International Journal of Orthopaedics and Rheumatology
www.orthopaedicsjournal.net
Online ISSN: 2664-9705, Print ISSN: 2664-9691
Received: 12-10-2021; Accepted: 26-10-2021; Published: 13-11-2021
Volume 3, Issue 1, 2021, Page No. 1-6

Immunomodulation with Iguratimod– A Novel molecule for the management of rheumatoid arthritis

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Abstract
Rheumatoid arthritis (RA) is a chronic inflammatory condition that results in release of various inflammatory mediators which causes destruction of bone, cartilage, and tendons. RA affects less than 1% population worldwide. The treatment of RA includes disease-modifying anti-rheumatic drugs (DMARDs), non-steroidal anti-inflammatory drugs (NSAIDs), and glucocorticoids. The remission rates of RA with available treatment are low. Iguratimod (IGU) is newly developed molecule, approved for its use in Japan and China is reported to significantly reduce the effects of various inflammatory mediators that results in progression of RA. IGU through its anti-inflammatory, immunomodulatory, and osteoprotective mechanisms may result in overall management of RA. IGU is reported to be safe and effective in various clinical trials as a monotherapy or when combined with other DMARDs. The current review summarizes various effects of IGU and considers it as a promising therapeutic option for RA management.

Keywords: Rheumatoid arthritis, Inflammation, Immunomodulator, DMARDs, Iguratimod

Introduction

Rheumatoid arthritis (RA), a chronic inflammatory and autoimmune disease, primarily targets synovial fluid present between the bones [1]. It is usually characterized by T-lymphocyte activation, elevated interleukin (IL) and tumor necrosis factor (TNF), and severe chronic inflammation of the joints [2]. This severe chronic inflammation of the joints results in erosion and destruction of cartilage, bone, and tendon. [1, 2] The causal factors that play an important role in RA pathogenesis include genetics, environmental, and immune cells [3].

Worldwide, RA affects less than 1% adults suggesting it to be relatively common joint disorders affecting adults. The prevalence of moderate to severe RA in patients above 60 years is reported to be 1.7millions in high-income countries and 3.7 millions in low- and middle-income countries [1].

Currently the early use of traditional disease-modifying anti-rheumatic drugs (DMARDs), such as methotrexate (MTX), salazosulfapyridine (SASP), leflunomide, and cyclophosphamide to minimize or prevent joint damage are recommended in patient with RA. Moreover, biologic agents such as necrosis factor-α blocker, anti-interleukin antibody, and CD20 monoclonal antibody are also used to treat RA [1].

Rheumatism requires long course and long-term treatment. Current drugs for the treatment of rheumatic diseases mainly include non-steroidal anti-inflammatory drugs (NSAIDs), DMARDs and glucocorticoids [4]. However, the remission rate of RA with these available treatments remains low and the drugs used to treat rheumatism are limited [4, 5]. Furthermore, the economic burden of RA in developing countries is high. Therefore, there is an urgent need for development of new drug moiety for the management of RA [4].

Iguratimod (IGU), a small-molecule compound, was developed as an anti-rheumatic agent, and is used in China and Japan for RA management. IGU is reported to inhibit the production of various inflammatory cytokines, including interleukin (IL)-1, IL-6, IL-8 and tumor necrosis factor (TNF), reduce the production of immunoglobulin and accelerate bone formation by inhibiting the activation of osteoclasts and promoting osteoblast differentiation in various pharmacological studies. Research suggests effective role of IGU for pulmonary fibrosis. The discovery of these mechanisms has facilitated the widespread clinical use of IGU [4].

Mechanisms of Iguratimod action

Anti-inflammatory mechanism

Synovial proliferation inhibition and inflammation reduction is key to control the RA activity [4]. *Wang et al* [4]. performed an intervention experiment of fibroblast-like synoviocytes (FLSs) *in vitro* to evaluate the effect of IGU on synovial inflammation, and found that IGU can significantly inhibit the proliferation of synoviocytes, reduce the expression of interleukin (IL)-8, and improve inflammatory status [6]. IGU is noted to interfere with TNF-α-induced translocation of nuclear factor (NF)-κB to the nucleus from the cytoplasm, and suppresses TNF-α-induced production of IL-6, IL-8, and monocyte chemoattractant protein 1. Thus, IGU can regulate the NF-κB signalling pathway and affect the expression of inflammatory factors [4].

