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A review on Iguratimod: Bridging Hope for Arthritis Patients through the Dual Power of Immunomodulation and Anti-inflammation

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Iguratimod is a small novel compound considered as a disease-modifying anti-rheumatic drug (DMARD), which exhibits anti-inflammatory and immunomodulatory effects. Iguratimod acts directly on B cells by inhibiting the production of inflammatory cytokines (tumor necrosis factor-α, interleukin (IL)-1β, IL-6, IL-8, IL-17), thereby suppressing the production of immunoglobulin and inhibiting the activity of nuclear factor kappa-light chain enhancer of activated B cells. Preclinical studies demonstrate its positive impact on arthritis models in animals by reducing immunoglobulin production and various inflammatory cytokines. Iguratimod demonstrates its efficacy as well as tolerance when used as an additional therapy for rheumatoid arthritis patients who exhibit an insufficient response to both methotrexate and biological disease-modifying anti-rheumatic drugs.

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Additionally, iguratimod was found to possess an anabolic effect on bone metabolism, through both stimulations of osteoblastic differentiation and inhibition of osteoclastogenesis.
Further, the mechanism also involves suppressing nuclear factor kappa B (NF-κB) activation without blocking NF-κB inhibitor α (IκBα) degradation. Although the true target molecules of iguratimod have been unclear, it would be necessary to suppose the multiple mechanisms including suppression of NF-κB. Clinical trials of rheumatoid arthritis patients have shown more effectiveness and tolerability when compared to salazosulfapyridine, making iguratimod a promising DMARD with unique novel properties and positive clinical outcomes. Further research will determine its suitability as an alternative for patients unable to use biologics.

Keywords: Anti-inflammation; iguratimod; arthritis; immunomodulation.

1. INTRODUCTION

1.1 Rheumatoid Arthritis

"Rheumatoid arthritis (RA) is a persistent autoimmune disorder with an unknown cause, marked by synovial inflammation in the joints, gradual bone damage, and a decline in joint functionality. In the absence of treatment, deteriorating joints can result in pain and stiffness, which limit physical function and lead to long-term disability" [1]. "The development of RA is associated with genetic, environmental, and immune factors. The objective of treating individuals with RA is to achieve clinical remission or maintain low disease activity, ultimately preventing damage to joint function, Current treatments for RA include non-steroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), and biological disease-modifying anti-rheumatic drugs (bDMARDS). the use of biological DMARDs to treat RA is not suitable for all patients for various reasons, including complications, side effects, uncertain efficacy, and high costs that prevent their use" [2].

1.2 Iguratimod

"Iguratimod, is a small novel compound considered as a disease-modifying anti-rheumatic drug (DMARD), which exhibits anti-inflammatory and immunomodulatory effects.IGU suppresses the production of inflammatory cytokines in cultured monocyte THP-1 cells and synovial cells derived from RA patients by inhibiting the activation of nuclear factor kappa-B (NF-κB)" [3]. "Additionally, it hinders immunoglobulin production through a direct impact on B cells without inducing cytostatic effects" [4]. "IGU exhibits anti-inflammatory effects and improves abnormal immunological conditions in various animal models of inflammation and autoimmune diseases, including RA" [5,6]. "Recently, it has been noted that IGU inhibits receptor activator of NF-κB ligand (RANKL)-induced osteoclast differentiation and migration in RAW264 cells by modulating the NF-κB and mitogen-activated protein kinase (MAPK) pathways. This finding is especially intriguing in relation to its stimulatory effect on osteoblastic differentiation" [7].

