites had approval from the respective Institutional Ethics Committees prior to the study initiation. All procedures followed the tenets of the Declaration of Helsinki, were in accordance with all regulatory standards, were approved by an Institutional Review Board and all subjects signed an informed consent form. Protocols and Inform consent were approved by Indian Regulatory authority and Institutional Ethical Committee.

Subjects

Both male and female subjects suffering from Active Rheumatoid Arthritis were included in the study for the duration of 28 weeks. They were randomized (simple block randomization) by computer generated system to either of the study arms in 1:1 proportion (Test: Reference).

Study Eligibility Criteria

Male and female subjects of age of 18 to 65 years, both inclusive, Subjects who had been diagnosed with active RA, according to the 2010 American College of Rheumatology/European League Against Rheumatism (ACR/EULAR) Classification Criteria for Rheumatoid Arthritis (ACR) criteria, and Disease Activity Score 28 (DAS28) greater than or equal to 3.2, Tender joint count/swollen joint count ≥6. Subjects meeting at least one of the following three conditions: erythrocyte sedimentation rate of at least 28 mm/hour, C-reactive protein (CRP) of at least 15 mg/liter or morning stiffness for at least 45 minutes. Patients who have failed at least one cycle of DMRD therapy, defined as subject who has failed to achieve remission after Methotrexate 15mg/week regime for 3 months and Subjects willing to sign informed consent form (ICF) were included in the study were included in the study.

Subjects treated with any biological injection within last 3 months, subjects with inadequate bone marrow function (defined as an absolute neutrophil count of not more than 2.5×10^9/liter). AST>1.5×ULN (AST= 10 to 34 IU/L), ALT>1.5×ULN (ALT= 10 to 40 IU/L), Cr= 1.534 mg/dL WBC<4×10^9/L, HGB<8.5g/L PLT<100×109/L. were excluded from the study, subjects on current therapy Leflunomide, Hydroxychloroquine and Sulfasalazine receiving live vaccines within 3 months prior to study entry, a history of hypersensitivity to any of the study drugs were excluded. Pregnant women, nursing mothers and during treatment requirements of women of childbearing age. Subjects with infection, active gastrointestinal ulceration / bleeding, or history of peptic ulcers, known or suspected positive serology for human immunodeficiency, malignancies, hepatitis B or C virus, Subjects suffering from severe serious hepatic, cardiovascular, renal, hematologic or endocrine diseases, Subjects with dosage of steroids more than 7.5mg/day, patients not on a stable dose of steroids for last 1 month, Patients with significant systemic manifestations of rheumatoid arthritis Rheumatic auto-immune disease other than rheumatoid arthritis/overlap syndromes and any surgery of bone fractures within 8 weeks, and alcohol or drug abuse within 6 months were excluded from the study.

Treatment and Compliance

Both test and reference product formulations were administered as one tablet once daily of Iguratimod

25mg + Methotrexate 15mg or Methotrexate 25mg every day. Duration of participation in the study for each patient was planned to be 28 weeks.

The compliance was observed through drug accountability and subject diary. Adherence to assigned regimen was assessed by recording the amount of returned investigational products at the end of study treatment. Treatment compliance was considered adequate, when provided patients have used at least 75% of scheduled doses.

Time and Events Schedule

The subjects were dispensed study medication and advised to take 2 tablets daily (one in morning and one in evening) either of Iguratimod + Methotrexate or Methotrexate alone every day after meals till week 4 (visit 2). The dosing schedule was changed to 3 tablets daily (one in morning, one in afternoon and one in evening) either of Iguratimod + Methotrexate or Methotrexate alone from visit 2 to End of study visit. The treatment continued for the 28 week ±3 days with interim follow-up on week 4 ±3 days, week 8 ±3 days, week 12 ±3 days, week 18±3 days and week 24±3 days from the start of treatment. The end of study visit was conducted on week 28±3 days. The compliance was observed through drug accountability and patient diary. Subject's ICF, Demographic data and medical history was taken on screening visit only.

Physical examination and vital signs were done at all visits. Laboratory tests (CBC, Potassium, Serum Creatinine and Routine Urine), RF Factor, anti CCP antibodies, ECG, X-ray were performed on screening visit and visit 7/end of the study visit. Urine pregnancy test was performed for women with child bearing potential on all the visits from screening visit to end of study visit except visit 1. The laboratory tests of LFT (SGOT, SGPT & Total Bilirubin) were performed on all visits except visit 1. The assessment of ESR/CRP was performed on all the visits from screening visit to end of study visit. Assessment of efficacy, safety, patient diary, treatment compliance and monitoring of adverse events were done from baseline.

