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IGURATIMOD: A COMPREHENSIVE REVIEW OF ITS MECHANISM, CLINICAL APPLICATION AND ANALYTICAL METHOD DEVELOPMENT

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ABSTRACT

Iguratimod (IGU) is a novel synthetic small molecule Disease-Modifying Anti-Rheumatic Drug (DMARD) approved in Japan and China for rheumatoid arthritis (RA). IGU demonstrates unique immunomodulatory properties by inhibiting cytokine production, regulating T lymphocyte subsets, and promoting bone formation while inhibiting bone resorption. This review explores IGU's mechanisms of action, including its anti-inflammatory, immune-regulatory, and bone metabolism-modulating effects. Clinical studies highlight IGU's efficacy and tolerability, particularly in combination therapies for patients unresponsive to standard treatments. Additionally, this article discusses recent advancements in analytical methods for IGU, including HPTLC, UPLC-MS/MS, and HPLC, which enhance its pharmacokinetic and pharmacodynamic evaluations. Future translational studies may broaden IGU's applications to autoimmune conditions beyond RA, cementing its role in innovative therapeutic strategies.

KEYWORDS: Rheumatoid arthritis, Iguratimod, Clinical application, Analytical methods.

INTRODUCTION

1. Rhemautic arthritis: Rheumatoid arthritis is a chronic inflammatory disorder that can affect more than just your joints. In some people, the condition can damage a wide variety of body systems, including the skin, eyes, lungs, heart and blood vessels.[1]

An autoimmune disorder, rheumatoid arthritis occurs when your immune system mistakenly attacks your own body's tissues.

Unlike the wear-and-tear damage of osteoarthritis, rheumatoid arthritis affects the lining of your joints, causing a painful swelling that can eventually result in bone erosion and joint deformity.

The inflammation associated with rheumatoid arthritis is what can damage other parts of the body as well. While new types of medications have improved treatment options dramatically, severe rheumatoid arthritis can still cause physical disabilities.

Signs and symptoms of rheumatoid arthritis may include.

- Tender, warm, swollen joints
- Joint stiffness that is usually worse in the mornings and after inactivity
- Fatigue, fever and loss of appetite

Early rheumatoid arthritis tends to affect your smaller joints first — particularly the joints that attach your fingers to your hands and your toes to your feet.

As the disease progresses, symptoms often spread to the wrists, knees, ankles, elbows, hips and shoulders. In most cases, symptoms occur in the same joints on both sides of your body.

About 40% of people who have rheumatoid arthritis also experience signs and symptoms that don't involve the joints. Areas that may be affected include.

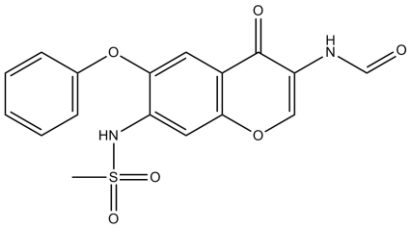
- Skin
- Eyes
- Lungs
- Heart
- Kidneys
- Salivary glands
- Nerve tissue
- Bone marrow
- Blood vessels

Rheumatoid arthritis signs and symptoms may vary in severity and may even come and go. Periods of increased disease activity, called flares, alternate with periods of relative remission — when the swelling and pain fade or

disappear. Over time, rheumatoid arthritis can cause joints to deform and shift out of place.[2]

2. Iguratimod: Iguratimod is a synthetic anti-rheumatoid drug used to treat rheumatoid arthritis. Iguratimod (IGU or T-614) is a novel synthetic small molecule disease modified anti-rheumatic drug approved only in Japan and China. 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 Ikappa Balpa in lipopolysaccharide-stimulated THP-1 cells (human monocytic leukemia cell line).[3] Similar results were also confirmed in cultured human synovial cells and the rat alveolar macrophage.[4][5] Other studies in macrophages and microglia showed that IGU inhibited nuclear translocation of NF-κB 65 and pro-inflammatory response.[6] Based on the above evidences, IGU is widely used as a new csDMARD in China and Japan for RA treatment possibly by directly inhibiting the production of immunoglobulins and a variety of inflammatory cytokines.[7] In addition, IGU can promote bone formation and inhibit bone resorption.[8][9]

Iguratimod structure



- Molecular Formula: $C_{17}H_{14}N_2O_6S$
- Average mass: 374.368 g/mol

MECHANISAM OF ACTION OF IGURATIMOD(IGU)[11][12]