2. MECHANISM OF IGURATIMOD

2.1 Anti-Inflammatory

"Iguratimod possesses anti-inflammatory properties, as demonstrated by its ability to restrain the release of bradykinin in a mouse model of kaolin-induced arthritis. Initially created as an innovative nonsteroidal anti-inflammatory drug (NSAID)" [8]. Research has extensively documented the anti-inflammatory, analgesic, and antipyretic properties of Iguratimod in diverse animal models. Its mechanism involves suppressing the metabolism of arachidonic acid metabolite prostaglandin E2 [9], inhibiting the release of bradykinin, decreasing the production of interleukin (IL)-1 and interleukin (IL)-6 [10,11], and selectively inhibiting the activity of cyclooxygenase-2 [12]. "In different models of autoimmune disorders, Iguratimod demonstrated notable inhibitory effects. These effects were observed in experimental autoimmune encephalitis, chronic contractile injury linked with neuropathic pain, and dextran sodium sulfate-induced colitis" [4,12-20]. "Significantly, iguratimod's ability to selectively inhibit COX-2 is crucial, leading to a reduction in prostaglandin levels and accomplishing its anti-inflammatory effects. Importantly, iguratimod is less prone to causing gastrointestinal ulcers because of its selective inhibition of COX-2, distinguishing it from nonsteroidal anti-inflammatory drugs (NSAIDs) that inhibit both COX-1 and COX-2"

[12]. “Iguratimod also hampers the secretion of inflammatory cytokines induced by TNF-α and curtails NF-κB activation in human synovial cells. This interference includes impeding the translocation of NF-κB P65 into the nucleus. Through the inhibition of NF-κB activity, it modulates transcriptional regulation to suppress the production of cytokines and chemokines, thereby exerting anti-inflammatory effects” [16,17]. “Iguratimod has been observed to disrupt the TNF-α-induced translocation of NF-κB from the cytoplasm to the nucleus. This interference leads to the inhibition of TNF-α-induced production of IL-6, IL-8, and monocyte chemoattractant protein 1. Hence, iguratiomud has the potential to modulate the expression of inflammatory factors by regulating the NF-κB signaling pathway” [18]. “In the regulation of neutrophils, it has been discovered that Iguratimod suppressed the expression of CPs by downregulating PAD in neutrophils from RA patients. Notably, this effect was comparable to the impact of MTX and DXM at suitable concentrations. These results offer valuable insights for refining the treatment of rheumatoid arthritis (RA). Iguratimod, at an optimal concentration comparable to MTX and dexamethasone, effectively hinders the expression of citrulline proteins in neutrophils from RA patients. This inhibitory effect is attributed to the downregulation of peptidyl arginine deiminase, shedding light on the mechanism of Iguratimod in RA treatment. The findings from this study can provide valuable guidance for the treatment of rheumatoid arthritis and facilitate the identification of additional therapeutic targets” [19].

2.2 Immune Response

2.2.1 Regulating humoral immunity

“In 2003, researchers initially observed that IGU had a direct inhibitory impact on B lymphocytes in both mouse and human subjects, leading to a decrease in the synthesis of immunoglobulins. Notably, this inhibition did not influence the proliferation or apoptosis of B cells [4]. In MRL/LPR mice, IGU demonstrated the ability to decrease circulating plasma cells through a mechanism that does not involve anti-proliferative effects” [21]. “In a recent study, it was shown that IGU did not influence the activation and proliferation of B cells within the established in vitro human antibody-secreting cell differentiation system. However, its inhibitory effects were observed in the differentiation of human antibody-secreting cells, achieved by targeting the protein kinase C (PKC) and early growth response 1 (EGR1) axis” [22].

