WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 7.523
Volume 6, Issue 5, 1557-1573. Review Article ISSN 2277– 7105

THE COMBINATION THERAPY OF IGURATIMOD AND METHOTREXATE FOR THE TREATMENT OF RHEUMATOID ARTHRITIS

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Article Received on
20 March. 2017,
Revised on 10 April. 2017,
Accepted on 30 April. 2017
DOI:10.20959/wjpr20175-8448

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ABSTRACT

Rheumatoid arthritis (RA) is a collective autoimmune disease largely exhibiting as chronic synovitis, consequently leading to an alteration in joint integrity. The objective of this review is to clarify the safety and effectiveness of combine use of Iguratimod (IGU) and Methotrexate (MTX). Antirheumatic drugs are efficient of controlling synovial inflammation and are thus termed as 'disease-modifying antirhematic drugs' (DMARDs). MTX is highly recognized as the 'anchor drug' for patients with RA, with advanced and prolonged effectiveness, acceptability, and safety than any other disease modifying antirhematic drugs. Conversely, about 20% to 40% of patients feel inadequate reactions to MTX and need additional therapy, thus a prevalent combination recently use is MTX and IGU in China and Japan. Normally, this combination treatment is well accepted and related through no substantial raise in the degree of adverse actions competed beside the monotherapy. Furthermore, the combination therapy showed a significant improvement in American college of rheumatology (ACR) 50 and ACR70 and disease activity score (DAS) 28. This review presents a summary of seven controlled, double blind trials documenting the safety and effectiveness of IGU in combination with MTX.

KEYWORDS: Rheumatoid arthritis, Iguratimod, Methotrexate, Disease modifying antirheumatic drugs, Disease activity score, American college of rheumatology.

INTRODUCTION

Rheumatoid arthritis (RA) is mainly classified as an inflammatory condition specific to synovial joint. Several reports indicate that approximately 1% of the global population is suffering from the symptoms of this type of arthritis. Proper treatment of the condition is essential to prevent the stiffness of the joints and pain caused by this stiffness.[1] Lack of treatment is directly associated with lasting disability condition and quality of the health of the patient is also compromised. The theory, treatment, and management of rheumatoid arthritis are still considered a risky arena as the diagnosis and etiology of the disease is not limited to the prevalence of specified condition. Rheumatologists are working tirelessly to obtain effective treatment methodologies that can help the patient by relieving pain and improving their quality of life.[2]

RA is often defined as an autoimmune disorder that leads towards the declination of the normal structuring of cartilage, bones, and tendons. It can be said that medical advancement helps in revolutionize the treatment strategies associated with the cure of rheumatoid arthritis in past few years.[3] However, researchers are still unable to define a single treatment method that can assist the medical professionals in the treatment of this condition. The current treatment practice of the treatment of RA includes the administration of biological response modifiers, non-steroidal anti-inflammatory drugs (NSAIDs), and disease modifying anti rheumatic drugs (DMARDs) in the dosage regime of the patient.[4] DMARDs are effective in dealing with the treatment of synovitis that is also linked to the radiation of radiologic manifestation of the disease condition. Methotrexate (MTX) can be regarded as one of the utmost effective option for the management of RA and the administration of the drug is linked with the improvement of the underlying indications of the disease.[5]

Management of patients with RA has proceeded significantly over the previous two periods within previous treatment with MTX, other DMARDs, low dose glucocorticoids, and new biologic agents, targeted to low disease activity or reduction.[6,7]

MTX is the most frequently recommended DMARD[8] and is reflected the “anchor drug” in RA.[9] Nevertheless, about 20% to 40% of patients suffer imperfect responses with MTX as monotherapy. MTX in sequence with other DMARDs has been exposed to be efficient in many of these patients to attain satisfactory low disease activity.[10] In it’s above 30 years of treatment in RA, this medicine has existed widely examined and recurrently showed current as monotherapy and in association with additional DMARDs. In addition, it has an extra

advantage while using with biologic therapies. The currently considered European League Against Rheumatism (EULAR) approvals on the control of RA recommend MTX be part of the primary care scheme in cases with functional RA.[11]