Anti-Inflammation and Analgesia: IGU was originally developed as a novel NSAIDs. In 1992, the anti-inflammatory, analgesic, and antipyretic effects of IGU in different animal models, and the mechanism was related to the inhibition of the metabolism of arachidonic acid metabolite prostaglandin E2, the inhibition of the release of bradykinin, the production of interleukin (IL)-1 and IL-6, and selective inhibition of the activity of cyclooxygenase-2. In some autoimmune disease models, IGU exhibited significant inhibitory effects in experimental autoimmune encephalitis, chronic contractile injury with neuropathic pain, and dextran sulphate sodium-induced colitis. 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-g, IL-1b, 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. In addition, IGU inhibited the upregulation of IL-6, IL-8, and monocyte chemoattractant protein 1 induced by tumor necrosis factor alpha (TNF-a) in RA synovial cells in a concentration dependent manner.

Regulation of Immune Response: CD4 + T cells and activated B lymphocytes play an important role in the chronic inflammation of RA. IGU can exert immunomodulatory effects on these cells during the progression of RA.

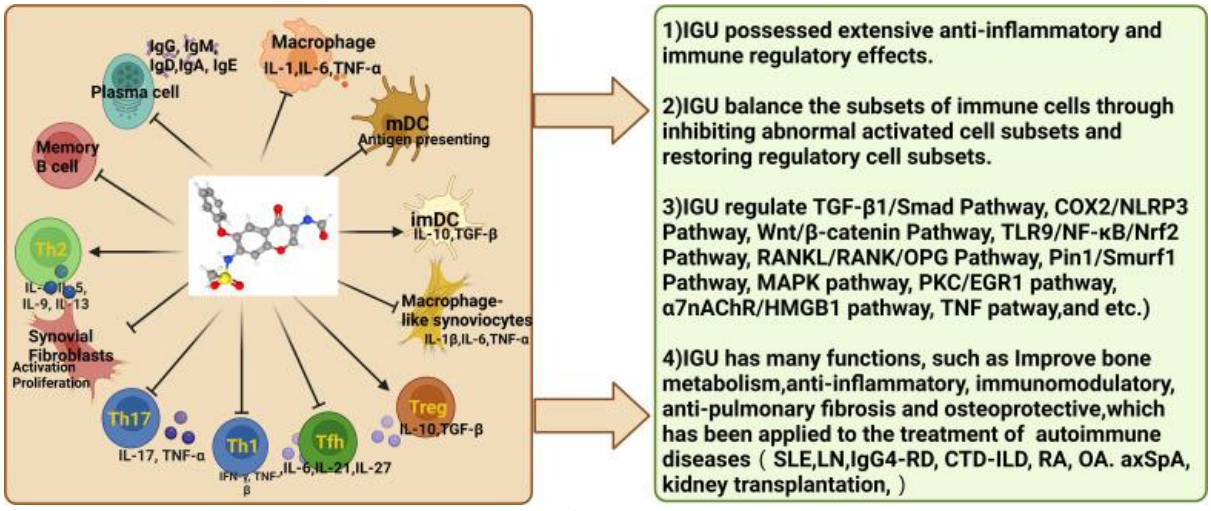


Figure 1.

Regulatory mechanism of Iguratimod on immune cells (Iguratimod has been found to modulate immune cell function and activity to balance immune cell subsets, thereby further reducing inflammation and tissue damage in autoimmune diseases. mDCs, mature DCs; imDCs, immature dendritic cells.).

a) Regulating T Lymphocyte Subsets: The pathogenesis of RA involves chronic inflammatory response of autoreactive T cells. T cell lineages include Th1, Th17 cells, CD4 + CD25 + regulatory T cells (Treg) and follicular helper T cells (Tfh). A clinical study showed that Th1 and Th17 were downregulated while Treg was upregulated in patients with RA after IGU treatment,

accompanied by decreased levels of Th1, Th17, Tfh associated inflammatory cytokines and transcription factors, and increased levels of Treg associated cytokines and transcription factors. In a mouse model of dextran sulphate sodium-induced colitis, IGU relieved the symptoms of colitis and reduced intestinal tissue damage, perhaps due to the downregulation of Th17 cells and the upregulation of Treg cells. In addition, IGU has a significant protective effect on cartilage and bone erosion in a rat model of collagen-induced arthritis by distorting Th17-driven response and inhibiting the production of anti-type II collagen antibodies. IGU can inhibit IL-17 signal pathway by reducing the mRNA stability and MAPK phosphorylation, targeting Act1, and disrupting the interaction of Act 1 with TRAF5 and Ikki.

b) Regulating Humoral Immunity: IGU directly inhibited B lymphocytes in mouse and human to reduce the production of immunoglobulins although it had no effect on the proliferation or apoptosis of B cells. IGU could reduce circulating plasma cells with a non-anti-proliferative mechanism in MRL/LPR mice. Recently, Demonstrated that IGU did not affect the activation and proliferation of B cells in the established in vitro human antibody secreting cell differentiation system, but inhibited the differentiation of human antibody-secreting cell by targeting the protein kinase C (PKC) and early growth response 1 (EGR1) axis.

