Iguratimod (T-614): a novel disease-modifying anti-rheumatic drug

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Abstract

Iguratimod is a small molecule compound with anti-inflammatory and immunomodulatory actions, which has been developed as a disease modifying anti-rheumatic drug (DMARD). Non-clinical studies of this compound revealed that inhibition of the production of immunoglobulins and various inflammatory cytokines mainly contributes to its improvement effect on various arthritis models in animals. In addition, iguratimod was found to possess anabolic effect on bone metabolism, through both stimulation of osteoblastic differentiation and inhibition of osteoclastgenesis. Regarding a more detailed mechanism of its action, the suppression of nuclear factor kappa B (NF-κB) activation without blocking NF-κB inhibitor α (IκBα) degradation has been indicated. Although the true target molecules of iguratimod have been unclear, it would be necessary to suppose the multiple mechanisms including suppression of NF-κB. Its effectiveness and tolerability comparable to salazosulfapyridine were examined by the clinical trials of Japanese patients with rheumatoid arthritis. Thus, iguratimod is a promising DMARD with novel properties and good clinical response. Further clinical study will clarify whether this drug is one of the useful options for treatment of patients who cannot use biologics.

Introduction

Rheumatoid arthritis (RA) is a chronic, systemic, inflammatory disease of the joints, which often causes joint destruction, deformity and functional impairment.[1] It follows a progressive course with evidence of structural joint damage occurring as early as four weeks after the onset of symptoms and usually gets fully established by two years in untreated patients.[2] Based on this observation, current treatment guidelines emphasize the early use of disease-modifying anti-rheumatic drugs (DMARDs), a class of therapeutic agents that have the potential to minimize or prevent joint damage.[3] The discoveries[4-6] that the macrophage-derived proinflammatory cytokines such as tumor necrosis factor α (TNFα), interleukin-1β (IL-1β) and interleukin-6 (IL-6) play a central role in the pathogenesis of RA led to the introduction of anti-cytokine drugs, a new biological class. The remarkable advance and benefit of biologics, such as anti-TNFα therapeutics, are practically guaranteed in the control of disease activity and joint destruction in patients with RA.[7,8] However, it is also apparent that these biologics fail to achieve an American College of Rheumatology (ACR) 70 response in about 40% of patients with RA. Additionally, primary or secondary resistance to biological therapy represents a substantial complication in a significant group of patients. Thus, there is still unmet therapeutic need in the management of inflammatory autoimmune diseases and drug development research is actively seeking new solutions.[9,10]

Therefore, even now anti-rheumatic drugs with a novel mechanism of action, better efficacy and safety are required. Most of the commonly used drugs, including DMARDs such as azathioprine, cyclosporin A, gold, salazosulfapyridine (SASP) and methotrexate (MTX), are small molecules. In contrast to biologics, small molecules are orally bioavailable and their manufacturing is cost-effective, which is an important advantage for patients and the healthcare system. Iguratimod (T-614) is a small molecule with novel immunomodulatory and anti-inflammatory properties and has shown promising results in terms of efficacy and safety for the treatment of RA. Originality and production rights for this compound belong to Toyama Chemical Co., Ltd., and the clinical developments are advanced in cooperation with Eisai Co., Ltd., in Japan.

Chemical structure

Iguratimod (*N*-[7-[(methanesulfonyl) amino]-4-oxo-6-phenoxy-4*H*-1-benzopyran-3 -yl]-formamide) is a chromone derivative which has two amide groups, formamide and methanesulfonamide functionalities (Figure 1). Structure-activity relationship of a series of chromone derivatives was investigated using several inflammation animal models and a preparative-scale synthetic route to iguratimod has been reported.[11] Regarding the important pharmacological profiles of iguratimod, we found that it showed low gastro-ulcerogenic liability and notably activity against progressive joint destruction in mouse collagen-induced arthritis (CIA). Especially, iguratimod significantly reduced serum IL-6 levels in the animal model[11] and at this point it differed from nimesulide,[12] a non-steroidal anti-inflammatory drug (NSAID) which has a similar chemical structure. Thus, this compound was selected as a prospective DMARD.

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Key words: iguratimod, anti-rheumatic drug, anti-inflammatory action, immunomodulatory action.

Acknowledgments: I thank Drs. Kenzo Muramoto, Yukihiko Aikawa and Ms Junko Funaki for their extensive advice and assistance.

Received for publication: 16 March 2009.
Revision received: 21 May 2009.
Accepted for publication: 3 July 2009.