The slightly short half-life of MTX of approximately 5–8h is salaried by intracellular polyglutamation, which leads to accretion of MTX, thus prolonging the half-life. Cellular uptake is sustained by a permeating membrane transport system, the reduced folate carrier. Additionally, specific folate receptors, which are articulated on cells that are significant in the pathophysiology of RA, such as synovial macrophages and lymphocytes, provide to the transport of MTX.[12,13]

The effect of MTX is clarified by modest restraint of folate-dependent enzymes such as thymidilate synthase, dihydrofolate reductase, and 5-aminoimidazole-4-carboxamide ribonucleotide-transformylase.[14] Genetic transformations in these enzymes can mark in different effectiveness of MTX. MTX inhibits *de novo* purine and pyrimidine production, which are necessary for RNA and DNA synthesis. Afterwards, proliferation of lymphocytes, which maintains the inflammatory process, is reduced.[14] Moreover, anti-inflammatory properties are used by increased extracellular levels of 5-aminoimidazole-4-carboxamide ribonucleotide, thus prominent to an inhibition of adenosine- and adenosine mono phosphate (AMP) deaminase. Hereby, adenosine and AMP stores in the extracellular area and by attachment to the adenosine-A_{2a} receptor, enhance of the anti-inflammatory cytokine IL-10 and restriction of the proinflammatory transcription factor NF-kB are noted.[15]

To treat RA, a typical dosage of 15–25 mg of MTX once a week is suggested, managed either orally or subcutaneously, and is usually trailed by 5 mg of folic or folinic acid the time later to decrease side effects.[16] One meta-analysis accounts effectiveness of MTX to placebo[17], and mentions five randomized organized trials comprising 300 patients in which MTX was directed between 12–26 weeks with 7.5–25 mg per week.[18-22] Higher doses of MTX (20–30 mg) are more applicable than lower ones (7.5–15 mg), as is subcutaneous associated with oral application.[23-25] The ability of MTX to decrease radiographic progression was clearly established.[26] MTX has proven its ability as monotherapy and in combination, and the long-term safety outline is clinically satisfactory.[11] Consequently, the approvals from the European League Against Rheumatism (EULAR) state that MTX monotherapy must be the primary choice and introduced at the initial time point if no contraindications are existent.[11]

It is of relevance whether new annotations that found initiation treatment with a combination of DMARDs enhanced than MTX monotherapy will make their way into the next apprise of suggestions.[27]

Iguratimod (IGU) also recognized as T-614, is mainly regarded as a minor molecule of antirheumatic drug. It is reported to have a unique mechanism of action related with the suppression of tumor necrosis factor (TNF).[28] It is also reported to inhibit the release and production of nuclear factor kappa B. IGU can also suppress the production of immunoglobin, and it directly affects the human B lymphocyte without affecting the proliferation of B-lymphocytes. The rheumatoid factor is significantly decreased in the patients suffering from rheumatoid arthritis as the production of IgA, IgM, and IgG decreases significantly.[28] IGU can also be regarded as an antirheumatic drug belonging to the class of methanesulfonanilide. It is classified as DMARD, which had been developed and presented by China and Japan. It is also reported to inhibit the production of interleukins and immunoglobin thus decreasing the extent of RA.[29] It is also reported to exert anabolic effect on the metabolism associated with the bone by initiating the osteoblastic inhibition and differentiation of osteoclastogenesis. The tolerability and efficacy of IGU is reported to be related to the class of salazosulfapyridine drugs and it is directly associated with the use of MTX for the treatment of rheumatic arthritis.[30] It is also used in combination with MTX to synergize its effect in the cure of rheumatic arthritis. It is also associated with the elevation of liver enzymes and reported to cause the initiation and development of thrombocytopenia. It can be regarded as one of the most advanced and effective drug in the action and management of RA[31]

This review provides a descriptive account of systemic review published clinical studies to assess safety and efficacy of IGU monotherapy with IGU in combination alongside MTX.