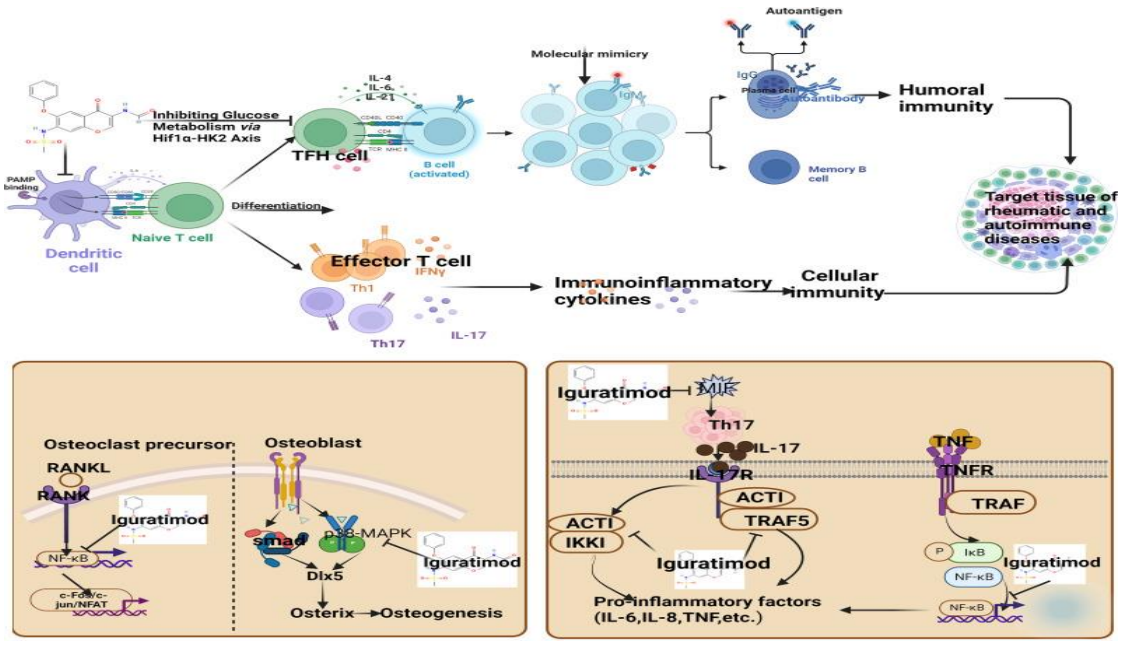
Regulation of the Metabolism of Bone and Cartilage

a) Promoting Bone Formation: IGU could promote osteoblastic differentiation of stromal cell line and preosteoblastic cell line in vitro and bone formation induced by recombinant human bone morphogenetic protein-2 in vivo. Another study demonstrated that IGU promoted osteoblast differentiation by upregulating DLX5 and the phosphorylation of p38, increasing Osterix expression, and inhibiting phosphorylated NF-kB levels. Moreover, clinical studies found that IGU and methotrexate (MTX) combined therapy was more effective in stimulating bone formation.

b) Inhibiting Bone Absorption: Discovered in the rat with collagen-induced arthritis model that IGU could inhibit cartilage and bone erosion and protect joint integrity. Subsequently, in vitro studies revealed that IGU significantly inhibited nuclear factor kB ligand (RANKL)-induced RAW264.7 cell differentiation and migration and bone resorption. The mechanism was related to inhibiting the activation of osteoclastogenesis through MAPKs and NF-kB pathways. Clinical studies showed that IGU would counteract bone resorption by regulating the RANKL/ RANK/osteoprotegerin (OPG) system without influencing Dickkopf-1 levels. In IL-6-stimulating rheumatoid arthritis synovial fibroblasts, IGU reduced RANKL expression and RANKL/OPG ratio, and ERK 1/2 pathway may be involved in the regulation of RANKL expression by IGU. IGU also played protective role in the model of benign bone loss induced by oophorectomy. The mechanism may be through the inhibition of peroxisome proliferator-activated receptor-g/cfos in RANKL-induced osteoclastogenesis. In addition, IGU can reduce bone damage caused by tumors, but has little effect on tumor cell proliferation and invasion.