Visit/randomization visit/visit 1 to end of study visit/visit 7. The data was collected on paper CRFs. The data analysis was performed for predefined parameters to correspond with the primary and secondary outcome measures**.**

OBJECTIVES

Primary Study objective

The primary study objective was to evaluate the efficacy of Iguratimod Tablets vs. Methotrexate Tablets for the treatment of patients with active rheumatoid arthritis symptoms.

Secondary Study objective

The secondary study objective was evaluate the safety and tolerability of Iguratimod Tablets vs. Methotrexate Tablets for the treatment of patients with active rheumatoid arthritis symptoms.

STUDY ASSESSMENT

Primary Efficacy Parameters

The primary efficacy parameter was percentage of subjects meeting the American College of Rheumatology 20% (ACR20) response criteria, (ACR50) response criteria and 70% (ACR70) response criteria.

Secondary Efficacy Parameters

The secondary efficacy parameter was Mean Reduction in Disease Activity Score 28 (DAS28) from baseline and Mean Change from baseline in Health Assessment Questionnaire (HAQ).

Safety Parameters

Percentage of patients reporting AE and/or SAE during the study, its frequency, severity, pattern and causal relationship to the drug were assessed.

Mean change in the laboratory parameters from baseline to end of therapy [28th week±3days].

Adverse Events (AEs) and Serious Adverse Events (SAEs) were summarized by counting both the number of separate events and the number of subjects experiencing any of these events during the study period was recorded. Furthermore, similar summaries were provided and stratified according to the seriousness, severity and relationship to the study medication.

Statistical methods

Statistical analysis was done using SAS 9.4. Continuous variables were statistically tested using 2-sample t-test. Categorical variables were tested using Chi-square test. Primary efficacy analysis was done using Chi-square test. Secondary efficacy analysis was done using 2-sample t-test test. All safety parameters were analyzed using, 2-sample t-test and descriptive statistics

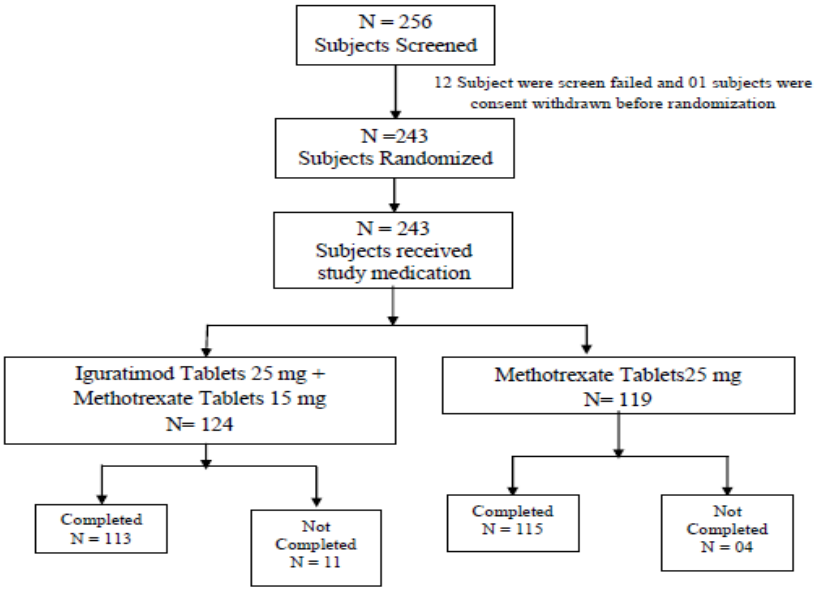
RESULTS

Total of 256 subjects were screened out of which 243 subjects were randomized in the study.

12 Subjects were screen failed while 01 were consent withdrawn before randomization.

08 Subjects were lost to follow-up, 07 subjects were consent withdrawn after randomization and 00 Subject was discontinued from the study. Total 124 subjects were randomized in test arm i.e. Iguratimod Tablets 25 mg + Methotrexate Tablets 15 mg and 119 subjects were randomized in reference arm i.e. Methotrexate Tablets 25 mg. None of the subject was terminated from the study for any adverse event as per the protocol. Total 113 subjects in the test arm and 115 subjects in the reference

arm were completed the study. Following figure shows the summary of the subject disposition in the study.



