



ISSN Print: 2664-9691
ISSN Online: 2664-9705
Impact Factor: RJIF 5.46
IJOR 2024; 6(1): 12-16
www.orthopaedicsjournal.net
Received: 19-12-2023
Accepted: 18-01-2024

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Clinical Scenarios-based guide for iguratimod in rheumatoid arthritis and ankylosing spondylitis

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DOI: <https://doi.org/10.33545/26649691.2024.v6.i1a.12>

Abstract

Iguratimod (IGU) is disease modified anti-rheumatic drug, it is a synthetic small molecule which is approved for treatment of Rheumatoid arthritis and autoimmune disease only in Japan and China. Immunomodulatory role of IGU in rheumatoid arthritis is by regulating T lymphocyte subsets, inhibiting the production of immune globulins and cytokines in the synovial tissue. IGU inhibit osteoclast differentiation, migration, and bone resorption also stimulate bone formation thus regulating bone metabolism. In clinical trials, it was shown that combined therapy of IGU with other disease-modifying anti-rheumatic drugs significantly improved disease activity also and IGU monotherapy was shown to be superior to placebo and not inferior to salazosulfapyridine. In patients of rheumatoid arthritis who showed inadequate response to methotrexate and biological disease-modifying anti-rheumatic drugs, IGU has good efficacy and tolerance as an additional treatment.

Keywords: Iguratimod, rheumatoid arthritis, ankylosing spondylitis, primary Sjögren's syndrome, iguratimod in rheumatoid arthritis, iguratimod in ankylosing spondylitis

Introduction

Rheumatic immune disease is an inflammatory disease with complex pathogenesis that adversely affects immune system which involves musculoskeletal system joints and their surrounding soft tissues also. The prevalence of rheumatic immune diseases like rheumatoid arthritis (RA), systemic lupus erythematosus (SLE) and ankylosing spondylitis (AS) has been on upward thrust in recent years. More advanced cases are characterized by joint deformation and functional limitations, and some important internal organs, such as the lungs, heart, kidneys, and digestive tract might also be involved, with a continuous and recurrent process, which is a key health issues worldwide and causes a tremendous psychological burden on patients and an economic burden on society. The current treatments for rheumatic diseases and autoimmune diseases aims at reducing inflammatory damage controlling the progression of inflammation and are precision medicine based on drugs. There are three general classes of drugs commonly used in the treatment of rheumatoid arthritis: non-steroidal anti-inflammatory agents (NSAIDs), corticosteroids, and disease modifying anti-rheumatic drugs (DMARDs). NSAIDs and corticosteroids have a short onset of action while DMARDs can take several weeks or months to demonstrate a clinical effect. DMARDs are classified as biologics DMARDs, conventional synthetic DMARDs, and synthetic targeted DMARDs. Biological DMARDs have two categories: biological agents (bDMARDs) and synthetic targeted (tsDMARDs). bDMARDs include the tumor necrosis factor inhibitor class of adalimumab, infliximab, etanercept, and the IL-6 antagonist tocilizumab. tsDMARDs include the Janus kinase (JAK) inhibitor tofacitinib. Although the efficacy of the above drugs has been demonstrated but because of their high cost it is not possible for patients in developing countries, including China, to continue or take full advantage of these regimes (Drosos *et al.*, 2020) [17]. Studies have shown that patients in developed countries are also becoming increasingly prominent due to poor compliance and high recurrence rates related to medication problems (Tanaka, 2016; Ghabri *et al.*, 2020) [15-16]. Traditional DMARDs are class of drugs that are affordable and have less side effects hence are widely used for patient management, Methotrexate (MTX) is one of the most prescribed DMARDs for the treatment of RA (Wang W. *et al.*, 2018) [29] due to its effectiveness, low side effects, and affordable price, In the initial treatment regimen for RA patients ACR recommends it as the first-choice

drug (Cronstein and Aune, 2020) [30]. However, there are still about 30%–40% of patients who are insensitive to MTX treatment, have poor treatment effect, or fail to benefit from it because of side effects (Cronstein and Aune, 2020) [30]. Strand *et al.* reported that the ACR50 of MTX in RA was 46%, and the ACR70 was 23% (Strand *et al.*, 1999) [31]. According to multiple clinical trials, the combined use of DMARDs is one of the effective ways to improve the efficacy (Kremer *et al.*, 2002; Ichikawa *et al.*, 2005; Capell *et al.*, 2007) [32–34].