c) Preventing Cartilage Erosion: Matrix metalloproteinases (MMPs) are produced by fibroblast like synoviocytes and play an important role in the destruction and erosion of articular cartilage in RA. IGU inhibits the production of MMP-1 and MMP-3 by rheumatoid synovial fibroblasts, thereby inhibiting the invasion of fibroblast-like synoviocytes stimulated by inflammatory cytokine. Clinical study reported that serum MMP-3 level predicted the response in RA patients with IGU and bDMARDs combined treatment.

The mechanism of iguratimod on signaling pathway were summarized in Figure 2.



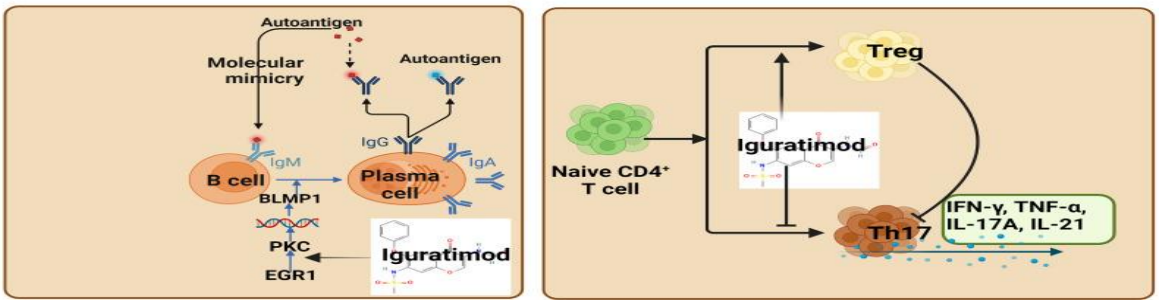


Figure 2: Regulatory Mechanism of Iguratimod on Signaling Pathway (IFN, interferon; TNF, Tumor necrosis factor; IL, Interleukin; Th, helper T cells; Treg, Regulatory T cells).

SUMMARY

Taken together, IGU can significantly inhibit the initiation and progression of RA by multiple mechanism such as regulating T cell differentiation, reducing the production of pro-inflammatory cytokines and immunoglobulins, promoting bone formation, and inhibiting bone resorption (Figure 3).