Efficacy of the investigational product was analyzed on basis of comparison of ACR 20, ACR 50, ACR 70, DAS and HAQ score of Rheumatoid Arthritis As per the statistical analysis plan, the efficacy data was analyzed for effect on individual and cumulative efficacy parameters.

EFFICACY RESULTS

Analysis of Efficacy

Primary efficacy of the investigational product was analyzed on the basis of Percentage of subjects meeting the American College of Rheumatology 20% (ACR20) response criteria from baseline to end of study. Percentage of subjects meeting the American College of Rheumatology 50% (ACR50) response criteria from baseline to end of study. Percentage of subjects meeting the American College of Rheumatology 70% (ACR70) response criteria from baseline to end of study. Secondary efficacy was analyzed on the basis of mean reduction in Disease Activity Score 28 (DAS28) from baseline to end of study. Mean Change from baseline in Health Assessment Questionnaire (HAQ) from baseline to end of study. As per the statistical analysis plan, the efficacy data was analyzed for effect on individual and cumulative efficacy parameter.

Primary efficacy parameter

ACR

Percentage of subjects meeting the American College of Rheumatology 20% (ACR20), 50% (ACR70), 70% (ACR70) response criteria from baseline to end of study.

Table 1: Acr Summary From Baseline To End of Study.

Visit	Parameters	Iguratimod Tablets 25 mg + Methotrexate Tablets 15 mg (n/N) %	Methotrexate Tablets 25mg (n/N) %	P-value
Visit 2	**ACR 20 %**	18(14.63%)	10(8.47%)	0.4684
	ACR 50 %	00(00%)	00(00%)	-
	ACR 70 %	00(00%)	00(00%)	-
Visit 3	**ACR 20 %**	47(39.17%)	39(33.05%)	0.4984
	ACR 50 %	02(1.67%)	00(00%)	0.5257
	ACR 70 %	00(00%)	00(00%)	-
Visit 4	**ACR 20 %**	94(78.99%)	82(70.09%)	0.4107
	ACR 50 %	06(5.04%)	05(4.27%)	0.5049
	ACR 70 %	00(00%)	00(00%)	-
Visit 5	**ACR 20 %**	105(91.30%)	97(82.91%)	0.5018
	ACR 50 %	18(15.65%)	17(14.53%)	0.5280
	ACR 70 %	03(2.61%)	00(00%)	0.4285
Visit 6	**ACR 20 %**	111(98.23%)	110(95.65%)	0.4302
	ACR 50 %	66(50.41%)	59(51.30%)	0.4986
	ACR 70 %	07(6.19%)	00(0.0%)	0.2855

Visit 7	**ACR 20 %**	113(100.00%)	112(97.39%)	0.3936
	ACR 50 %	83(73.45%)	71(61.74%)	0.4146
	ACR 70 %	22(19.47%)	12(10.43%)	0.3286

Note: p-value is obtained using chi-square test to compare to baseline values of Iguratimod Tablets 25 mg + Methotrexate Tablets 15 mg and Methotrexate Tablets 25 mg.

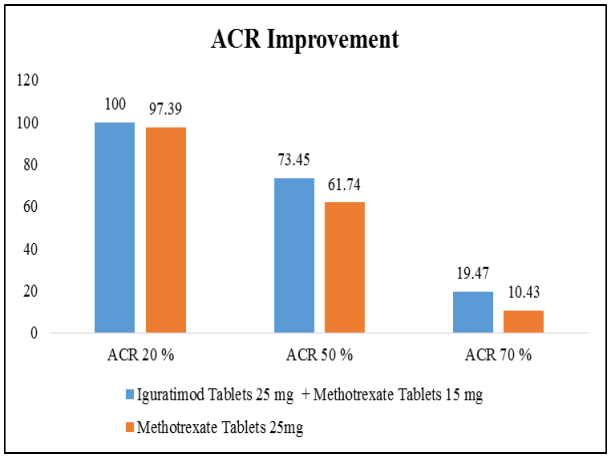


Figure 1: ACR improvement from baseline to end of study.