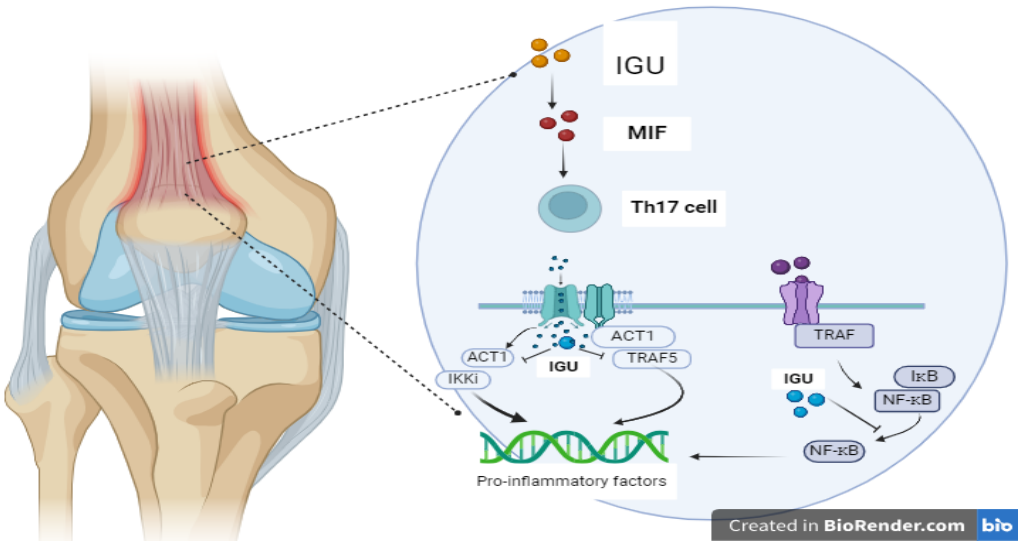

Fig. 1. Depicts the anti-inflammatory mechanism of IGU (Iguratimod)

IGU effectively suppresses inflammation through several pathways. Firstly, it inhibits the activity of MIF (macrophage migration inhibitory factor) and counteracts MIF-induced proinflammatory effects. Additionally, IGU disrupts IL-17-mediated signaling by interfering with the interaction between Act1 and TRAF5, as well as IKKi, thereby reducing the expression of various inflammatory factors induced by IL-17. Moreover, IGU interferes with the TNF-α-induced translocation of NF-κB from the cytoplasm to the nucleus, consequently suppressing the production of IL-6 and IL-8 induced by TNF-α

2.2.2 Suppression of immunoglobulin synthesis

"In subsequent clinical trials, it was noted that iguratimod exhibited favorable therapeutic outcomes concerning both clinical symptoms and biological markers, including rheumatoid factor (RF) levels and immunoglobulin concentrations in plasma. Consequently, our investigations were directed toward assessing its impact on B-cell functions, particularly about immunoglobulin production and proliferation. In cultures of murine B-cells, iguratimod exhibited a notable reduction in IgM production and the isotype-switch to IgG1 class induced by lipopolysaccharide (LPS) and/or IL-4. Additionally, it inhibits spontaneous IgG production without affecting cell proliferation in a human plasmacytoma cell line (ARH-77). Moreover, when human peripheral B cells were stimulated with autologous T cells and anti-CD3 antibody, iguratimod demonstrated a concentration-dependent inhibition of both IgM and IgG production" [4].

In contrast, iguratimod did not exhibit any influence on the mitogen-induced proliferation response [23,24] and thymus and activation-regulated chemokine (TARC) production in human B cells stimulated with anti-CD40 antibody and IL-4 [25]. Hence, it seems that this compound hinders the production of immunoglobulins by B cells without causing a cytostatic effect.Subsequently, to elucidate the hyper-immunoglobulinemia observed in rheumatoid arthritis (RA) patients and the inhibitory effects of iguratimod, we examined the secretion of immunoglobulins from RA synovial tissues. The experimentation was conducted utilizing severe combined immune deficiency (SCID) mice that were implanted with human rheumatoid arthritis (RA) tissue.Consequently, the sera of the mice exhibited elevated concentrations of polyclonal human IgG. Furthermore, the iguratimod-treated group demonstrated a noteworthy reduction in IgG levels compared to the group treated with the vehicle. In chronic arthritis models such as adjuvant-induced arthritis (AIA) rats and MRL/lpr mice [11], the alleviation of arthritic lesions by iguratimod was concomitant with the improvement of hyperimmunoglobulinemia [3,26]. About the clinical effectiveness of B-cell-targeted anti-CD20 antibody in rheumatoid arthritis (RA) patients, [27] these findings hold significant importance in understanding the mechanisms behind the anti-rheumatic effects exhibited by small molecule disease-modifying antirheumatic drugs (DMARDs).