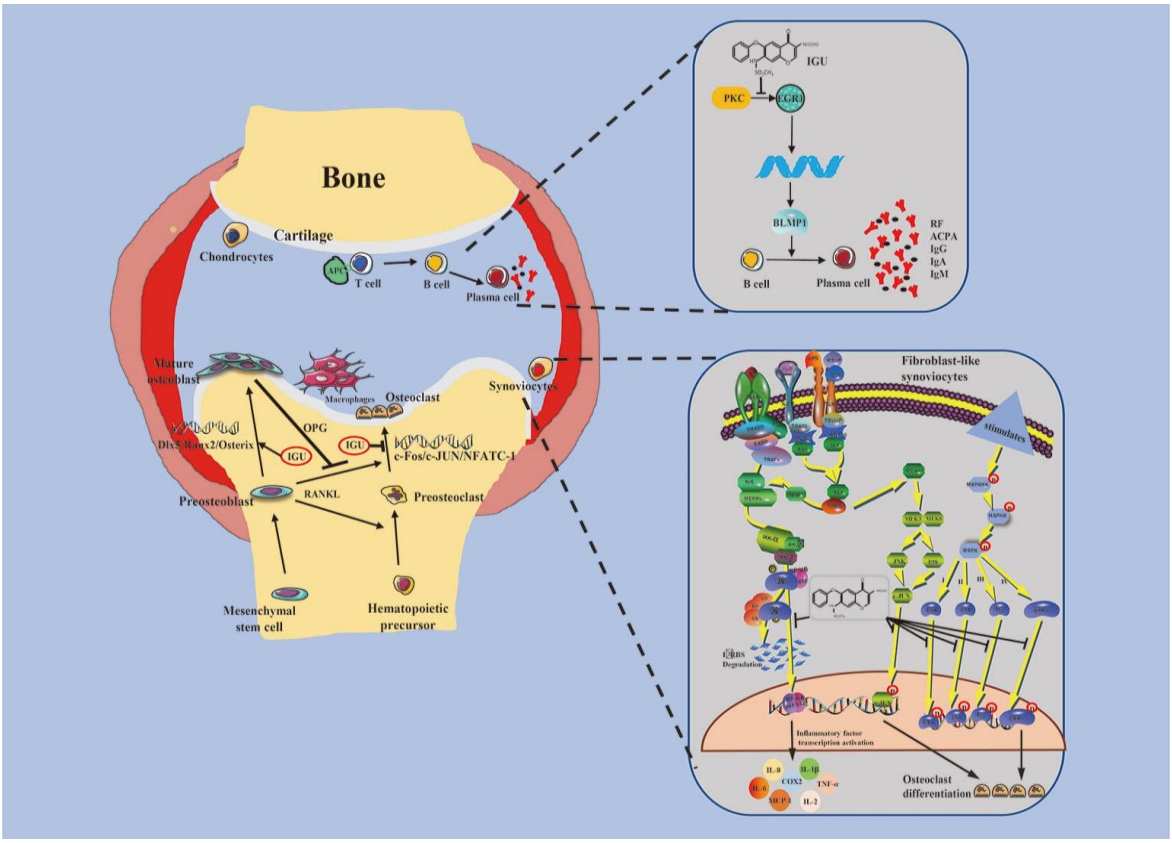


Figure 3: Schematic representation of pharmacological actions of iguratimod. ⟵ Stimulation by iguratimod, ⊣ Inhibition by iguratimod.

CLINICAL APPLICATION OF IGURATIMOD

Iguratimod (IGU) is a small-molecule anti-rheumatic drug that is used to treat a variety of autoimmune and rheumatic diseases, including.

- Rheumatoid arthritis (RA)- Rheumatoid arthritis (RA) is a chronic and systemic autoimmune disease. The main clinical features of the disease are erosive and symmetrical polyarthritis, in which the involvement of hands, wrists, knees, ankles and feet is the most common.[12]
- Ankylosing spondylitis (AS)- Ankylosing spondylitis (AS) is a chronic inflammatory disease that invades the spine and joints. As a chronic progressive autoimmune disease characterized by aseptic inflammation of the axial joints, cytokines such as IL-1, IL-6, IL-17, IL-18, TNF-α, and vascular endothelial growth factor are associated with AS activity.[13][14]
- Sjögren's syndrome- Primary Sjögren ‘s syndrome (pSS) is a chronic inflammatory autoimmune disease characterized by progressive exocrine gland damage

and lymphocyte proliferation, and can involve multiple organs and systems.[15]

- Systemic lupus erythematosus (SLE)- Systemic lupus erythematosus (SLE) is an autoimmune-mediated systemic inflammatory disease.[16] Lupus nephritis (LN) is one of the most common complications of SLE and a major predictor of poor prognosis.[16][17]
- Interstitial lung disease- Connective tissue-related interstitial lung disease, also known as CTD-ILD, refers to systemic lupus erythematosus, myositis, dermatomyositis, systemic sclerosis, scleroderma, rheumatoid arthritis, Sjogren 's syndrome and other connective tissue diseases caused by lung involvement, resulting in disease.[18]
- IGG4-RD- IgG4-RD is a chronic progressive autoimmune disease characterized by elevated serum IgG4 levels and infiltration of IgG4-positive cells in multiple organs at a relatively early stage.[19]
- Systemic sclerosis- Systemic sclerosis (SSc), also known as scleroderma, is a systemic autoimmune disease characterized by localized or diffuse skin thickening and fibrosis.[20] The lesion is characterized by skin fibrosis and vascular onion-like changes, eventually leading to skin sclerosis and vascular ischemia. This disease is clinically characterized by localized or diffuse skin thickening and fibrosis. In addition to skin involvement, it can also affect internal organs (heart, lung and digestive tract).[20]Multiple sclerosis- Multiple sclerosis (MS) is an autoimmune disease of the central nervous system characterized by inflammatory cell infiltration, neuronal degeneration, axonal damage, and reactive gliosis.[21]
- Other related inflammatory disease- In anti-tumor, the purpose of a study was to evaluate the anti-angiogenic and anticancer properties of iguramod (an anti-inflammatory drug similar to rheumatoid arthritis) against hepatocellular carcinoma.

IGU is a disease-modifying antirheumatic drug (DMARD) that works by: Inhibiting inflammatory factors, Inhibiting B cells from producing immunoglobulins and autoantibodies, Downregulating T-cell-mediated cellular immunity, and Accelerating bone formation.

IGU can be used as a monotherapy or in combination with other drugs, such as methotrexate (MTX). The combination of IGU and MTX is especially effective for patients who don't respond well to other DMARDs.