Current Treatment Options

The managment goals of RA are associated with the prevention of further damage to bones and joints, prevent the further complications associated with the progression of the disease, relieve the symptoms of the disease, and decrease the inflammation caused by the disease.[32] Pain relief is a main goal in the treatment of RA, but is only moderately attained by NSAIDs or opioids.

The first strategy of the treatment is associated with the reaction of inflammation while the second strategy of the treatment is based on the achievement of the remission.[28] The treatment of the patient of RA patient is target specific and target specific treatment is mainly provided to the patient. There are several classes of drugs that are currently being used for the managment of RA and tend to decrease the course of action of the disease.[28] NSAIDs are non-steroidal anti-inflammatory drugs and they are reported to decrease the inflammation and minimize the level of pain. They are available as over the counter drug and available as ibuprofen, Advil, and Motrin. There are stronger prescriptions of NSAIDs and they are available by the prescription of the physicians.[29] The side effects of the medication include stomach irritation, kidney damage, and liver damage. Corticosteroids are also prescribes as the treatment regimen of the disease. Corticosterone's are applicable in decreasing and managing the swelling, decrease the level of pain, and decrease the joint damage.[33] Side effects are associated with the weight gain, diabetes, and thinning of the bones. Acute symptoms of the disease are also associated with the relief of acute symptoms of the disease. The tapering off the drugs is also directly linked with gradual decrease of the dosage.[31] DMARDs or disease-modifying antirheumatic drugs is also effective to treat slow and minimal progression of the disease.

This article objective is to give synopsis of the current immunotherapy in the combination use of IGU and MTX in RA patients. Currently there are three options available to treat RA patients: conventional disease-modifying antirheumatic drugs (cDMARDs), biological DMARDs (bDMARDs) and new mediators for the management of RA.

Conventional disease-modifying antirheumatic drugs for the treatment of rheumatoid arthritis

MTX is the first-line therapy of RA and should be commenced soon after diagnosis. It is usually escorted by low-dose glucocorticoid therapy and folate supplementation.[34]

Leflunomide, sulfasalazine and injectable gold salts are also effective in moderate-to-severe RA, whereas (hydroxy) chloroquine as monotherapy is mostly reflected for minor disease forms only.

Triple therapy of MTX with sulfasalazine and hydroxychloroquine shows similar efficacy to a combination of a biological agent with MTX and is reasonable. Side effects are generally perceived and should be observed closely. If treatment reaction cannot be accomplished

within the first 3–4 months, therapy should be examined and altered or addition of drugs is suggested.[34]

Biological disease-modifying antirheumatic drugs for the treatment of RA

perceptions of biological therapy have remained favoured for the treatment of RA: fused receptor molecules, chimeric, humanized or human monoclonal antibodies, pegylated antibody fragments or receptor antagonists. Including the different targets are TNF-a, IL-1, IL-6 receptor, CD20 and CD80/86.

In most of the circumstances, a biological therapy is combined with, and started after a conventional drug such as MTX has failed but most work also as monotherapy, here alterations between the agents exist. New targets such as B-cell-activating factor of the TNF group or optimization of pharmacokinetics are presently tested. Biosimilar for the treatment of RA will be available soon.[34]

New mediators for the management of RA

In the current ten years, IGU has stayed expended to consider RA as a unique modulator. It operates by overpowering the formation of certain inflammatory cytokines comprising tumour necrosis factor, interleukin-1 (IL-1), IL-4, IL-6, IL-17, nuclear factor-kappa B, and interferon and in vivo (mouse models) in vitro (synovial cells and some cell lines).[35,36]

Tofacitinib is the earliest permitted kinase moderator in RA affecting mainly JAK1 and JAK3.