2.2.3 Suppression of cytokine synthesis

"Another clear difference between iguratimod and classical NSAIDs is the inhibitory effect on cytokine production, as mentioned above. When tested on cultured monocytes/macrophages, iguratimod demonstrated the ability to inhibit the production of IL-1β, TNFα, IL-6, IL-8, and monocyte chemoattractant protein-1 (MCP-1) with IC50 values ranging from 1 to 20 μg/mL" [28-31]. "In synovial cells obtained from rheumatoid arthritis (RA) patients, iguratimod markedly decreased the synthesis of IL-6, IL-8, and colony-stimulating factors (CSFs) within concentration ranges of 0.3 to 30 μg/mL" [28,32,33]. "The suppression of mRNA expression coincided with iguratimod's inhibitory effect on the production of these cytokines"(29,31,33). Therefore, it is reasonable to suggest that iguratimod suppresses the expression of inflammatory cytokines at the gene level. Additionally, the research findings demonstrate [32] that iguratimod also impedes the increased expression of co-stimulatory molecules like CD54, CD58, and CD106 in synovial cells upon stimulation with IFN-γ. "This mechanism of action seems to involve the prevention of nuclear factor-kappa B (NF-κB) activation. The inhibitory effect on cytokine production was similarly observed in animal models. In a mouse air-pouch inflammation model, oral administration of iguratimod at doses of 30 and 100 mg/kg significantly decreased MCP-1 production induced by TNFα injection" [29]. "Moreover, at doses of 10 and 30 mg/kg, iguratimod reduced the rise in serum TNFα and IFN-γ levels in the concanavalin A-induced hepatitis model in mice, along with serum transaminase levels" [29]. "Iguratimod was also found to suppress the onset of active experimental autoimmune encephalomyelitis (EAE) in rats" [33]. "In this model, it was observed to inhibit TNFα and IFN-γ production by antigen-specific T cells and the infiltration of cells into the spinal cord of rats. Notably, iguratimod exhibited an anti-cachectic effect on adenocarcinoma colon-induced cachexia in mice by inhibiting IL-6 gene expression" [34]. "Furthermore, recent reports indicate that CIA rats treated with iguratimod showed reductions in mRNA expression of IL-17 in peripheral lymphocytes and circulating IL-17, suggesting that the compound exerts its immunoregulatory and bone-preserving effects by shifting responses away from IL-17-producing T cells (Th17 cells)" [35]. These findings suggest that iguratimod's inhibition of cytokine production may

contribute to its clinical efficacy in treating rheumatic conditions, making it a characteristic feature of this drug.

2.3 Osteoprotective Mechanism

"Osteoporosis frequently arises as a secondary consequence of rheumatoid arthritis (RA), potentially resulting in joint stiffness, malformation, and significant impairment in functionality. Employing early and efficient measures to safeguard bone health and enhance bone metabolism can be advantageous in thwarting joint deterioration.Several signaling pathways are crucial for osteoblast proliferation, differentiation, and the regeneration of damaged bone and cartilage. These include the bone morphogenetic protein (BMP)2–Smads pathway, the p38 mitogen-activated protein kinase (MAPK) pathway, and the TNF-α/NF-κB pathway.Research has demonstrated that IGU enhances the expression of osterix (Osx), a key factor in osteoblast differentiation. BMP2 has the ability to stimulate Osx expression by inducing the upstream transcription factor Dlx5. Additionally, the p38–MAPK pathway collaborates with the BMP2–Smads pathway to enhance Osx phosphorylation" [36].

"IGU has been found to boost osteoblast differentiation by upregulating the expression of Osx and Dlx5" [37]. "The p38 MAPK belongs to the MAPK superfamily and plays a role in the initial phases of osteoblast lineage proliferation by phosphorylating Dlx5, runt-related transcription factor (Runx)2, and Osx (36). IGU has the potential to enhance the activation of p38, thereby promoting osteoblastic differentiation. Additionally, the TNF-α/NF-κB signaling pathway is implicated in osteoblast proliferation, apoptosis, and differentiation" [38]. NF-κB facilitates the deterioration of osteocytes by diminishing the expression and phosphorylation of the BMP-Smad1 signaling pathway. IGU has the capacity to sustain decreased NF-κB activation, thus mitigating the inhibitory effects of TNF-α on osteoblasts.