Rheumatology Reports 2009; 1:e4
doi:10.4081/rr.2009.e4

Pharmacological profile

Anti-inflammatory activities

Our pharmacological studies,[13] at an early stage around 1990, revealed that iguratimod showed anti-inflammatory and analgesic activities in acute and chronic inflammatory models, such as carrageenin paw edema and adjuvant-induced arthritis (AIA) but it had virtually no gastrointestinal ulcerogenic action in fasted rats, unlike classical NSAIDs. Additionally, iguratimod inhibited the increased release of bradykinin in a kaolin-induced inflammation in rats.[14] On the whole, it was suggested that iguratimod would be different from nimesulide and other NSAIDs in several pharmacological properties.

On the other hand, the biochemical studies on arachidonate cascade have shown that this compound possessed a similar profile to selective cyclooxygenase (COX)-2 inhibitors, i.e. it effectively inhibited prostaglandin (PG) E_2 production by cultured fibroblasts and reduced the

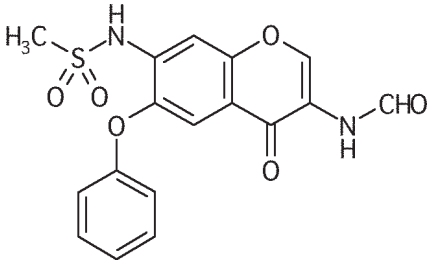

Figure 1. Chemical structure of iguratimod.

PGE_2 contents in inflammatory exudates without affecting the gastric mucosal PG levels in rats with carrageenin-induced inflammation.[15] In fact, the COX-2 selective inhibition by iguratimod was demonstrated in the enzyme assays using purified sheep COX proteins.[16] Riendeau *et al.*[17] have also reported that it showed the weakest potency against COX-1 among compounds that have been reported to show the selectivity for COX-2 in human microsomal assays. In addition, iguratimod has been found to suppress COX-2 mRNA expression induced with inflammatory stimuli in cultured fibroblasts.[16]

Inhibition of immunoglobulin production

In the clinical trials, as described later, it was observed that iguratimod had a good therapeutic effect on the clinical symptoms and biological markers, including plasma levels of the rheumatoid factor (RF) and immunoglobulins. So, our studies were focused on the effect on B-cell functions, such as immunoglobulin production and proliferation. In murine B-cell cultures, iguratimod significantly decreased the IgM production and the isotype-switch to IgG1 class induced by lipopolysaccharide (LPS) and/or IL-4.[18] It also inhibited the spontaneous IgG production without influencing cell proliferation in a human plasmacytoma cell line (ARH-77). Furthermore, in human peripheral B cells stimulated with autologous T cells and anti-CD3 antibody, iguratimod inhibited both IgM and IgG production in a concentration-dependent manner.[18] By contrast, iguratimod showed no effect on the mitogen-induced proliferation response[19,20] and TARC (thymus and activation-regulated chemokine) production from human B cells stimulated with anti-CD40 antibody and IL-4.[21] Therefore, it appears that this compound inhibits the immunoglobulin production by B cells without inducing a cytostatic effect.

Next, to clarify the hyper-immunoglobulinemia in RA patients and the suppression by iguratimod, we investigated the immunoglobulin secretion from RA synovial tissues using the severe combined immune deficiency (SCID) mice engrafted with human RA tissue. As a result, high concentrations of polyclonal human IgG were detectable in the sera of the mice. In addition, a significant decrease in the IgG level was observed in the iguratimod-treated group compared with the vehicle-treated group.[18] In the chronic arthritis models, such as AIA rats and MRL/lpr mice,[22] its improvement effect on arthritic lesions was accompanied by the amelioration of the hyper-immunoglobulinemia.[19,23] In connection with the clinical efficacy of B-cell-targeted anti-CD20 antibody on RA patients,[24] these results are of great interest to the mechanisms of anti-rheumatic effect for small molecule DMARDs.