IGU *via* the NF-κB and T helper (Th)17 signalling pathways inhibits inflammation. Th17 cells play a crucial role in RA patients as effector cells. IL-17A is a marker cytokine belonging to Th17 cell lineage, and IL-17 receptor recruits Act1 to produce a complex that stimulates inflammatory responses. FLSs are resident mesenchymal cells of synovial joints. IL-17 activates FLSs which results in production of large number of pro-inflammatory factors (such as IL-6 and TNF) which results in RA pathogenesis [4]. *Luo et al* [7]. reported that IGU effectively prevents the inflammation of synovium in collagen-induced arthritis, and possesses a

specific inhibitory effect on IL-17 in dose-dependent manner. IGU inhibits IL-17-mediated signalling by disrupting Act1, which is the key adaptor protein in IL-17 signalling, interaction with tumor necrosis factor receptor-associated factor 5 (TRAF5) and IKKi, which inhibit expression of various inflammatory factors induced by IL-17 [7].

Macrophage migration inhibitory factor (MIF) is known to stimulate IL-17 production through regulation of IL-17 inducers and promotes pathogenic Th17 cells that mediate autoimmunity [4]. In inflammatory diseases such as RA, MIF, a pleiotropic cytokine, involved in a wide range of inflammatory and neoplastic diseases has important pathological effects [8]. IGU may interact with MIF trimmers, inhibits the MIF tautomerase activity, and blocks MIF-induced pro-inflammatory effects such as, B cell proliferation and monocyte cytokine release, and inflammatory relief. Thus, IGU can be identified as MIF inhibitor to exert an anti-inflammatory effect [4].

In conclusion, IGU acts on multiple targets of multiple signalling pathways to inhibit the production of inflammatory factors.

Immunomodulatory mechanism

Large number of T cells and T-cell derived cytokine area known to play an important role in the auto-immune response of RA. T cells that induce auto-immune response include Th1 cells, Th17 cells, T regulatory (Treg) cells and T follicular helper (Tfh) cells [9]. Treatment with IGU potentially reduces Th1 cells, Th17 cells, Tfh cells, Treg-associated transcription factors and cytokines, such as Tbet, IL-17, retinoic-acid-receptor-related orphan nuclear receptor (ROR)γt, signal transducer and activator of transcription (STAT)3, Bcl-6, IL-21, interferon (IFN)-γ, TNF-α and IL-17A; whereas, the levels of Treg-associated cytokines and transcription factors are increased. IGU is also observed to induce peripheral blood mononuclear cell apoptosis and decrease CD3+ T cell IFN-γ production and secretion of IL-8 in peripheral blood. IGU is noted to induce peripheral blood mononuclear cell apoptosis and reduce CD3+ T-cell IFN-γ production and secretion of IL-8 in peripheral blood. This indicates that IGU regulates the immune balance by enhancing Treg cells and by reducing the production of pro-inflammatory cytokines [4].

A Phase III clinical trial of IGU demonstrated that treatment of active RA with IGU significantly reduced the levels of IgG, IgM and IgA. IGU decreases the peripheral antibody secreting cell population without hindering the activation, proliferation or apoptosis of B cells [10]. Investigation studies of IGU showed that IGU suppresses the regulation of B cell terminal differentiation by inhibiting the PKC pathway and downstream target EGR1. Consequently, expression of BLIMP1 is inhibited, resulting in a blockade of plasma cell differentiation [11].

B-cell terminal differentiation is inhibited by IGU and reduces the production of autoantibody and is associated with improved disease activity [4].

Due to role of IGU in regulating the immune balance, IGU is considered as an “immunomodulator” and not as an “immunosuppressive” agent.