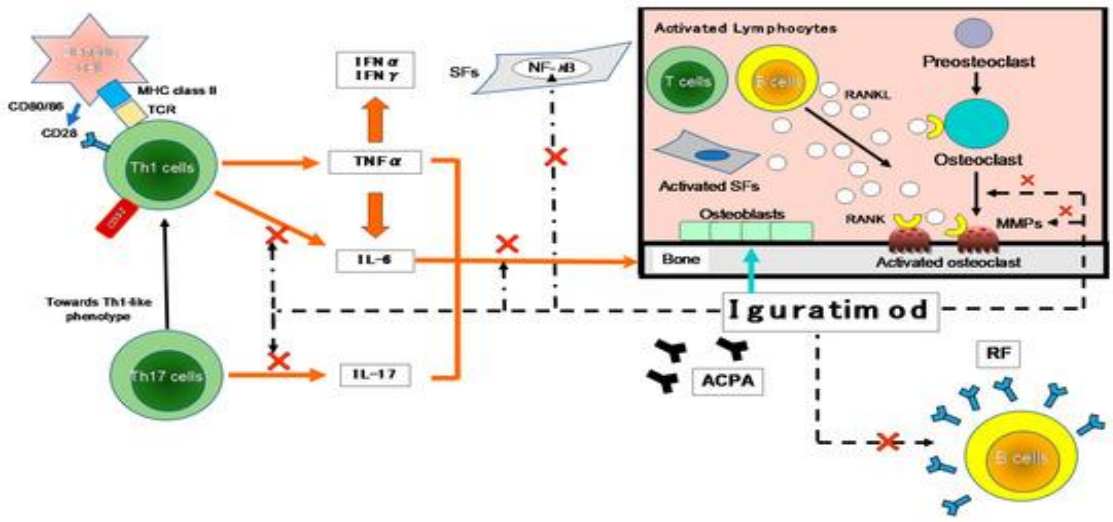

Fig. 2. Illustrates the inhibitory effects of IGU on the immune response, particularly in the context of rheumatoid arthritis (RA)

In RA, the initial interaction between Th1 cells and antigen-presenting cells (APCs), such as dendritic cells, involves T-cell receptors (TCRs) and major histocompatibility complex (MHC). Various environmental factors influence the production of autoantibodies like anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF). These immune complexes activate synovial fibroblasts (SFs) and macrophages, leading to the production of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and IL-6. Additionally, they affect Th17 cells, which produce IL-17, further contributing to joint destruction. IGU intervenes in this process by impacting the production of pro-inflammatory cytokines in both Th1 and Th17 cells, as well as affecting the production of immunoglobulins and antibodies in B cells. It also influences bone metabolism by inhibiting osteoclast activation and promoting osteoblast differentiation. NF-κB, a central player in the pathogenesis of RA, perpetuates the chronic cycle of inflammation underlying its pathology. Inflammatory mediators like TNF-α activate cells in the synovium, particularly macrophages and SFs, largely through NF-κB activation. SFs, in response to TNF-α or IL-1, synthesize many NF-κB-induced genes, including chemokines and matrix metalloproteinases (MMPs), which further promote inflammation and joint destruction

"Additionally, IGU fosters the formation of calcium nodules in vitro" [37]. "Osteoclast differentiation is primarily regulated by two essential cytokines: macrophage colony-stimulating factor (M-CSF) and receptor activator of nuclear factor kappa-B ligand (RANKL)" [39]. "The RANKL/osteoprotegerin (OPG) system is crucial in bone erosion associated with rheumatoid arthritis (RA). An increase in the RANKL/OPG ratio contributes to bone erosion. IGU has the ability to reduce the production of RANKL, leading to a significant decrease in the RANKL/OPG ratio both in serum and in RA fibroblast-like synoviocytes (FLSs) induced by IL-1β after treatment" [40]. "RANKL and its receptor RANK interact with osteoclast precursor cells, initiating downstream pathways such as peroxisome proliferator-activated receptor (PPAR)-γ, c-Fos, and nuclear factor of activated T cells (NFAT)c1" [41]. "IGU has the ability to inhibit osteoclast formation and bone resorption stimulated by RANKL through the PPARγ/c-Fos signaling pathway. Furthermore, it decreases the expression of NFATc1 and subsequent osteoclast marker genes" [42].