Inhibition of cytokine production

Another clear difference between iguratimod and classical NSAIDs is the inhibitory effect on cytokine production, as mentioned above. Concerning inflammatory cytokines, the experimental results reported until now are summarized in Table 1. Against cultured monocytes/macrophages, iguratimod showed the suppression of production of IL-1β, TNFα, IL-6, IL-8 and monocyte chemoattractant protin-1 (MCP-1) with IC_{50} values of 1-20 μg/mL.[25-28] In synovial cells derived from patients with RA, it significantly reduced the production of IL-6, IL-8 and colony stimulating factors (CSFs) at the concentration ranges from 0.3 to 30 μg/mL.[25,29,30]

The inhibition of these cytokine productions by iguratimod accompanied the suppression of the mRNA expression.[26,27,29] Therefore, iguratimod might inhibit gene expression of these inflammatory cytokines. In addition to cytokines, Kawakami *et al.*[30] have shown that the up-regulated expression of co-stimulatory molecules including CD54, CD58, and CD106 in synovial cells stimulated with IFN-γ was also inhibited by iguratimod. As more fully described below, the involvement of prevention of nuclear factor-kappa B (NF-κB) activation is also suggested to the mechanism of this action.

Such inhibition of cytokine production was also observed in *in vivo* animal models. In an air-pouch type inflammation model in mice, iguratimod at the doses of 30 and 100 mg/kg *p.o.* significantly decreased the MCP-1 production induced with injection of TNFα.[25] This compound at 10 and 30 mg/kg reduced the elevation of serum TNFα and IFN-γ levels in concanavalin A-induced hepatitis model of mice in addition to the serum transaminase levels.[25] Iguratimod has been found to suppress the development of active experimental autoimmune encephalomyelitis (EAE) in rats.[31] In this model, it was also observed that it inhibited TNFα and IFN-γ production by antigen-specific T cells and the cell infiltration to spinal cord of rats. As an interesting experiment result, we have observed that iguratimod exerted an anti-cachectic effect on adenocarcinoma colon 26-induced cachexia in mice through the inhibition of IL-6 gene expression.[32] Furthermore, it has recently been reported that CIA rats treated with iguratimod exhibited decreases in mRNA expression of IL-17 in peripheral lymphocytes and circulating IL-17, suggesting that this compound exerts its immunoregulatory and bone preserving effects by skewing responses away from IL-17-producing T cells (Th17 cells).[33] These results indicate that inhibition of the cytokine production by iguratimod may contribute to its clinical anti-rheumatic effect and such effect would be a characteristic of this drug.

Anabolic effect on bone metabolism

Based on the observation of the apparent improvement on the progression of articular destruction in the animal arthritis models, effects of iguratimod on bone metabolism have been examined *in vitro* and *in vivo*. Firstly, the effect on osteoblastic differentiation and bone formation was investigated using stromal cell line (ST2) or pre-osteoblastic cell line (MC3T3-E1) and a bone morphogenetic protein-2 (BMP-2)-induced ectopic bone formation model in mice, respectively.[34] It was found that iguratimod at the concentrations of 1-10 μg/mL stimulated the osteoblastic differentiation of both cell lines in the presence or absence of BMP-2. Calcium content of mineralized nodules was elevated by the addition of iguratimod in ST2 cells with rhBMP-2. Oral administration of this compound at 10 mg/kg/day to mice also promoted BMP-2 induced bone formation *in vivo*.

In contrast, we found that osteoclast differentiation was strongly inhibited by iguratimod.[35] In the culture of a murine osteoclast precursor cell line (RAW264.7) stimulated with soluble receptor activator of NF-κB ligand (sRANKL), this compound inhibited the increase of tartrate resistant acid phosphatase (TRACP) activity with an IC_{50} value of 0.74 μM

Table 1. Inhibition of cytokine production by iguratimod *in vitro*.

Cells	Stimuli	Cytokines	Concen. (μg/mL) range	Ref.
Mouse peritoneal macrophages	Zymosan	TNFα	0.3-30	25
THP-1 cells human monocytes	LPS	IL-1β, TNFα, IL-6, IL-8, MCP-1	0.3-30	26, 27
NR8383 cells rat alveolar macrophages	LPS	TNFα	5-20	28
Synovial fibroblastic cells from RA patients	TNFα or IL-1β	IL-6, IL-8	0.3-30	25, 29
	IL-1β or TPA	IL-6, IL-8, G-CSF, GM-CSF	2	30

TPA: 12-O-tetradecanoyl phorbol 13-acetate.

(0.27 μg/mL), and the formation of TRACP-positive multinucleated cells. Moreover, the immunoblot analysis for the cell lysates revealed that the induction of nuclear factor of activated T cells c1 (NFATc1) stimulated with sRANKL was significantly suppressed by 1 μM of iguratimod. Taken together, these results suggested that iguratimod possessed anabolic effect on bone metabolism, besides improvement effect on arthritis.