Osteoprotective mechanism

Osteoporosis is often a secondary symptom of RA, and results in joint rigidity, deformity, and severe functional damage. Early effective bone protection and improved bone metabolism is the key to prevent joint destruction. Various signalling pathways play an important role in osteoblast proliferation and differentiation and the repair process of bone and cartilage damage, including the bone morphogenetic protein (BMP)2–Smads, p38 mitogen-activated protein kinase (MAPK) and TNF-α/NF-κB pathways [12].

IGU is reported to increase the expression of osterix (Osx), which is crucial in osteoblast differentiation. BMP2 can activate expression of Osx, through the induction of upstream transcription factor Dlx5. The p38–MAPK pathway interacts with the BMP2–Smads pathway to improve Osx phosphorylation [12].

IGU promotes osteoblast differentiation by increasing the expression of Osx and Dlx5 [13]. The p-38 MAPK is a member of the MAPK superfamily, which is involved in the early stages of osteoblast lineage proliferation through the phosphorylation of Dlx5, runt-related transcription factor (Runx)2 and Osx [12]. IGU may elevate the activation of p38 and promotes osteoblastic differentiation [4].

The TNF-α/NF-κB signalling pathway plays an important role in osteoblast proliferation, apoptosis and differentiation [14].

The RANKL/osteoprotegerin (OPG) system is involved in RA-associated bone erosion. Upregulation of RANKL/OPG ratio enhances bone erosion. IGU suppresses the production of RANKL and the RANKL/OPG ratio significantly. This decreases both, serum and IL-1β-induced RA FLSs after treatment [15]. RANKL and its receptor RANK bind to osteoclast precursor cells to stimulate downstream pathways, such as peroxisome proliferator-activated receptor (PPAR)-γ, c-Fos, and nuclear-activated T cell factor (NFAT)c1 [16]. IGU inhibits osteoclastogenesis and bone resorption induced by RANKL in the PPARγ/c-Fos signaling pathway, and also reduces expression of NFATc1 and downstream osteoclast marker genes [4].

Gan et al. [17] demonstrated that IGU significantly inhibited RANKL-induced osteoclast differentiation, migration and bone resorption in RAW264.7 cells in a dose-dependent manner. The mechanism of which is related to the activation of the MAPK and NF-κB pathways [17]. This shows that IGU has a direct inhibitory effect on the formation and function of osteoclasts.

The TNF-α/NF-κB signalling pathway can inhibit the production of matrix metalloproteinases (MMPs) [14]. MMPs, mainly produced by FLSs, play a crucial role in the destruction of RA cartilage. *Du et al.* in an *in vitro* study, treated FLSs with different doses of IGU, and then stimulated them with TNF-α, IL-1β or IL-17A. MMP-3 was significantly inhibited by IGU (5 μg/ml), but MMP-1 was significantly inhibited at higher dose of IGU (50 μg/ml). The clinical trials found that, the levels of MMP-1 and MMP-3 were significantly reduced after 24 weeks of treatment with IGU (25 mg, twice daily) [18]. These results demonstrate that IGU prevents MMP-1 and MMP-3 from destructing the cartilage.

OPG is known to act as a natural inhibitor of RANKL, preventing RANKL from binding to its osteoclast receptor. RANKL/OPG balance is crucial for maintenance of osteoclast homeostasis [19]. IGU inhibits the expression of MMP-3, RANKL/OPG induced by blocking phosphorylation of ERK1/2, thereby blocking the destruction of RA bone [20].

IGU promotes differentiation of osteoblasts, inhibits osteoclastogenesis, and promotes production of matrix proteins through interaction with multiple signalling pathways. Thus, IGU plays a vital role in bone protection [4].

Summary of mechanisms

Taken together, IGU can significantly inhibit the initiation and progression of RA by multiple mechanisms such as regulating T cell differentiation, reducing the production of pro-inflammatory cytokines and immunoglobulins, promoting bone formation, and inhibiting bone resorption (Figure 1) [21].