Numerous different kinase inhibitors are presently in clinical Phase II and III trials exhibiting promising results, between the most progressive is the concept of Syk inhibition.

Literature Review

In this study, it was exhibited that IGU treatment indicated huge clinical adequacy in RA patients equally with and without associative MTX.[5] We additionally obtained the ideal time apex for foreseeing the accomplishment of LDA at 24 weeks in the wake of starting IGU treatment, giving a time period most appropriate to settle on regardless of whether to proceed with treatment.[28] Multivariate examination uncovered that DAS28-ESR at every time point was an autonomous critical indicator of accomplishing LDA at 24 weeks. Clinical reaction up to 12 weeks amid the intial period of treatment is essential for foreseeing mid-term accomplishment of the objective results.[28] Reliable through this, past studies described those 12 weeks is ideal for choosing whether TNF inhibitors are successful. The study likewise

beforehand stated that 12 weeks essentially calculates LDA accomplishment with abatacept, with a cut-off estimation of 3.3h, this time is steady with our outcomes for IGU. In the treatment board system, a choice should be managed in the matter of whether to discontinue or proceed with treatment at 3 months.[29] The summary for IGU uncovered in this research ought to be valuable in clinical training. Up to 2010, the extreme measurements of MTX in Japan were restricted to 8 mg/week. Along these lines, in clinical trials, IGU was utilized as a part of a foundation of low-dosage MTX.[35] In the nearby study, 42% of patients who were cured with attendant MTX were directed a measurements of >8 mg/week, in spite of the fact that MTX measurement did not altogether affect LDA accomplishment at 24 weeks.[31] A late study stated a relationship concerning MTX measurements and clinical outcomes when MTX is utilized as a part of blend with adalimumab. Regarding DMARD mix treatment, assist findings will be expected to recognize the proper dosage of MTX to aid in blend with IGU.[1]

Results in early RA might be enhanced by quickly setting up a steady and successful DMARD treatment schedule. Notwithstanding, patients who have remained endorsed DMARD therapy might have a lacking reaction to or are narrow minded of the medication.[33] Flow pharmacologic treatment for RA intends to soothe indications and to alter the illness procedure, among the objective of accomplishing abatement or a condition of low ailment action. The existing study is an imminent trial that intends to research the utilization of IGU in addition to MTX as a mix treatment in DMARD-practiced grown-up patients with dynamic RA contrasted with IGU or MTX monotherapy as far as adequacy and patient and clinician fulfillment with treatment.[3] This information may give helpful data to building up compelling DMARD treatment schedule for DMARD-felt grown-up patients with dynamic RA who have ensured an insufficient reaction to or are narrow minded of different DMARDs.

Iguratimod as Monotherapy

The earliest scientific report of Japanese patients with RA for IGU was began in 1992 and phase III reports were underway in 1998. A well-ordered, double blind, randomized, similar group study[37] on 376 patients discovered that the ACR 20 reaction amount of IGU that was directed orally at a regular dose of 25 mg aimed at the initial four weeks and 50 mg for the following 24 weeks was greater to placebo (53.8% vs. 17.2%). Moreover, it remained not lesser to salazosulfapyridine (SASP) (63.1% vs. 57.7%) after 28 weeks. All of ACR essential set information comprising patient's assessment of pain with the visual analog scale, tender

joint count, swollen joint count, patient's global assessment of disease activity with the scale and so on, at the result of study therapy remained considerably superior to those at standard in both the SASP and IGU groups. Moreover, to C-reactive protein, IGU considerably lessened the increase in blood absorptions of RF, IgG, IgM, and IgA linked with placebo. A distinguishing adverse result within the IGU group was improved hepatic enzyme.[38]