Putative mechanism of action

As described above, the pharmacological actions of iguratimod are extremely variegated. Therefore, its actions on a wide kind of cells involved to the joint destruction of RA[36] are illustrated in Figure 2. Although it would be difficult to explain such versatile actions by a single molecular mechanism, one of the putative mechanism of actions (MOAs) is the suppression of NF-κB activation.

Iguratimod inhibited the cytokine production in several types of cultured cells with a decrease in their mRNA levels.[26,27,29] The studies followed by these experiments also demonstrated that iguratimod suppressed the NF-κB activation. An electrophoretic mobility shift assay using the nuclear extracts from THP-1 cells stimulated with TNFα or LPS showed that iguratimod prevented the activation of NF-κB, and Western blot analysis proved that iguratimod did not affect degradation of IκBα protein.[27] These results suggested that the inhibition of the inflammatory cytokines production by iguratimod might involve transcriptional regulation through suppression of NF-κB activation without interfering with IκBα degradation. Similar experiments have been reported by Jiang *et al.*[28] and they showed that iguratimod inhibited LPS-stimulated mRNA expression of TNFα as well as DNA binding activity of NF-κB in rat alveolar macrophage cell line (NR8383). Furthermore, Kohno *et al.*[29] reported that this compound interfered with the TNFα induced translocation of NF-κB p65 to the nucleus from the cytoplasm in RA synovial cells. The true target molecules of iguratimod have been unclear, but it would be necessary to suppose the multiple mechanisms including suppression of NF-κB and NFATc1 etc.

There are numerous reports[37-40] suggesting that NF-κB system is a useful and valuable therapeutic target in RA and many compounds have been reported to act on several steps of signal transduction pathways of NF-κB as an inhibitor.[41-43] However, the majority of these compounds have not reached acquisition of evidence in clinical studies in rheumatic diseases in the development stages. A straightforward suppression of NF-κB system might cause safety problems, because NF-κB plays an important role in not only inflammatory responses but also hematopoietic system and tissue homeostasis. Thus, the multiple molecular targets assumed in iguratimod may be advantageous in the balance between efficacy and safety.

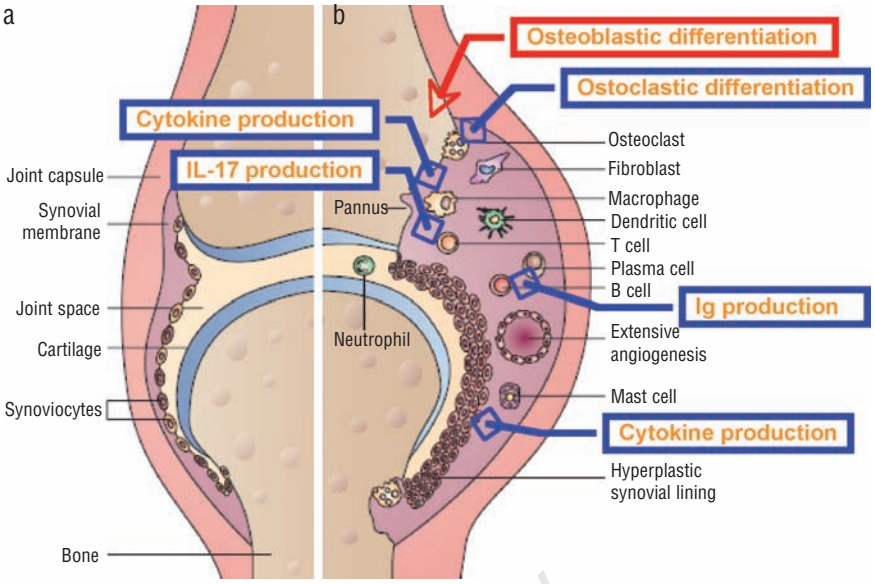

Figure 2. Schematic representation of the pharmacological actions of iguratimod. The master drawing was quoted from the report by Strand *et al.*[36] (a) In the healthy joint. (b) In rheumatoid arthritis.

Stimulation by iguratimod. **Inhibition by iguratimod.**

Table 2. Inhibition of IgG production and proliferative response by DMARDs in human lymphocytes.

	Iguratimod	DMARDs in clinical use			
		SASP	AUF	MTX	LEF
IgG production: IC_{50} (μg/mL)	0.19	25	0.11	0.010	4.2
Proliferation: IC_{50} (μg/mL)	>30	*ca.*100	0.75	0.038	3.4*
Ratio of concentration IgG production: proliferation	1 : >150	1 : ca.4	1 : 6.8	1 : 3.8	1 : 0.81
C_{max} in clinical use (μg/mL)	1-2	8-12	0.1-0.7	0.1-0.2	43

SASP: salazosulfapyridine, AUF: auranofin, MTX: methotrexate, LEF: leflunomide (active metabolite A77 1726). *Quoted from reference #47.