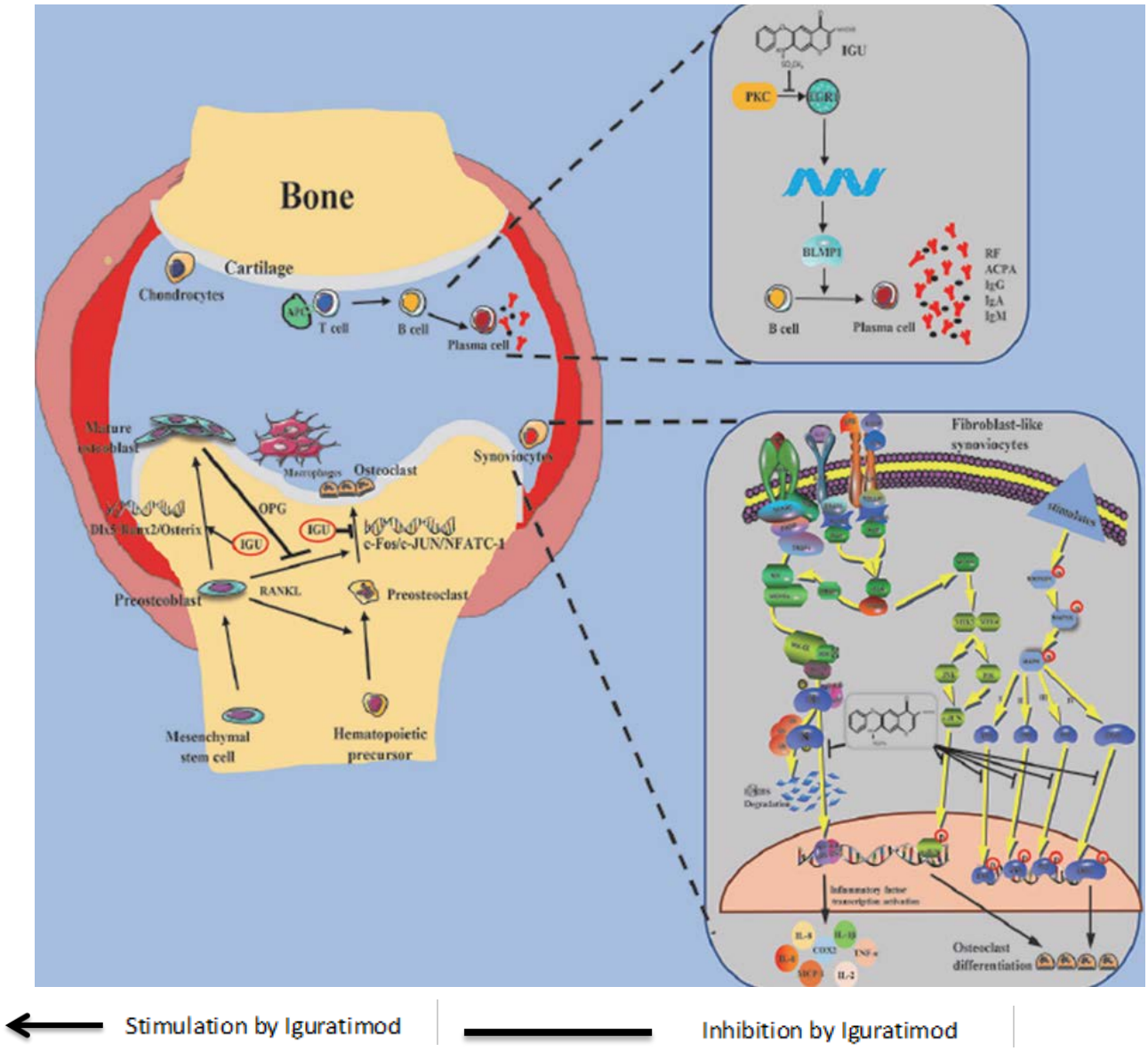

Fig 1: Pharmacological actions of Iguratimod [21]

COX- 2: Cyclooxygenase-2; IL: Interleukin, TNF-α: Tumor necrosis factor- α; NF-κB: Nuclear factor kappa-light-chain-enhancer of activated B cells

Adapted from: Xie S, Li S, Tian J, Li F. Iguratimod as a New Drug for Rheumatoid Arthritis: Current Landscape. Front Pharmacol. 2020 Feb 26;11:73.