While this result comprised temporary increase, care must be given to hepatic function facts throughout IGU treatment established on the incident of augmented hepatic enzymes around our analysis. Additional distinguishing harmful incident in this class was dermatological condition, of which regularity was comparatively low. Consideration would also be forfeited to anemia, abdominal pain, and further signs and symptoms associated to gastrointestinal complaint during the treatment since peptic ulcer was stated in the IGU class. To assess the durable safety of this medication, a 52-week experimental survey in 394 Japanese patients beside RA was also managed.[39] Certain patients sustained the action for 100 weeks intended for their assistance. The increasing frequency of undesirable actions for 100 weeks remained 97.6%. The increasing prevalence of unfavorable effects was 65.3%; adverse signs and indications accounted for 33.2% of the responses, and irregular laboratory data alterations accounted for 50.4% at week 100. Concerning raised hepatic enzyme that appeared to be a typical adverse effect of IGU, frequency of enlarged aspartate aminotransferase and alanine aminotransferase was 18.3% and 19.4%, correspondingly. The best familiar planning of beginning of the response was among weeks 4 and 8. The outcome was committed naturally through the sustained research treatment or by the termination of study therapy. At week 28 and week 52, the sustained behavior rate was 66.8% and 53.6% respectively. For reference, at week 28 the ACR 20 response rate was 46.9% and 41.0% at week 52. To consume IGU carefully for a extended time, patients must be perceived carefully for harmful reactions, i.e. enhanced hepatic enzymes.[38]

In the meantime, in China, a placebo- controlled, randomized, 24-week clinical phase II research in 280 patients was also managed and Lü *et al*[40], have lately narrated that IGU at regular amounts of 25 mg and 50 mg was applicable in cure of RA and was totally accepted.

Iguratimod in combination with Methotrexate

Of seven studies identified, two studies compared the combination of IGU with or without MTX. In one study, a 52-week safety and efficacy of IGU, and in another study a 24 week add on combination with or without MTX was determined. Koichi Okamura *et al.*[3] initially

showed that IGU-MTX combination significantly decrease the disease activity score (DAS) 28. Moreover, the existence rate at week 52 was 53.7%. While Yutaka Yoshioka *et al.*[41] 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.

The remaining five studies, four studies were completed in china and one study was performed on patients in japan. Most of the studies done were randomized, double blind, placebo controlled trails. Z.Xia *et al*[1], 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*[33], 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.*[39] 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.[2]

MENG Deqian *et al.*[42] done his study on 60 patients. The results showed that at 16 weeks the DAS28 score of the IGU+MTX decrease significantly then before treatment ($P< 0.01$).

Synergistic Effects of Iguratimod and Methotrexate Therapy

The effects of IGU appear after the administration of the drug for the period of four to 10-weeks. It is even effective for the patients who previously exhibited minor or poor response

to the treatment option of DMARDs.[5] The option of combination therapy of methotrexate and IGU can be regarded as a better option comparing to the option of monotherapy of the individual drug. It is also reported and concluded by the studies that IGU monotherapy is effective as compared to the mono therapy of MTX.[3]