Secondary efficacy parameter

A. Change in DAS score

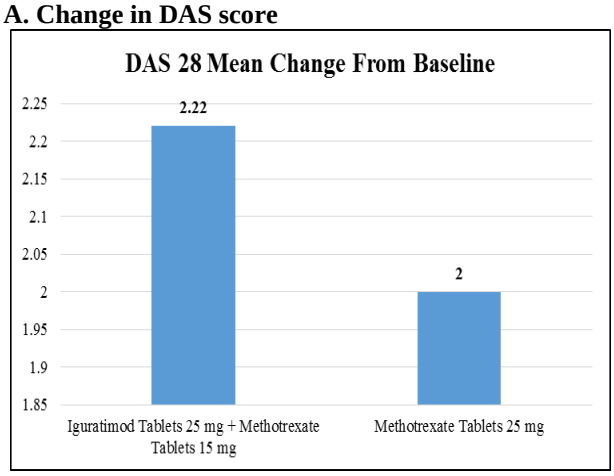


Figure 2: Mean DAS28 Change from Baseline to end of study.

B. Change in HAQ score

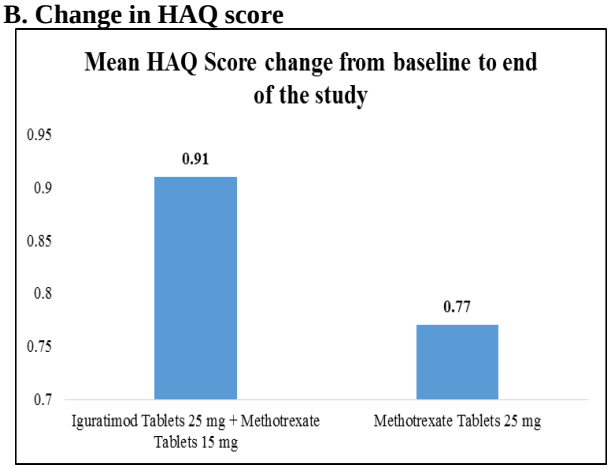


Figure 3: Mean HAQ Score Change from Baseline to end of study.

SAFETY AND TOLERABILITY EVALUATION

There were 61 clinical adverse events reported in 45 subjects. The adverse events were Headache, cold, cough, fever, Gastritis Diarrhea, Nausea, and Dizziness Etc. All the adverse events were followed up until they were completely resolved. No adverse event led to serious adverse event.

All Adverse events were followed up until they were completely resolved. No adverse event led to serious adverse event.

DISCUSSION

This Double Blind, Randomized, Active Control, Parallel, Noninferiority Clinical study assessed efficacy and safety of Iguratimod tablets Vs methotrexate tablets in patients of Active Rheumatoid Arthritis. The comparison of primary efficacy between both the arms indicates statistical equivalence of Iguratimod Tablets 25 mg + Methotrexate Tablets 15 mg to that with Methotrexate Tablets 25 mg for treatment Active Rheumatoid Arthritis. The comparison of secondary efficacy between both the arms indicates statistical superiority of Iguratimod Tablets 25 mg + Methotrexate Tablets 15 mg to that with Methotrexate Tablets 25 mg for treatment Active Rheumatoid Arthritis Add on therapy of Iguratimod Tablet 25 mg to Methotrexate Tablets 15 mg was well tolerated and observed to have better safety profile than Methotrexate tablets 25 mg. No death or hospitalization occurred in both the arms.

Similar findings were noted with previously conducted studies on Iguratimod.

Ishigaro et al conducted a study in patients with active rheumatoid arthritis despite stable doses of methotrexate to investigate the efficacy and safety of iguratimod (T-614) in Japanese patients with active rheumatoid arthritis who had inadequate response to stable background methotrexate (MTX) alone. The rate of 20% improvement in American College of Rheumatology criteria (ACR20) at week 24 was 69.5% in the iguratimod group compared with 30.7% in the placebo group ($P < 0.001$). Significant improvements in the ACR50, ACR70, Health Assessment Questionnaire Disability Index, Disease Activity Score 28 <3.2, and rheumatoid factor were also observed. The most commonly reported adverse events (AEs) were blood iron decrease, nasopharyngitis, and lymphocyte decrease. These AEs were mild or moderate in severity. No deaths occurred.[10]

Okamura k1 et al. evaluated the Efficacy at 52 weeks of daily clinical use of iguratimod in patients with

rheumatoid arthritis. The survival rate at week 52 was 53.7%. The disease activity score (DAS) 28-erythrocyte sedimentation rate, DAS28-C-reactive protein, simplified disease activity index, and clinical disease activity index were all significantly decreased at week 52.[11]