Gan et al. found that "IGU effectively inhibited RANKL-induced osteoclast differentiation, migration, and bone resorption in RAW264.7 cells, with the effect varying depending on the dosage administered". "This effect was attributed to the activation of the MAPK and NF-κB pathways" [43]. "it indicates that IGU directly suppresses the formation and activity of osteoclasts. Additionally, the TNF-α/NF-κB signaling pathway inhibit the production of matrix metalloproteinases (MMPs)" [38]. "MMPs are pivotal in the degradation of cartilage in rheumatoid arthritis (RA), predominantly synthesized by fibroblast-like synoviocytes (FLSs). Du et al. conducted in vitro experiments treating FLSs with varying concentrations of IGU, followed by stimulation with TNF-α, IL-1β, or IL-17A. They observed a significant inhibition of MMP-3 at 5 μg/ml IGU, while MMP-1 inhibition occurred at 50 μg/ml. Clinical trials revealed a significantly reduction in MMP-1 and MMP-3 levels following 24 weeks of IGU treatment (25 mg, twice daily)" [44]. These findings indicate that IGU effectively prevents MMP-1 and MMP-3, thus preserving cartilage integrity. Moreover, OPG serves as a natural antagonist to RANKL, preventing its binding to the osteoclast receptor. The equilibrium between RANKL and OPG is critical for sustaining osteoclast homeostasis [45].

IGU can suppress the expression of MMP-3 and the RANKL/OPG ratio by inhibiting the phosphorylation of ERK1/2, consequently thwarting the degradation of bone in rheumatoid arthritis [46]. IGU not only enhances osteoblast differentiation but also suppresses osteoclast formation and the production of matrix proteins through its interaction with various signaling pathways. Consequently, IGU plays a crucial role in safeguarding bone health. Fig. 3 illustrates the intricate adjustments made by IGU within the signaling pathways.

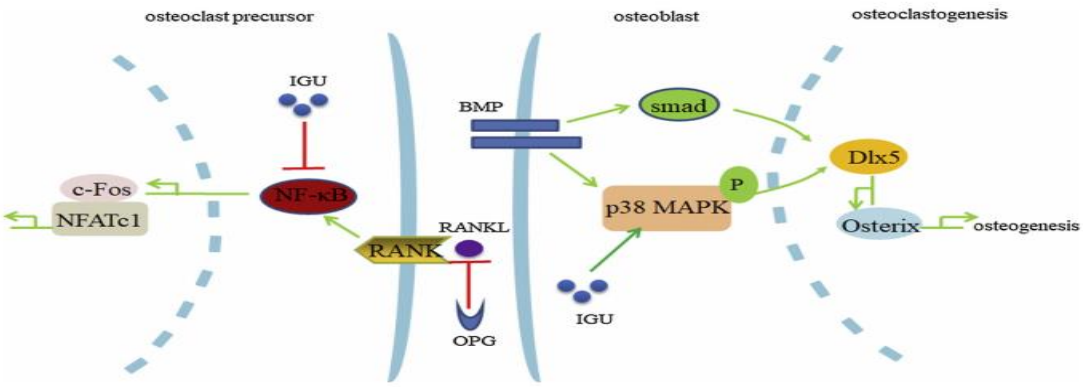

Fig. 3. Illustrates the osteoprotective mechanism of IGU, highlighting its impact on various signaling pathways crucial for osteoblast proliferation, differentiation, and bone/cartilage repair