Iguratimod (IGU or T-614) is a novel synthetic small molecule disease modified anti-rheumatic drug approved only in Japan and China As an immune modulator, through immunomodulation, it reduces immune response, inhibits collagenous arthritis, and relieves the destruction of bone and cartilage tissue (Li *et al.*, 2013; Mizutani *et al.*, 2021) [5, 11]. IGU can inhibit nuclear factor-kappa B (NF-κB) activation by interfering with NF-κB translocation from the cytoplasm to the nucleus without affecting the degradation of IkappaB α in lipopolysaccharide-stimulated THP-1 cells (Human monocytic leukemia cell line) (Aikawa *et al.*, 2002) [39]. Similar results were also confirmed in cultured human synovial cells (Kohno *et al.*, 2001) [40] other studies in macrophages and microglia showed that IGU inhibited nuclear translocation of NF-κB 65 and pro-inflammatory response (Li *et al.*, 2018) [41]. In synovial cells, IGU can significantly inhibit the expression of cytokines including IL-6, IL-8, granulocyte colony-stimulating factor, and granulocyte macrophage colony-stimulating factor induced by interferon- γ , IL-1 β , or 12-O-tetradecanoyl phorbol 13-acetate, and IGU can alleviate the expression of costimulatory molecules including CD54, CD58, CD106, Human Leukocyte Antigen-DR, IGU also significantly inhibited synovial cell-mediated antigen-specific T cell proliferation (Kawakami *et al.*, 1999) [45], (Li *et al.*, 2013; Xie S. *et al.*, 2020) [5, 35] and inhibiting the production of immunoglobulins to exert, anti-immune, and anti-inflammatory effects, in addition, IGU inhibited the up-regulation of IL-6, IL-8, and monocyte chemo attractant protein 1 induced by tumor necrosis factor alpha (TNF- α) in RA synovial cells in a concentration dependent manner (Kohno *et al.*, 2001) [40]. Several studies have shown that IGU has good efficacy in rheumatic diseases and autoimmune diseases, such as improving RA, AS, systemic lupus erythematosus, IG4-RD, pulmonary interstitial disease, primary Sjögren's syndrome (PSS), etc. (Harjacek, 2021; Pu *et al.*, 2021; Zeng *et al.*, 2022a) [6, 8, 36].

Materials and Methods

Search criteria

This study was carried out in Accordance to the approach outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins Julian and Green, 2011a) and is presented as per the Preferred Reporting Items for Systematic Reviews and Meta Analyses (PRISMA) (Higgins *et al.*, 2015). A thorough search of the Cochrane Central Register of Controlled Trials (CENTRAL), PUBMED and Google scholar was conducted to identify all citations of original research studies with key words: autoimmune disease, iguratimod, rheumatoid arthritis, ankylosing spondylitis, primary Sjögren's syndrome, To find any pertinent articles that the initial search missed, a manual check of all eligible articles' references was conducted. Two reviewers separately screened the title,

abstract, and complete text from the selected papers. Disagreements from the title and abstract screening stage were carried over to the following round for a more thorough examination. Any disputes were discussed among the reviewers, and any unresolved issues were then brought up with a senior author. In accordance with keywords total 119 studies were identified from Google scholar, Pubmed and Cochrane central register out of which 80 matched as per inclusion and Exclusion criteria. 32 studies were found to be duplicate studies so and out of total 119 studies 48 were analyzed after they were found to be appropriate as per the eligibility criteria,

Outcomes

Outcomes are the disease activity indices (Such as BASDAI and ACR20), inflammatory factor indicators (Such as ESR, CRP, RF) and adverse events

Inclusion criteria

- Original literature with Human models with established Arthritis disease
- Randomized control trials, Comparative studies, Clinical trials, Real world Study, Prospective studies on IGU for rheumatic and autoimmune diseases were included
- There are no restrictions on publication year and publication journal, etc.
- Studies in English language

Exclusion Criteria

- Duplicate studies
- Studies with no relevance with current study or keywords
- case reports
- Studies which cannot be extracted from true source
- Animal studies
- Other language.