IGU can also be used as a coating on biomaterials used in prosthetic surgery, such as orthopedic implants, orthodontics, and cardiovascular stents. This coating can reduce inflammation and the rejection rate of the biomaterial.

PATENT OF IGURATIMOD[22]

Approval Date	Approval Time	Trade Name	Indication	Dosage Form	Strength	Company
2012.06.29	Marketing approval	Careram	Rheumatoid Arthritis	Tablet, Film coated	25mg	Eisai
2012.06.29	Marketing approval	Kolbet	Rheumatoid Arthritis	Tablet, Film coated	25mg	Toyama Chemical, Taiso Toyama
2011.08.15	Marketing approval	Iremod	Rheumatoid arthritis	Tablet, Film coated	25mg	Simcere

Iguratimod was first approved by China Food and Drug Administration (CFDA) on August 15, 2011, then approved by Pharmaceuticals and Medicals Devices Agency of Japan (PMDA) on June 29, 2012. It was developed by Simcere and marketed as Iremod® by Simcere and as Kolbet® by Taisho Toyama and by Eisai in Japan.

Iguratimod is a nuclear factor NF-kB activation inhibitor used in the treatment of rheumatoid arthritis.

Iremod is a available as tablet for oral use, containing 25mg of free Iguratimod, and the recommended dose is 25mg once daily or 25mg at a time, twicw daily.

IGURATIMOD FROM DIFFERENT FORMULATIONS, including.

- **Ailamode**: The general name for iguratimod, with the chemical name N-[3-(formamido-) by name-4-oxygen-6-phenoxy group-4H-1-chromene-7-yl]-amsacrine.
- **Sodium salt compound**: The chemical name for this formulation is N-[3-(formamido-)-4-oxygen-6-phenoxy-4H-1-chromene-7-yl]-NSC-249992 sylvite.
- **Ailamode potassium**: This formulation can be in various solids or dissolved salts.

VARIOUS ANALYTICAL METHOD DEVELOPMENTS OF IGURATIMOD

Methods	Mobile phase / Solvent system	Detection wavelength
Development and validation of Stability Indicating HPTLC method for determination of Iguratimod in Bulk and Pharmaceutical Dosage Form.[23]	n- Hexane: Ethyl Acetate (5:5 v/v)	256 nm

HPTLC Method

UPLC-MS/MS

Method	Mobile phase	Flow rate
Simultaneous determination of Iguratimod and its metabolites in rat plasma by using a UPLC-MS/MS.[24]	Acetonitrile and water with 0.1 % formic acid	0.3 ml/min

HPLC Methods

Methods	Mobile Phase with ratio	Flow rate	Wavelength	Retention Time (RT)	Correlation Coefficient (r^2)
Determination of Iguratimod in human plasma by HPLC Method.[25]	Acetonitrile: Water with glacial acetic acid (pH-3) (40:60 v/v)	1 ml/min	257 nm	9.033 mins	0.9551
Preparation of a major metabolite of a Iguratimod and simultaneous assay of Iguratimod and its metabolites by HPLC in rat plasma.[26]	Methanol : Water contain 0.1 % trifluoroacetic acid (55:45 v/v)	1 ml/min	257 nm	8 mins	0.9999
Development and validation of HPLC method for the Iguratimod.[27]	Buffer: Acetonitrile (50:50v/v),	1ml/min	257nm	19 mins	0.9995
Identification, characterization and synthesis of Iguratimod process and degradation related impurities.[28]	Buffer : Acetonitrile (50:50v/v)	0.8ml/min	257nm	17.4 mins	-
Analytical method development and validation of cleaning methodology for residual determination of Iguratimod.[29]	buffer (pH 2.5) and methanol in a ratio of 58:42 v/v	2.0ml/min.	257nm	4.073 mins	0.999
Formation of newer analytical methods that have been verified for determining Iguratimod in tablet dosage form.[30]	Water: Acetonitrile (50:50 v/v)	1 ml/min	260 nm	4.100 mins	0.998
A Study of method development and validation for quantification of Iguratimod in pharmaceutical dosage form by RP-HPLC method.[31]	Buffer with pH 2.5 and methanol in a ratio of 58:42	1.2ml/min	257nm	20 mins	0.9995

Gas Chromatography Method

Method	Solvents	% Recovery	Co-efficient of Variation
Analytical method development and validation by Headspave Gas Chromatography for residual solvents in Iguratimod.[32]	Ethanol, Acetone, Isopropyl alcohol, Acetonitrile, Dichloromethane, Ethyl acetate, Methanol, Pyridine, Dimethyl formamide, Benzene, Nitrobenzene.	80-120 %	Not less than 0.99