These pathways include the BMP2-Smads signaling pathway, the P38-MAPK pathway, and the NF-κB pathway. IGU, or Iguratimod, facilitates osteoblast differentiation by upregulating the expression of Osx and its upstream regulator Dlx5, while also enhancing P38 activation. Furthermore, IGU inhibits osteoclastogenesis and bone resorption induced by RANKL via the PPARγ/c-Fos signaling pathway. Additionally, IGU decreases the expression of nuclear factor in activated T cell c1 and downstream osteoclast marker genes

3. PROGRESS IN CLINICAL RESEARCH

Numerous clinical trials have validated IGU as a promising novel treatment for rheumatoid arthritis (RA). Phase I, II, and III trials have demonstrated the effectiveness and safety of IGU monotherapy over a span of 24 weeks. Typically, IGU exhibits its therapeutic effects within 8 weeks, demonstrating a faster onset compared to methotrexate (MTX). IGU treatment exhibits early and sustained efficacy. Furthermore, the efficacy of a 50 mg dosage of IGU (25 mg twice daily) is comparable to that of a 15 mg dose of MTX (15 mg per week).

A multicenter, prospective observational study was conducted to assess the long-term safety and efficacy of IGU in rheumatoid arthritis (RA) patients. The study enrolled all eligible RA patients who had been treated with IGU since its introduction to the market in 2012. Efficacy was evaluated using Disease Activity Score 28 (DAS28), while adverse drug reactions such as liver and renal dysfunction, interstitial lung disease, gastrointestinal and blood disorders, and infections were monitored up to week 52. The findings indicated that extended use of IGU demonstrated a manageable safety profile and led to enhanced control of rheumatoid arthritis (RA) activity. Additionally, another study assessing the 3-year efficacy of IGU in RA patients confirmed its effectiveness and safety. These outcomes suggest that IGU can be utilized for prolonged treatment durations.

Methotrexate (MTX) serves as a cornerstone in the management of rheumatoid arthritis (RA), often forming the foundation of treatment. Typically, RA management entails a combination of several anti-rheumatic medications. Consequently, the combination of IGU with MTX has become a prevalent and novel therapeutic approach for RA.

Ren et al. conducted a randomized study involving 82 patients, dividing them into two groups. The control group received MTX at a dose of 10 mg once weekly, which was escalated to 15 mg once weekly after 2 weeks. The observation group received IGU at a dose of 25 mg twice daily in addition to the regimen followed by the control group, over a period of 6 months. The total effective rate in the observation group was 90.24%, markedly surpassing that of the control group, which stood at 78.05% [41]. The findings indicated that IGU enhances the therapeutic efficacy of MTX.

When used in conjunction with leflunomide (LEF) for rheumatoid arthritis (RA) treatment, methotrexate (MTX) frequently leads to an increased incidence of adverse reactions. In the Tranmod Study, 66 patients with refractory rheumatoid arthritis (RA) were randomly assigned to two groups. The observation group received a combination of methotrexate (MTX) at a dose of 10 mg once weekly and iguratimod (IGU) at a dose of 25 mg twice daily, while the control group received MTX (10 mg once weekly) combined with leflunomide (LEF) at a dose of 10 mg once daily for a duration of 16 weeks. Results showed that both groups experienced reductions in Disease Activity Score 28 (DAS28) scores compared to before treatment. At 8 weeks, there was a significant difference between the two groups in terms of achieving American College of Rheumatology (ACR)20 and ACR50 response criteria. However, by 16 weeks, there was no significant difference in ACR20, ACR50, and ACR70 response rates between the two groups. Compared to the combination of MTX and LEF, the combination of MTX and IGU demonstrated superior short-term clinical efficacy and fewer adverse reactions in RA patients. Furthermore, IGU is frequently employed in conjunction with biological agents like tocilizumab and etanercept. This underscores the versatility of IGU, as it can be combined with various anti-rheumatic medications for the treatment of rheumatoid arthritis (RA).