Iguratimod: Clinical efficacy and safety in RA treatment

Phase I clinical study

Phase I clinical trial conducted in healthy adult volunteers showed that IGU was well-tolerated at 3.125–50 mg dose range and caused no serious adverse reactions. No statistically significant variations were reported with respect to T_{max}, $T_{1/2}$, K_a, and V/F between IGU at doses of 25, 50, and 75 mg. $AUC_{0\text{-last}}$ and C_{max} were in linear range at doses from 25-75 mg. No accumulation of drug was reported at repeated administration. Food intake had no effect on the bioavailability of IGU and was able to promote the absorption of IGU [22].

Multi-centre clinical studies

In a 24-week, multi-centre, randomized, double-blind, placebo-controlled study, 280 patients were randomly assigned to receive placebo (n = 95) or IGU at 50 mg (n = 93) or 25 mg (n = 92) daily. Within 8 weeks of treatment, American College of Rheumatology (ACR) 20, ACR50, and ACR70 scores were significantly higher in IGU treatment groups than in placebo group. At the end of 24 weeks of treatment, ACR 20 among IGU groups of 25 mg/d was 39.13%, 50 mg/d was 61.29% and placebo was 24.21%, whereas, ACR50 was 23.91 for 25 mg/d, 31.18 for 50 mg/d, and 7.37% for placebo groups. Significant difference was

reported in erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) between the two dosages of treatment group. The incidence of adverse reactions was greater IGU treated groups than in placebo treated group; however, the incidence was insignificant [23].

A 28-week, multi-centre, randomized, double-blind study reported that IGU (50 mg/d) was superior to placebo in ACR 20 (53.8% vs. 17.2%; P <0.001) and non-inferior to salazosulfapyridine (SASP) (63.1% *vs.* 57.7%, 95% confidence interval (CI) −7.9%~18.7%). no significant difference in the incidence of adverse events and adverse reactions between IGU and SASP (P > 0.05) were noted [24]. Another multi-centre, randomized, double-blind, controlled trial reported that after 24-weeks, the ACR 20 was not statistically significantly different between methotrexate (MTX) treated group and IGU treated group. However, side-effects were fewer and milder in IGU treated group compared to MTX treated group. IGU was reported to be safe, effective, well-tolerated, and non-inferior to MTX in treatment of patients with RA [25].

Post marketing surveillance and other clinical studies

A 52-week post-marketing surveillance study conducted in Japanese and mid-term safety analysis of 2,679 patients at week 24. The total incidences of adverse events (AEs) were 38.41%, adverse drug reactions (ADRs) were 31.65, and severe ADRs were 3.21%. The most common adverse reactions reported were liver dysfunction and gastrointestinal disease. Liver dysfunction events commonly reported was abnormal laboratory test values. The most common serious adverse reactions noted were bacterial pneumonia, interstitial lung disease, and pneumocystis pneumonia. When warfarin and IGU was used in combination, drug-drug interaction was produce resulting in serious adverse events, such as alveolar hemorrhage and elevated internationally standardized prothrombin time ratio (PT-INR). This suggested that IGU can improve anticoagulant activity of warfarin [26]. However, the adverse reactions peaked around 4 weeks of treatment. For next 28 weeks, frequency of adverse reactions decreased. IGU significantly reduced the levels of DAS28-CRP from baseline to 52 weeks, demonstrating the efficacy of IGU [27]. Another retrospective analysis conducted for 104 weeks reported early and sustained efficacy in group of IGU, and higher frequency of gastric bleeding or gastric perforation was reported in subjects administered NSAIDs and oral prednisolone compared to those receiving IGU [28]. In a clinical study, the 3-year survival rate with IGU alone was 40.6% [29].