Discussions

In 2012 China and Japan approved IGU for the treatment of RA. In 2014, IGU was recommended by Asia Pacific Association of Rheumatology (APLAR) for treatment of Refractory RA (Li *et al.*, 2013; Li J. *et al.*, 2019) [5, 38] Use of IGU has increased recently because apart from effectively treating autoimmune diseases it also controls the inflammation. (Nozaki, 2021) [9]. In comparison to other traditional DMARDs drugs, apart from inhibiting the production of immunoglobulin and various inflammatory cytokines (IL-1, IL-6, IL-8 and TNF), IGU also facilitate the differentiation of bone cells, prevents osteoclasts generation, decreases bone resorption and joint destruction and controls the expression of matrix metalloproteinases by inhibiting the production of MMP-1 and MMP-3, thereby playing an anti-inflammatory role (Liu *et al.*, 2021a; Mizutani *et al.*, 2021; Mu *et al.*, 2021; Tanaka, 2021) [10–13]. In addition, IGU can also inhibit COX-2 and reduce the short-term synergistic effect of pain and inflammation (Mu *et al.*, 2021; Tanaka, 2021) [12–13]. They found that IGU + MTX therapy can improve ACR20, ACR50, ACR70, DAS28, reduce ESR, CRP, RF, and have a lower incidence of adverse events than the control group. However, IGU alone only significantly improved CRP, but IGU + MTX may be a better combination of IGU in the treatment of RA, because it has obvious efficacy, can reduce inflammatory factors,

and has a lower incidence of adverse events than the control group therapy mainly MTX.

A recent 52-week randomized, double-blind, parallel-controlled, multicenter study showed that IGU (Use alone) was more effective than MTX in the treatment of RA (Du F. *et al.*, 2021) [18]. In terms of efficacy, the ACR20 response rate of IGU was 77.44%, which was significantly better than that of MTX (65.87%). In the direction of imaging improvement, the results showed that the proportion of patients with no imaging progression in IGU or combined therapy for 1 year was higher than that in MTX therapy, indicating that IGU therapy was significantly better than MTX therapy. The efficacy of IGU + MTX is similar to that of IGU only, suggesting that patients with early RA can consider IGU alone, and only when the single drug is not effective, combined with other drugs such as biological agents. They also found that IGU or combination therapy can delay the imaging progress of RA patients, which provides an important reference for clinical medication. Another important factor for RA patients and doctors when choosing a drug is the efficacy, safety and cost of the drug. Reported data from a real-world pharmaco-economics study on IGU and other drugs in RA at the 2022 EULAR meeting. Their results show that IGU combined with MTX in the treatment of RA is both safe and effective, and the price is moderate, providing a treatment plan for RA patients that takes into account efficacy, safety and economic cost.

The current study shows that IGU, as a new type of DMARD, mainly acts through anti-inflammatory and immune regulation. For example, IGU can inhibit the production of inflammatory cytokines (Such as IL-1 and TNF- α), block the IL-17 signaling pathway and inhibit cyclooxygenase, and regulate the balance of osteoclasts (Liu *et al.*, 2021b; Harjacek, 2021) [6, 14], so it may be effective against AS/SpA in mechanism. Therefore, a number of exploratory RCTs have previously applied IGU to AS/SpA (Li Y. *et al.*, 2021) [38].

Conclusion

However, present day research and studies on IGU have certain limitations.

1. The modern-day clinical information assets are particularly of China and Japan. The study is focused on populace is specifically East Asians, without different ethnic groups
2. The actual action or targets of IGU are not present day studies on the mechanisms of anti-irritation, immunity regulation, and bone metabolism are restrained, and the real targets are still unknown.
3. The scientific research on this drug are in particular of short-time period, there are not any lengthy-time period scientific facts for greater than 3 years. Therefore, multi-middle and long-time period safety data and comparisons of the protection and effectiveness of IGU with other pills are essential. In addition to RA, the anti-inflammatory and anti-rheumatic effects of IGU are shown in other autoimmune diseases, such as Sjogren's syndrome, ankylosing spondylitis, systemic lupus erythematosus, multiple sclerosis, and IgG4-related diseases, which are mainly reported in China. Consequently, extra information at the efficacy and safety of IGU in the treatment of different autoimmune diseases have to be suggested, in particular the ones related to excessive immunoglobulin. Furthermore,

considering the fact that IGU can lessen the infection related to biomaterials and the rejection price, we are hoping that extra statistics on using IGU for biomaterials will be mentioned.

In summary, IGU is a new synthetic disease-modifying anti-rheumatic drug. We hope that IGU will not only be used in China and Japan, but also become an effective choice for patients with RA worldwide.

Conflict of Interest: None.

Source of Funding: None.

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How to Cite This Article

Rastogi DR, Khanna M. Clinical Scenarios-based guide for iguratimod in rheumatoid arthritis and ankylosing spondylitis. *International Journal of Orthopaedics and Rheumatology.* 2024;6(1):12-16.

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