In real-world clinical scenarios, certain rheumatoid arthritis (RA) patients exhibit insufficient response to multiple disease-modifying antirheumatic drugs (DMARDs). A study verified that the effectiveness and tolerability of IGU in combination with MTX therapy persisted for a duration of up to 52 weeks in active RA patients who had shown inadequate response to MTX alone. In another study, 131 patients previously treated with traditional disease-modifying antirheumatic drugs (DMARDs) were divided into three groups. Group 1 consisted of 44 patients treated with a combination of IGU (25 mg, twice daily, orally) and MTX (10 mg weekly, orally). Group 2 included 38 patients who received IGU alone (25 mg twice daily, orally), while Group 3 comprised 49 patients who received MTX alone (10 mg weekly, orally). Therapeutic effects with IGU were observed between 4 and 10 weeks after treatment initiation, effectively addressing patients with inadequate responses to prior DMARD treatments. The combination of IGU with MTX exhibited superior efficacy compared to IGU

or MTX monotherapy. IGU has demonstrated supplementary effectiveness in rheumatoid arthritis (RA) patients who exhibit inadequate responses to methotrexate (MTX). Consequently, combining IGU with MTX presents a promising emerging approach for treating active RA in individuals who have either inadequate responses to or intolerance to traditional disease-modifying antirheumatic drugs (DMARDs). Moreover, IGU has shown additional effectiveness and safety in RA patients who demonstrate inadequate responses to biological DMARDs, such as tocilizumab.

Wang et al. conducted a self-controlled study involving 20 rheumatoid arthritis (RA) patients with leukopenia to address the challenge of clinical drug selection due to the myelosuppressive adverse effects of many disease-modifying antirheumatic drugs (DMARDs). They administered IGU (25 mg twice daily) in combination with methylprednisolone (Medrol; 8 mg once daily) during the early stage of the disease. As white blood cell counts returned to normal with the help of hormones during the mid-stage, MTX was added to the regimen (7.5 mg once weekly), and methylprednisolone was gradually discontinued. Subsequently, IGU (25 mg twice daily) and MTX (7.5 mg once weekly) were employed as long-term maintenance therapy for a duration of 12 weeks. Results indicated improvements in erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), Disease Activity Score 28 (DAS-28), and white blood cell counts compared to pre-treatment levels. The ACR20 and ACR50 response rates were 85% and 45%, respectively, and the overall rate of leukocyte elevation was 95%. Only one case experienced mild liver damage during the treatment period, which resolved with liver protection treatment without discontinuing anti-rheumatic therapy. This underscores the favorable therapeutic efficacy and high safety profile of phased treatment with IGU, methylprednisolone, and MTX in RA patients with leukopenia.

The aforementioned clinical trials have established that IGU is a valuable choice as an initial treatment for rheumatoid arthritis (RA), demonstrating notable effectiveness and safety whether used independently or in combination with other medications.

4. CONCLUSION

RA is a chronic autoimmune disorder characterized by synovial inflammation, joint damage, and decreased joint function. Treatment goals include achieving remission or low disease activity to prevent further joint damage. Iguratimod exerts its anti-inflammatory effects by inhibiting NF-κB activation, cytokine production, and COX-2 activity. It regulates humoral immunity by inhibiting immunoglobulin synthesis and B cell differentiation. Iguratimod's osteoprotective mechanism involves enhancing osteoblast differentiation and inhibiting osteoclast formation and activity.Clinical trials have demonstrated the efficacy and safety of iguratimod in RA treatment, both as monotherapy and in combination with other DMARDs. Combining iguratimod with methotrexate or other DMARDs has shown superior efficacy compared to monotherapy. Iguratimod has shown promise in patients with inadequate responses to traditional DMARDs or biological agents.Phased treatment with iguratimod, methylprednisolone, and methotrexate has been effective in RA patients with leukopenia. Iguratimod is a valuable treatment option for RA, offering early and sustained efficacy with a manageable safety profile. Its mechanism of action, including anti-inflammatory, immunomodulatory, and osteoprotective effects, makes it a promising candidate for RA therapy.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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