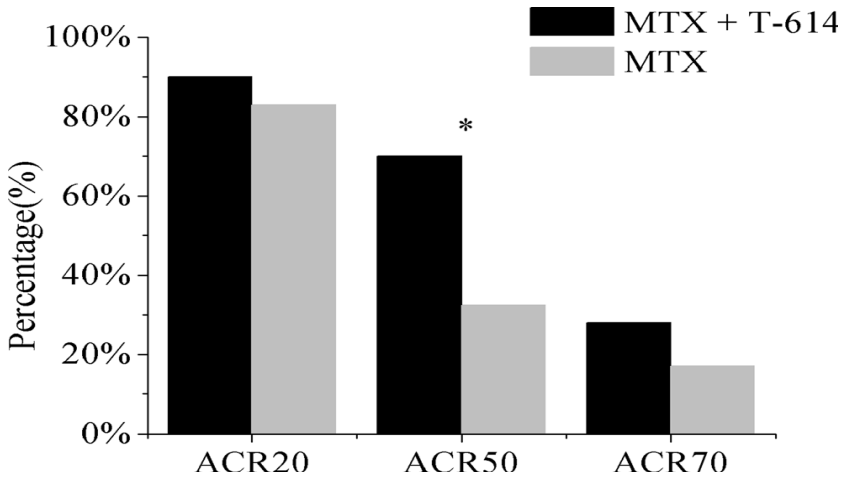

Fig. 1 Percentages of rheumatoid arthritis patients who met the American College of Rheumatology (ACR) criteria 20, 50, and 70 % improvement (ACR20, ACR50, and ACR70, respectively) during treatment with methotrexate (MTX) alone or with MTX plus iguratimod (T-614). *P<0.05 comparing between groups at the same criterion. (Xin-Wang Duan *et al*)[33]

The combination of methotrexate and IGU produces synergistic effect and can be regarded as the most suitable and effective option for the treatment of RA. Patients developing poor response to monotherapy or DMARDs can have the benefit from the combination therapy including both drugs. The data collected from the studies reflect the idea that the patient gets the benefit of the drugs at an extended scope.[1] MTX can also be classified as a concomitant therapy with the combination of IGU. The IGU monotherapy is also regarded as a suitable option for the patient who is intolerant to have the contradiction to the MTX. It is also effective for the patients who fail the therapy of MTX drug therapy.

IGU is also mainly suggested to be clinically effective DMARDs with an innovative mechanism of action. It is also regarded as more effective and safer option and possesses long lasting effect on the treatment option. The combination therapy produces synergistic effects with an option of controlling and limiting the adverse effects of the drug. The combination therapy improves the effectiveness of the drugs, increasing the efficacy of the therapy, and decreases the side effects of the drugs on the individual and combined basis.[2] IGU mainly

decrease and restrain the production of immunoglobulin. It also inhibits the making of inflammatory cytokines and exerts anabolic effect on the metabolism of the bones. It mainly stimulates the differentiation of osteoblasts and inhibits the process of osteoclastogenesis. MTX affects the same channel and produce synergistic effect that helps in controlling the symptoms of the disease. Rate and effectiveness of the treatment increase manifold by the administration of combination therapy of IGU and MTX.[33]

The effectiveness of the combination therapy is reflected in the following figures. The tables also help to realize the overall effect of the treatment on the health status of the patient and provide sufficient data to analyze the effect of the treatment on the disease status of the body.[1]

Tab. 1 Demographic characteristics and disease activity at baseline (0 weeks; mean ± SEM)

	Iguratimod + MTX	Iguratimod	MTX
Morning stiffness (min)	107.86±8.01	93.39±8.50	112.37±7.78
Pain VAS (mm)	62.34±2.36	64.84±2.43	63.41±2.13
Patient VAS (mm)	64.18±2.30	63.97±2.58	62.90±2.22
Physician VAS (mm)	62.68±2.29	60. 74±2.66	59.98±2.25
TEN28	12.09±0.83	13.58±1.00	12.14±0.85
SW28	7.61±0.64	8.26±0.73	8.31±0.59
ESR (mm/h)	69.39±3.95	73.68±3.95	62.34±4.08
CRP (mg/l)	38.68±6.25	42.24±6.72	44.86±4.80
DAS28-ESR	3.82±0.07	3.98±0.09	3.79±0.08
DAS28-CRP	4.55±0.09	4.74±0.12	4.70±0.10
HAQ	0.66±0.02	0.70±0.02	0.67±0.02

TEN28 the number of tender joints, *SW28* the number of swollen joints, *Pain VAS* pain visual analogue scale (VAS) score, *Patient VAS* patient-reported general health VAS score, *Physician VAS* physician satisfaction VAS score, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS28* Disease Activity Score in 28 joints, *HAQ* Health Assessment Questionnaire

Tab. 2 Demographic characteristics and disease activity at 4 weeks (mean ± SEM)

