Section: Miscellaneous

Original Research Article

IGURATIMOD: A NOVEL SMALL MOLECULE DISEASE-MODIFYING ANTIRHEUMATIC DRUG FOR SEROPOSITIVE RHEUMATOID ARTHRITIS-A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Rheumatoid arthritis (RA), is a chronic systemic inflammatory autoimmune disease. A seropositive patient has either rheumatoid factor (RA factor) or Anti-Cyclic- Citrullinated-Peptide (Anti CCP) or both in blood. They require intensive treatment approaches. Iguratimod-a new small molecule antirheumatic drug. Combined treatment with Iguratimod with Methotrexate was shown to yield result in reducing disease activity. **Objective:** To assess the effectiveness and safety of Iguratimod co-administered with Methotrexate in DMARD naive seropositive rheumatoid arthritis patients. **Materials and Methods:** This is a Prospective-observational-study which included patients coming to rheumatology clinic, Govt medical college Thrissur during the period December 2022 to June 2023. Patients with diagnosed of seropositive rheumatoid arthritis of less than two-year duration and Clinical-disease-activity-Index score (CDAI) >10 and have not received any DMARD during this period were taken. Thirty patients, who were on treatment with Methotrexate 15 mg per weekly orally and Iguratimod 25mg twice daily orally were included. Clinical effectiveness was assessed at baseline and after 2 months and 4 months using CDAI. Patients were directed to report any adverse drug reactions developed during study period. **Result:** There was markedly significant reduction in disease activity at 2nd month and 4th month. During the follow up, four patients reported dyspepsia symptoms. **Conclusion:** Methotrexate with Iguratimod combination is a better initial treatment strategy for patients with moderate to severe disease activity with favourable safety profile.

INTRODUCTION

Rheumatoid arthritis (RA) stands as a persistent autoimmune condition that incites systemic inflammation, predominantly affecting the joints.[1] Rheumatoid Arthritis significantly affects the well-being of individuals, leading to substantial morbidity, decreased functionality and independence, lower quality of life, and increased risk of mortality. Its occurrence is consistent worldwide, with a prevalence of 0.5% in our country.[1] Identifying RA early is crucial, as the condition can cause irreversible damage to joint within the first two years of activity. Therefore, prompt diagnosis is essential for achieving the most favourable outcomes. The diagnosis depends on the 2010 ACR- EULAR (American College of Rheumatology- European League Against Rheumatism) classification criteria for Rheumatoid arthritis.[2] Patients diagnosed as seropositive for RA possess either rheumatoid factor (RA factor), anti-cyclic citrullinated peptide (Anti CCP), or both within their bloodstream, which is suggesting a more severe progression of the disease, necessitating more rigorous treatment methodologies.[3]

Recent years have seen a substantial shift in how RA is managed, with current treatment objectives focusing on averting joint damage and maintaining functionality. Consequently, the initiation of Disease Modifying Antirheumatic Drugs (DMARDs) shortly after diagnosis is advocated for most individuals to mitigate the disease progression.[4] Despite ongoing debates regarding the early treatment strategy for patients diagnosed with RA, the universal

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effectiveness of available medications remains elusive, compounded by potential toxicity or high costs. This situation underscores the pressing need for the development of novel, cost-effective, and safer treatment options.[5] The efficacy of single DMARD therapy often falls short, prompting the use of DMARD combination therapies, despite the scarcity of data supporting their effectiveness.[6]

The European-League-Against-Rheumatism (EULAR) has suggested for DMARD-naive patients, a combined approach of conventional synthetic DMARDs as a viable alternative to monotherapy, possibly with the inclusion of glucocorticoids, considering individual patient preferences and potential side effects. Early intervention with drug combinations not only delays and slows disease progression but also proves to be cost-effective in the long term by enhancing patient productivity.[7] Among the novel therapeutic agents in this domain is Iguratimod, a small molecule drug with significant immunomodulatory effects on the synovial tissue of individuals with RA.

Iguratimod, belonging to the methane sulfonanilide family, plays a pivotal role by suppressing the production of immunoglobulins and various inflammatory cytokines, such as IL-1, IL-6, and TNF. It promotes bone health by encouraging osteoblastic differentiation and inhibiting osteoclastogenesis, in addition to blocking the NF-kB pathway. Its inhibition of COX-2 further synergizes its analgesic and anti-inflammatory actions.[8] Published reports have confirmed that a combination therapy involving Iguratimod and Methotrexate significantly outperforms the monotherapy of either drug, positioning this combination as a potential first-line treatment option.[5] This research is intended to assess the effectiveness and safety of co-administration of Iguratimod and methotrexate in DMARD naive seropositive rheumatoid arthritis patients.