Results in clinical trials

The first clinical study of Japanese patients with RA for iguratimod was started in 1992 and phase III studies were started in 1998. A controlled, randomized, double blind, parallel-group study[44] on 376 patients revealed that the ACR 20 response rate of iguratimod that was administered orally at a daily dose of 25 mg for the first four weeks and 50 mg for the subsequent 24 weeks was superior to placebo (53.8% vs. 17.2%) and was not inferior to SASP (63.1% vs. 57.7%) after 28 weeks. All of ACR core set data including tender joint count, swollen joint count, patient's assessment of pain with the visual analog scale, patient's global assessment of disease activity with the scale and so on, at the completion of study treatment were significantly better than those at baseline in both the iguratimod and SASP groups. In addition to C-reactive protein, iguratimod significantly reduced the increase in blood concentrations of RF, IgG, IgM, and IgA compared with placebo. On the other hand, no statistically significant difference was noted in the incidence of adverse reactions between iguratimod and SASP. However, the safety profile of iguratimod is different from that of SASP. A characteristic adverse event in the iguratimod group was increased hepatic enzyme. Although this event included transient increase, attention should be paid to hepatic function data during iguratimod therapy based on the frequency of increased hepatic enzymes in our study. Another characteristic adverse event in this group was dermatological disorder, of which frequency was relatively low. Attention should also be paid to abdominal pain, anemia, and other symptoms and signs related to gastrointestinal disorder during the therapy because

peptic ulcer was reported in the iguratimod group. Hematologic disorder does not seem to be an iguratimod-specific adverse event because the disorder reported in the iguratimod group did not differ from that in the SASP group. To evaluate the long-term safety of this drug, a 52-week clinical study in 394 Japanese patients with RA was also conducted.[45] Some of the patients continued the treatment for 100 weeks for their benefit. The cumulative incidence of adverse events for 100 weeks was 97.6%. The cumulative incidence of adverse reactions was 65.3%; unfavorable symptoms and signs accounted for 33.2% of the reactions, and abnormal laboratory data changes accounted for 50.4% at week 100. Regarding increased hepatic enzyme that seemed to be a characteristic adverse reaction of iguratimod, incidence of increased alanine aminotransferase and aspartate aminotransferase was 19.4% and 18.3%, respectively. The most common timing of onset of the reaction was between weeks 4 and 8. The reaction was resolved spontaneously during the continued study treatment or by the discontinuation of study treatment. The continued treatment rate was 66.8% at week 28 and 53.6% at week 52. For reference, the ACR 20 response rate was 46.9% at week 28 and 41.0% at week 52. To use iguratimod safely for a long time, patients should be observed closely for adverse reactions such as increased hepatic enzymes. As a result of discussions with the Japanese regulatory agency based on the results from these clinical studies, an additional clinical study should be conducted to assess the add-on efficacy of iguratimod to the standard DMARD therapy. It would be considered that the comparison between the efficacy of iguratimod alone and the recent remarkable usefulness of biologics had influenced such an outcome.

Meanwhile, in China, a randomized, placebo-controlled, 24-week clinical phase II study in 280 patients was also conducted and Lü *et al.*[46] have recently reported that iguratimod at daily doses of 25 mg and 50 mg was effective in treatment of RA and was well tolerated.

Conclusions

Iguratimod is a promising DMARD with novel properties and good clinical response. It is suggested that inhibition of the production of immunoglobulins and various inflammatory cytokines mainly contributes to its efficacy on patients with RA. In addition, the suppression of NF-κB activation without blocking IκBα degradation has been indicated as a more detailed mechanism of its pharmacological action.

Meanwhile, it has been reported that most DMARDs, including MTX, leflunomide[47] and auranofin, strongly inhibited the proliferation of lymphocyte within their plasma concentration levels in human; however, iguratimod had no effect on the proliferation response up to 30 μg/mL,[19,20] which is 10 times or more as high as the plasma concentration in humans (Table 2). Therefore, one of the notable features of iguratimod is that, unlike other DMARDs, it inhibits the production of immunoglobulins and cytokines without being due to the cytostatic effect. This point is very important when considering application of iguratimod to RA patients and the unique immunomodulatory effects promise to become an alternative for the treatment of RA.

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