CONCLUSION

Iguratimod (IGU) represents a groundbreaking advancement in the treatment of autoimmune and rheumatic diseases, particularly rheumatoid arthritis (RA). Its multifaceted mechanisms—spanning anti-inflammatory, immunomodulatory, and bone metabolism-regulating effects—set it apart from conventional therapies. IGU's ability to modulate T-cell

subsets, suppress pro-inflammatory cytokines, and promote bone formation while inhibiting resorption underscores its therapeutic versatility. Clinical evidence highlights its efficacy, especially in combination with methotrexate for patients unresponsive to standard treatments. Analytical methods like HPTLC, UPLC-MS/MS, HPLC methods and Gas Chromatography method were reported.

AUTHORS CONTRIBUTIONS: All the authors have contributed equally.

CONFLICT OF INTERESTS: Declared none.

REFRENCE

1. Nikita Gupta, Sana Begum, Varda Farooqui, Summaiya Afreen and Pranitha Avunoori *, "A review on Iguratimod: Bridging Hope for Arthritis Patients through the Dual Power of Immunomodulation and Anti-inflammation", a Department of Pharmacy Practice, St. Pauls College of Pharmacy, Hyderabad, Telangana-510.
2. https://www.mayoclinic.org/diseases-conditions/rheumatoid-arthritis/symptoms-causes.
3. Aikawa Y., Yamamoto M., Yamamoto T., Morimoto K., Tanaka K., "An anti-rheumatic agent T-614 inhibits NF-kappa B activation in LPS- and TNF-alpha-stimulated THP-1 cells without interfering with I-kappa B-alpha degradation," Inflammation Res, 2002; 51(4): 188–194.
4. Kohno M, Aikawa Y, Tsubouchi Y, Hashiramoto A, Yamada R, Kawahito Y, et al., "Inhibitory effect of T-614 on tumor necrosis factor-alpha induced cytokine production and nuclear factor-kappa b activation in cultured human synovial cells", J. Rheumatol, 2001; 28(12): 2591–2596.
5. Jiang Y, Lü W, Yu S, Yao L, Xu G, Zhang X, Yao Xue Xue Bao,"Inhibitory effect of iguratimod on TNF alpha production and NF-kappa B activity in LPS-stimulated rat alveolar macrophage cell line", 2006; 41(5): 401–405.
6. Li G., Yamasaki R., Fang M., Masaki K., Ochi H., Matsushita T., et al., "Novel disease-modifying anti-rheumatic drug iguratimod suppresses chronic experimental autoimmune encephalomyelitis by down-regulating activation of macrophages/microglia through an NF-κB pathway", Sci. Rep, 2018; 8(1): 1933.
7. Tanaka K., Yamamoto T., Aikawa Y., Kizawa K., Muramoto K., Matsuno H., et al, "Inhibitory effects of an anti-rheumatic agent T-614 on immunoglobulin production by cultured B cells and rheumatoid synovial tissues engrafted into SCID mice", Rheumatol. (Oxford), 2003; 42(11): 1365–1371.
8. Gan K, Yang L, Xu L, Feng X, Zhang Q, Wang F et al, "Iguratimod (T-614) suppresses RANKL-induced osteoclast differentiation and migration in RAW264.7 cells via NF-κB and MAPK pathways", Int. Immuno pharmacol., 2016; 35: 294–300.
9. Wang X., Ma C., Li P., Zhao F., Bi L. "Effects of iguratimod on the levels of circulating regulators of bone remodeling and bone remodeling markers in patients with rheumatoid arthritis", Clin. Rheumatol., 2017; 36(6): 1369–1377.
10. Xie S, Li S, Tian J and Li F," Iguratimod as a New Drug for Rheumatoid Arthritis: Current Landscape", Front. Pharmacol., 2020; 11: 73.
11. Long Z, Zeng L, He Q, Yang K, Xiang W, Ren X, Deng Y and Chen H, "Research progress on the clinical application and mechanism of iguratimod in the treatment of autoimmune diseases and rheumatic diseases", Front. Immunol., 2023; 14: 1150661.
12. Radu AF, Bungau SG, "Management of rheumatoid arthritis: An overview", Cells, 2021; 10(11): 2857.
13. Ward MM, Deodhar A, Gensler LS, Dubreuil M, Yu D, Khan MA, et al, "Update of the American College of Rheumatology/Spondylitis association of America/Spondyloarthritis research and treatment network recommendations for the treatment of ankylosing spondylitis and nonradiographic axial spondyloarthritis", Arthritis Care Res (Hoboken), 2019; 71(10): 1285–99.
14. Lau CS, Chia F, Harrison A, Hsieh TY, Jain R, Jung SM, et al, "Asia Pacific League of Associations for Rheumatology. APLAR rheumatoid arthritis treatment recommendations", Int J Rheum Dis, 2015; 18(7): 685–713.
15. Thalayasingam N, Baldwin K, Judd C, Ng WF, "New developments in Sjogren's syndrome. Rheumatol", (Oxford)., 2021; 60(Suppl 6): 53–61.
16. Robinson GA, Wilkinson MGL, Wincup C, "The role of immunometabolism in the pathogenesis of systemic lupus erythematosus", Front Immunol, 2022; 12: 806560.
17. Azar A, Aldaoud N, Hardenbergh D, Krimins R, Son J, Shiroky J, et al, "Systemic lupus erythematosus and common variable immunodeficiency", J Clin Rheumatol, 2022; 28(1): 245–8.
18. Wilson TM, Solomon JJ, Demoruelle MK, "Treatment approach to connective tissue disease-associated interstitial lung disease", CurrOpinPharmacol, 2022; 65: 102245.
19. Katz G, Stone JH "Clinical perspectives on igG4-related disease and its classification", Annu Rev Med, 2022; 73: 545–62.
20. Denton CP, Khanna D, "Systemic sclerosis", Lancet, 2017; 390(10103): 1685–99.
21. Olek MJ. Multiple sclerosis. Ann Intern Med, 2021; 174(6): ITC 81–96.
22. Reference: US4954518.
23. Santhosh V. Gandhi, Manisha Jagtap, "Development and Validation of stability indicating HPTLC method for determination of iguratimod in bulk and pharmaceutical dosage form", International Journal of Pharmacy and Pharmaceutical Sciences, 2022; 14(11).
24. Lu Shi, Jinyu Hu, Hualu Wu, Yuxin Shen, Xiaohai Chen, Qinghua Weng, Ren-ai Xu, Congrong Tang,