MATERIALS AND METHODS

This research is a Prospective observational study in patients coming to rheumatology clinic, Government medical college Thrissur-Kerala during the period December 2022 to June 2023. The study was initiated after getting permission from the Institutional-Research-Committee and Institutional Ethics Committee. Patients whose age more than 18 years and less than 75 years of either sex were included. Patients diagnosed with rheumatoid arthritis according to ACR/ EULAR 2010 classification criteria and those with Rheumatoid- factor or anti-cyclic-citrullinated peptides positive were taken. Patients having rheumatoid arthritis of less than two-year duration and Clinical-disease-activity-Index score (CDAI) >10 and have not received any DMARD during this period were taken. Thirty patients, who were on treatment with Methotrexate 15 mg per weekly orally and Iguratimod 25mg twice daily orally were included. Written informed consent was obtained from patients. Consecutive sampling method is used in which every subject meeting the criteria of inclusion is selected. Patients with impaired renal, liver, hematopoietic system, chronic infectious disease such as hepatitis B, hepatitis C, tuberculosis and pregnant and lactating women were excluded.

Baseline investigations like RA factor, Anti CCP, blood routine, LFT, RFT was done. LFT and blood routine repeated during follow up time. Clinical effectiveness was assessed at baseline and after 2 months and 4 months using CDAI.[9] CDAI is based on the simple summation of Tender Joint Count (TJC) and Swollen Joint Count (SJC) of 28 joints along with Patient Global Assessment (PGA) and Evaluator Global Assessment (EGA) on visual analogue scale VAS (0–10 cm) for estimating disease activity. The CDAI has range from 0 to 76. CDAI score components and its interpretations are showed in Figure 1. Paired t test was done to compare CDAI score between baseline and 2 months and between baseline and 4 months. Patients were directed to report any adverse drug reactions developed during study period.

RESULTS

Mean-age of the patients were 51.8+/-10.2 years. The median duration of illness was 12 +/- 18 months. 90% of the patients were females. The mean CDAI scores at baseline, 2nd month and 4th month were 36.47 ± 15.35, 22.27 ± 12.7 and 16.5 ± 11.11 respectively. Statistical analysis showed highly significant reduction in disease activity at 2 months (p value < 0.001) and at 4 months (p value < 0.001). These are presented in Table 1 & Figure 2. The mean changes in tender and swollen joint counts, patient and evaluator global assessment scores are depicted in Figure 3. During the follow up, four patients complained about dyspepsia symptoms which was showed in Figure 4.

Table 1: Paired t test

Disease activity score		Mean ±SD	t value	p value
CDAI score	0 weeks	36.47 ± 15.35	6.21	0.000
	2 weeks	22.27 ±12.71		
CDAI score	2 weeks	22.27 ±12.71	7.35	0.000
	4 weeks	16.5 ± 11.11		
CDAI score	0 weeks	36.47 ± 15.35	7.65	0.000
	4 weeks	16.5 ± 11.11		

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CDAI Variables	Range
Tender joint score (TJC)	(0-28)
Swollen joint score (SJC)	(0-28)
Patient global score (PGA)	(0-10)
Evaluator global score (EGA)	(0-10)
CDAI score	(0-76)

CDAI score interpretation score interpretation	
0.0-2.0.0-2.88	Remission
2.9-10.0	Low activity
10.1-22.01-22.0	Moderate activity
22.1-76.01-76.0	High activity