	Iguratimod + MTX	Iguratimod	MTX
Morning stiffness (min)	78.14±6.58	73.55±7.83	91.84±7.05
Pain VAS (mm)	47.14±2.29	45.18±3.23	46.73±2.41
Patient VAS (mm)	48.66±2.27	47.34±3.01	48.51±2.35
Physician VAS (mm)	47.45±2.27	45.00±2.89	45.78±2.16
TEN28	9.05±0.82	10.55±0.92	10.33±0.77
SW28	4.64±0.47*	5.97±0.72	6.78±0.60
ESR (mm/h)	34.39±3.46***,##	58.63±3.25	68.67±4.28
CRP (mg/l)	14.53±2.60***	22.29±3.29**	32.95±3.04
DAS28-ESR	3.11±0.09***,#	3.48±0.09	3.53±0.07
DAS28-CRP	3.80±0.09***	4.10±v0.11	4.31±0.09
HAQ	0.57±0.02	0.53±0.03	0.53±0.02

Compared with MTX group: *P<0.05, **P<0.01, ***P<0.001; Compared with iguratimod group: #P<0.01, ##P<0.001

Tab. 3 Demographic characteristics and disease activity at 10 weeks (mean ± SEM)

	Iguratimod + MTX	Iguratimod	MTX
Morning stiffness (min)	47.95±4.76**	66.71±6.88	77.04±5.94
Pain VAS (mm)	31.68±2.47	37.00±3.50	38.06±2.70
Patient VAS (mm)	34.32±2.33	39.00±3.12	39.67±2.45
Physician VAS (mm)	33.00±2.24	36.08±2.63	37.45±2.23
TEN28	6.20±0.74**	7.45±0.78	9.43±0.87
SW28	2.95±0.39***	4.11±0.66*	6.31±0.62
ESR (mm/h)	27.16±2.45***,##	50.92±3.72***	72.14±3.83
CRP (mg/l)	5.99±0.57***,#	13.34±1.88***	27.18±2.63
DAS28-ESR	2.58±0.10***,##	3.02±0.09*	3.35±0.10
DAS28-CRP	3.15±0.10***,#	3.57±0.11**	4.05±0.11
HAQ	0.39±0.02*	0.43±0.03	0.46±0.02

Compared with MTX group: *P<0.05, **P<0.01, ***P<0.001; Compared with iguratimod group: #P<0.01, ##P<0.001

(Xie *et al*., 2016)[1]

Research Findings

The finding of the research indicates that the combination of two small molecule drugs can assist in target specific therapy. IGU and MTX is found to an effective and useful combination for the treatment of RA and meaningful improvements were observed in the patient by the administration of this combination. It was also found that specific guidelines could be introduced for the management and treatment of rheumatic arthritis by the incorporation of the combination of methotrexate and IGU in the dosage regimen of the patient. As associated to the placebo group of the subjects, the test group reflects 69.5% decline in the symptoms of the disease.

CONCLUSION

The research analysis of the topic 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.

However, due to small sample size of the studies included, small number and methodological defects, whether IGU and MTX combination therapy is effective as other DMARDs combination therapy. We suggest that more high quality and large scale randomized control trial should be done to determine the safety and efficacy of combined use of IGU and MTX.

The current treatment options available for the managment of RA are related with the selection of combination therapies. The current studies in this arena help in understanding the synergistic effects of the combination and contribute in decreasing the chances of disease progression.

Conflict of Interest

It is impossible that the researches can agree to a single solution of the problem. In this regard, there are certain school of thoughts appreciating the idea of using combination therapy of IGU and MTX for the assistance of the symptoms connected with the disease of RA. Another school of thought pursued the idea that the combination of both drugs is associated with increasing the risk benefit ratio. It is also linked with increasing the individual and combined side effects of both drugs. So far, the combination therapy studies did not report the combined adverse or side effects of the drugs and it is regarded as a safe mode of treatment. Complications associated with the progression of the disease. Here it should be kept in mind that the treatment option of RA depends on the health condition and disease status of the patient. It is essential to identify the current health status of the patient and select the combination drug therapy according to it.

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