"Simultneous determination of iguratimod and its metabolite in rat plasma using a UPLC-MS/MS method: Application for drug-drug interaction", Journal of Pharmaeutical and Biomedical Analysis, June 2024; 243- 116079.
25. Mrinalini C. Damle* and Shital P. Ghode, "Determination of iguratimod in Human plasma by HPLC method", World Journal of Pharmaceutical Research, 2018; 7(14): 404-413.
26. Jun-ping Han, Zhen-han Zhu, Yue-zhang Wu, Wen Qian, Zhi-yu Li, Miyu Nishikawa, Toshiyuki Sakaki, Chang-qing Yang, "Preparation of a Major Metabolite of Iguratimod and Simultaneous Assay of Iguratimod and Its Metabolite by HPLC in Rat Plasma", Iranian Journal of Pharmaceutical Research, 2019; 18(2): 631-641.
27. Ravindra B.Nehete and Pushpendra Sharma, "Development and Validation of HPLC Method for the Iguratimod", Journal of Harmonized Research in Applied Sciences, 2018; 6(1): 01-08.
28. Bharat B. Kashid, Kishore R. More, Brajesh Sharma and Anil A. Ghanwat, "Identification, Characterization and Synthesis of Iguratimod Process and Degradation related impurities", ISSN 2277-7105, 2017; 6(14): 1212-1221.
29. Ravindra Bhaskar Nehete and Pushpendra Sharma, "Analytical Development and Validation of Cleaning Methodology for Residual Determination of Iguratimod", International Journal of Current Advanced Research, 2017; 7: 9746-9754.
30. P. Balakrishanaiah, Afreen Sultana, Ravindra Bairam and Manjunath S.Y, "Formation of Newer Analytical Methods that have been verified for Determination Iguratimod in Tablet Dosage Form", IAJPS, 2025; 12(01): 395-400.
31. Ravindra Bhaskar Nehete, Dr. Pushpendra Sharma, "A Study of Method Development and Validation for Quantification of Iguratimod in Pharmaceutical Dosage Form by RP-HPLC Method", JETIR (ISSN-2349-5162), January 2018; 5(1): 141-150.
32. Ravindra B. Nehete, Pushpendra Sharma, "Analytical Method Development and Validation by Headspave Gas Chromatography for Residual solvents in Iguratimod", Journal of Harmonized Research in Applied Sciences, 2018; 6(4): 254-264.