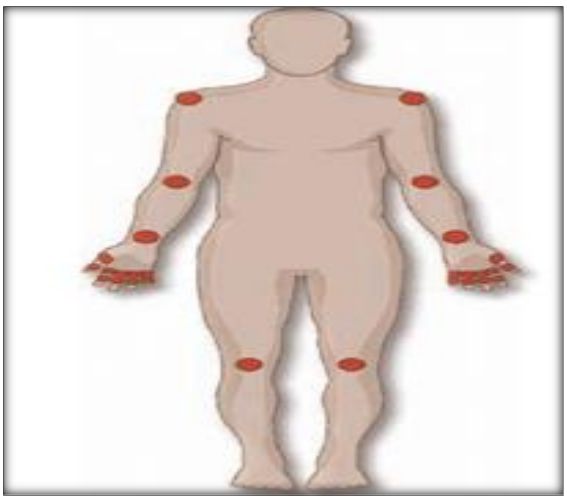

Figure 1: Clinical Disease Activity Index

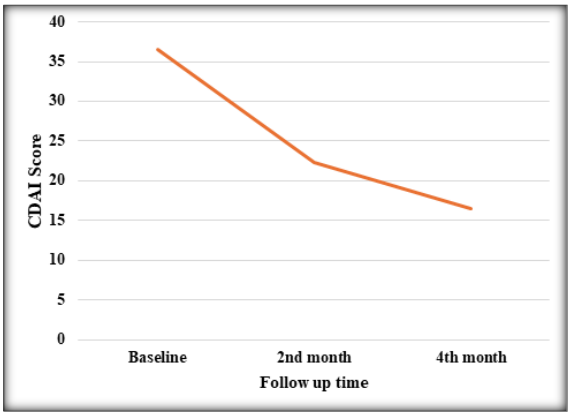

Figure 2: Clinical Disease Activity Index

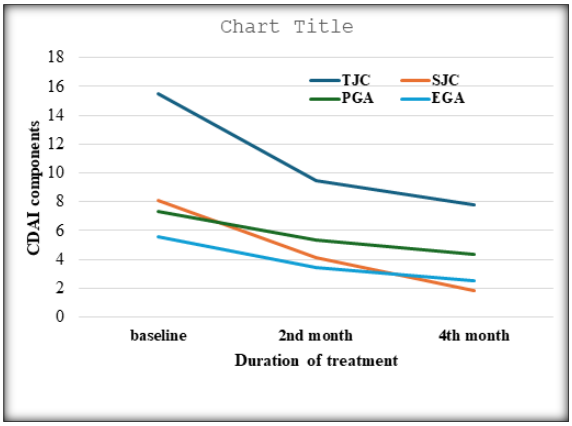

Figure 3: CDAI Components

TJC- Tender joint count, SJC- Swollen joint count PGA- Patient global assessment, EGA- Evaluator global assessment

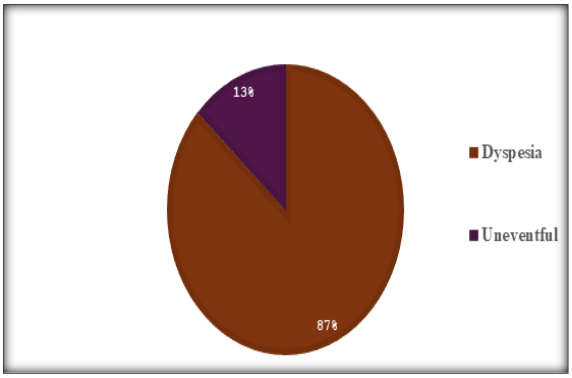

Figure 4: Adverse drug reactions

DISCUSSION

This study demonstrated a significant marked reduction in disease activity in the 2nd and 4th months post-treatment with Methotrexate at a dose of 15 mg weekly and Iguratimod at 25 mg twice daily, when taken orally. Merely four individuals reported symptoms related to dyspepsia because of the treatment. These findings are consistent with those of a national prospective real-world study conducted by Rong Mu et al., which verified the effectiveness and safety of Iguratimod in treating active rheumatoid arthritis, suggesting it as an affordable option for either solo or combined treatment regimes.[10] The primary safety concern identified in our research was gastrointestinal symptoms, mirroring the outcomes observed in the study by Mu et al. Comparable outcomes were noted in several other studies: L.J. Chen et al.'s meta-analysis of Randomized Controlled Trials (RCTs) suggested that a combination therapy of Iguratimod and Methotrexate was superior to Methotrexate monotherapy for rheumatoid arthritis, with adverse events being similar to Methotrexate treatment alone.[11] Jingya Tan et al. highlighted that combining Methotrexate with Iguratimod enhanced clinical results for patients with rheumatoid arthritis without raising the risk of

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adverse events.[12] Lastly, a systematic-review by Chao-Jun Hu et al. concluded that Iguratimod serves as reliable and tolerable option as either a standalone treatment or in combination, particularly with Methotrexate, for those suffering from active RA.[13] Additionally, a systematic review by Dan Ouyang et al. stated that combining Methotrexate with Iguratimod significantly enhances ACR 20 response rates without significant adverse effects.[14] Liuting Zeng et al.'s systematic review indicated that, compared to standard therapy, the combination of Iguratimod with Methotrexate may offer a safer and more efficacious treatment for RA patients, without noticeable side effects.[15]

CONCLUSION

Rheumatoid arthritis is a chronic and severely debilitating condition. Despite the availability of numerous treatment options, achieving complete remission remains challenging, and many treatments come with significant side effects. Iguratimod, a novel small molecule disease-modifying antirheumatic drug, has shown promising results. This research indicates that combining Iguratimod with methotrexate significantly lowers disease activity in patients newly diagnosed with seropositive moderate to severe rheumatoid arthritis, and this combination has been well-received by patients. Therefore, this approach could function as a initial treatment choice for individuals with moderate to severe seropositive rheumatoid arthritis.

The primary limitation of the study is short duration of assessment. Therefore large scale long term and comparative studies are recommended to more conclusively establish the effectiveness and tolerability of this drug combination in rheumatoid-arthritis.

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