Iguratimod in combination with other drugs

IGU+MTX

Two 24-week clinical studies both demonstrated that IGU combined with MTX had better outcomes than that of MTX alone. Various parameters such as Patient's clinical manifestations including joint tenderness and swollen joint count, pain visual analogue scale overall assessment of patients and physicians, ESR, CRP, health assessment questionnaire, DAS28, simplified disease activity index, and ACR 50 (p <0.05) improved significantly in combined group compared to MTX group alone Moreover, no significant difference in the incidence of adverse events were reported in IGU +MTX and MTX alone groups [30, 31]. MTX + IGU combination when studied in patients with active RA who had poor efficacy with MTX alone showed significantly better response with IGU + MTX combination than that of placebo plus MTX group at the end of 24 weeks (p <0.001) [32]. Another clinical study demonstrated that Efficacy and tolerance of iguratimod + MTX therapy was maintained to 52 weeks in patients with active RA with inadequate response to MTX. In the iguratimod + MTX group, significantly improvement was reported in ACR20 from 30.7% at week 24 to 72.1% at week 52. Frequently observed adverse events (mild to moderate severity) for 52 weeks within combination group were nasopharyngitis, upper respiratory tract inflammation, stomatitis, lymphocyte decrease, AST increase, ALT increase and blood iron decrease [33].

IGU + other DMARDS

A retrospective study conducted in patients with refractory RA reported a significant improvement in DAS-28, ESR, CRP, and health assessment questionnaire between the end of 24 weeks and baseline (P < 0.05) on treatment with MTX- Cyclosporin A-Hydroxychloroquine- Prednisone combined therapy and stable dose of IGU (25 mg twice a day). No serious adverse events were reported within 24 weeks of treatment [34].

IGU + bDMARDs

In a retrospective study, IGU when combined with biological DMARDs (bDMARDs) in patients with RA who responded inadequately to 24-week or longer with bDMARDs demonstrated a significant reduction in DAS28-ESR from baseline to 24 weeks (p < 0.001). Overall, clinical remission was achieved in 38.3% RA patients, and ultrasound investigations also demonstrated similar results in patients treated with combined therapy (p <0.001) [35]. Another multi-centre clinical study conducted in RA patients with unsatisfactory response to tocilizumab and other DMARDs (MTX, SASP, and tacrolimus), demonstrated that the addition of IGU may be effective complementary therapy. DAS28-CRP and clinical disease activity index improved significantly and 51.6% RA patients achieved ACR 20 at 24 weeks, on addition of IGU to other DMARDs [36].

Iguratimod *vs.* other DMARDS: Distinction based on various parameters

IGU can be distinguished from other DMARDs on the basis of mechanism of action, cytostatic effect, steroid sparing effects, anabolic effects, etc. The effects of IGU based on these parameters are demonstrated in Table 1 [37- 51].

Conclusion

IGU plays an important role as an immunomodulator in patients with RA. IGU possesses significant effects such as inhibition of immunoglobulins and cytokines and regulation of T lymphocyte subsets. IGU significantly regulates bone metabolism by stimulating bone formation while inhibiting osteoclast differentiation, migration, and bone resorption. In clinical trials, IGU was reported to be superior to placebo and non-inferior to other DMARDs. Combining IGU with other DMARDS or b DMARDS produced significant reduction in inflammation and improved the RA conditions in patients not responding monotherapies. Moreover, compared to other DMARDs, IGU shows steroid sparing

effect and anabolic effects. IGU administration does not require the use of NSAIDS or folic acid supplementation.
Thus, IGU can be considered as a promising molecule for treatment and management of patients with RA. IGU can be used as a monotherapy or combined with other DMARDs to reduce the RA associated complications in patients. IGU may prove to be treatment of choice for RA patients in near future.

Acknowledgement
Author acknowledges the contribution of Ms. Richa Deliwala, M. Pharm (Pharmacology) for her contribution in doing literature search & helping with the preparation of manuscript.

Financial Disclosure or Funding: Nil

Author Contributions: Prepared and reviewed the article.

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