Ishiguro N et al. conducted a study to obtain safety and efficacy data on combination treatment with iguratimod and methotrexate (MTX) in an open-label extension study in patients with active rheumatoid arthritis (RA). Following a 28-week, randomized, double-blind trial of adding iguratimod or placebo to stable MTX therapy, patients entered a 24-week extension. Patients randomized to the iguratimod + MTX group continued treatment. Patients treated with placebo + MTX switched to iguratimod + MTX [the (placebo/iguratimod) + MTX group]. In the iguratimod + MTX group, the rate of 20% improvement in American College of Rheumatology criteria (ACR20) at week 52 (71.3%) was similar to that at week 24 (69.5%). ACR50, ACR70 and Health Assessment Questionnaire Disability Index at week 52 significantly improved compared with the values at week 24. In the (placebo/iguratimod + MTX) group, the switch to iguratimod treatment significantly improved ACR20 from 30.7% at week 24 to 72.1% at week 52. Frequent adverse events for 52 weeks in the iguratimod + MTX group were nasopharyngitis, upper respiratory tract inflammation, stomatitis, lymphocyte decrease, AST increase, ALT increase and blood iron decrease. These adverse events were predominantly mild or moderate in severity. No deaths occurred.[12]

Yutaka Yoshioka *et al.*[13] showed that at 24 week IGU combination therapy resulted in meaningful clinical improvement. The outcomes of this investigation propose that, 12 weeks maybe adequate to estimate the safety and ability of IGU in patients given beside or lacking MTX.

Z.Xia *et al*[14] showed his study on a larger trial in 131 patients, all the patients were treated with 25mg twice daily of IGU and 10mg twice weekly of MTX. A beneficial effect with IGU was perceived amid 4 and 10 weeks, which shows that the blend of MTX with IGU was superior to MTX or IGU monotherapy. Another study done by Xin-Wang Duan *et al*[15] examine the efficacy and safety of IGU+MTX, sixty patients registered corresponding to the ACR 2010. IGU was dispensed orally at a quantity of 50mg/day for 24 weeks; MTX was directed at weekly dosage of 10mg/week. The results showed that ACR50 in the IGU+MTX showed statistical significant relating with the MTX group ($P<0.05$). There were no considerable increase in unfavourable events in the IGU+MTX group associating with MTX group. Therefore the pattern of IGU+MTX have a beneficial safety and usefulness for active RA and was greater to MTX only treatment.

Masako Hara *et al*,[16] did another 28-week safety and efficacy study of IGU and MTX. In the IGU+ MTX group, the frequency of 20% advance in ACR50 and ACR70 at week 52 considerably enhanced associated with the amounts at week 24. Therefore, the effectiveness and acceptance of IGU+MTX should be continued to 52 weeks in patients among active RA with insufficient reaction to MTX. In another study done on 60 patients in china, judged with the control group the ACR50, DAS 28 and other improved in combined group ($P<0.05$). Therefore, this study also conclude that IGU and MTX combination therapy is superior to MTX alone for treating RA with less adverse reaction and high safety.[15]

MENG Deqian et al.,[17] inhis study on 60 patients showed that at 16 weeks the DAS28 score of the IGU+MTX decrease significantly then before treatment ($P< 0.01$).

From this study, it can be concluded that the combination of IGU and MTX for the treatment of RA is an effective choice as it can help the physician to relive the symptoms associated with the disease. The combination of both drugs is reported to produce a synergistic effect that will contribute in dealing with the symptoms of the disease. The combination of methotrexate and IGU can be regarded as one of the most effective approach to deal with the complication and symptoms associated with the disease of RA. The level of pain and extent of inflammation are concluded to be decreased by prescribing the combination of IGU and MTX.

CONCLUSION

Evidence supports the use of Iguratimod for the improving the clinical features of patients with active rheumatoid arthritis.

The results of this study suggest that Iguratimod 25mg as an add on therapy to Methotrexate 15mg statistically equivalent in improving the clinical features of patients with active rheumatoid arthritis with better safety profile when compared to methotrexate tablets 25 mg.

Iguratimod could be effective even in patients who have a poor response to currently available DMARDs. Adverse reaction profiles of Iguratimod are different from those of Methotrexate If used carefully, Iguratimod could become a novel DMARD that is useful to improve physical condition and the quality of life in patients with rheumatoid arthritis.

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