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Iguratimod, A Synthetic Disease Modifying Anti-Rheumatic Drug (Sdmard), and Various Dmards Suppress Joint Destruction. The Pathophysiological Mechanisms of the Inhibition of Bone/Cartilage Destruction

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Abstract

Objective: To elucidate the radiographic outcomes for rheumatoid arthritis (RA) patients using the synthetic disease-modifying antirheumatic drug (sDMARD) Iguratimod (IGU) and other DMARDs including injectable sodium aurothiomalate, bucillamine, salazosulphapyridine, infliximab, etanercept, tocilizumab and/or abatacept.

Patients and Methods: 213 patients were enrolled in this study. Total Genant-modified Sharp scores (GSS) of hands/wrists and feet at baseline and at week 104 were calculated in 31 RA patients treated with a daily dose of 25 mg or 50 mg for 104 weeks.

Results: Total GSS of 31 patients at week 104 showed no progression (total GSS $\leq$ 0.84: the smallest detectable change) in 16 (52%) patients with a mean score reduction (95% CI) of -4.3 (-8.1~-0.5) ($p < 0.05$).

Conclusion: Treatment with the sDMARD, IGU showed no radiographic progression in 16 (52%) RA patients at week 104. Concerning the suppression mechanism of joint destruction by IGU and other DMARDs, we speculate that DMARDs prevent bone/cartilage destruction by inhibiting the receptor activator of nuclear factor-kappa B (NF- κ B) lig and (RANKL) and through other antirheumatic actions.

Keywords: Synthetic DMARD, Iguratimod, Biological DMARDs, Targeted tsDMARDs (JAK inhibitors), Bone/Cartilage destruction, Antirheumatic action, NF- κ B, RANKL-dependent osteoclastogenesis

Introduction

Iguratimod (IGU) in animal and in vitro studies demonstrates its antirheumatic actions and inhibitory effects on structural damage as follows: (1) anti-inflammatory and analgesic effects [1]; (2) inhibition of various cytokines production including interleukin (IL)-1 β , IL-6, IL-17, tumor necrosis factor- α (TNF- α) [2-7], and inhibition of the production of immunoglobulins [8]; (3) prevention of bone/cartilage destruction and

inflammation in collagen-induced arthritis in rats [7] and mice [9]; (4) stimulation of osteoblastic differentiation and of bone morphogenetic protein-2-induced bone formation [10]; (5) inhibition of the production of matrix metalloproteinase (MMP)-1 and MMP-3, which play a pivotal role in the structural destruction in RA [11]; (6) inhibition of nuclear factor-kappaB (NF- κ B) activation [5,6], promoting production of various cytokines, and monocyte chemoattractant protein-1 (MCP-1) [3,5]; and (7) suppression of the production of the receptor activator of

NF- κ B ligand (RANKL) playing a role in osteoclastogenesis, bone resorption, and structural damage, and IL-17 and MMP-3 expression [12]. IGU (N-[7-[(Methanesulfonyl)amino]-4-oxo-6-phenoxy-4H-1-benzopyran-3-yl]formamide, C₁₇H₁₄N₂O₆S) is classified as a conventional sDMARD (csDMARD) but not as a targeted synthetic (ts) DMARD (JAK inhibitor).

Clinically, Japanese and Chinese double-blind and/or clinical practice studies of IGU for active RA patients indicate an early and sustained efficacy [13-17] as well as the safety of the treatment [14,16,18]. Also, IGU shows a significant decrease in serum concentrations of Rheumatoid Factor (RF), immunoglobulin (Ig)A, IgG, IgM [13,15] and MMP-3 [19].

The purpose of this study is to review the radiographic outcome in patients treated with IGU for 104 weeks, and to clarify the pathophysiological mechanism of the prevention of osteoclastogenesis with various DMARDs.

Patients and Methods

Selection of patients

Patients met the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) classification criteria for RA [20]. A total of 213 patients who gave informed consent were enrolled in the post-marketing surveillance study (Clinical Trials: Japic CTI-152782) from September 2012 until February 2013. Exclusion criteria were as follows: impaired hepatic function, hematopoietic disorder, gastric and/or duodenal ulcer, severe infection, pregnancy and breast feeding.

Study design

The trial consisted of a 4-week observation period with a primary endpoint of 52 weeks. Some patients continued the treatment for more than 104 weeks due to the relief they experienced. The IGU was orally administered as a dosage of 25 mg/day for the first 4 weeks and subsequently 25 mg/day or 50 mg/day (25 mg tablet, twice a day). Concomitant medications of non-steroidal anti-inflammatory drugs (NSAIDs), oral prednisolone, conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) and a biological (b) DMARD were permitted, if the drugs had started to be administered for more than 12 weeks prior to the entry to this study, and they had shown inadequate response (IR) at baseline measurements. An increase in the dose of the drugs was prohibited at the physician's discretion.

Efficacy assessment

Efficacy was assessed for all patients and separately in patients with active RA (disease activity score (DAS) 28-erythrocyte sedimentation rate (ESR) mm/hour: DAS28-ESR $\geq$ 3.2) at baseline and who were treated with IGU continuously for more than 12 weeks. Data for efficacy were reported every 4 weeks by the authors and were evaluated according to the EULAR DAS28-ESR measurement criteria [21]. Simplified disease activity index (SDAI) scores using C-reactive protein (CRP) (mg/dl) were also calculated per the ACR measurement criteria [22]. The states of disease activity (remission, low disease activity (LDA), moderate disease activity (MDA), and high disease activity (HDA)) (Table 1) as listed by EULAR and ACR SDAI were measured by the EULAR and the ACR classification criteria [22,23], respectively. Outcome of DAS responses (good response, moderate response or no response) was measured by the EULAR DAS response classification criteria [24].

Radiographic assessment

Radiographs of hands/wrists and feet were taken using the x-ray generator Rodnex50 (Hitachi Medical Corp., Tokyo, Japan) and were digitally processed by a CR system (Fuji Medical Co.LTD., Tokyo, Japan). Radiographs at week 104 were acquired only for patients who had completed the treatment course for this period and who agreed to have radiographs taken. Radiographs at week 0 and at week 104 were assessed using the Genant-modified Sharp scoring system [25-28], independently by an experienced musculoskeletal radiologist (Prof. ST, MD) and a registered orthopedic surgeon (TT, MD). The two evaluators were blinded to the treatment performed and sequence of the film images. Genant-modified Sharp scoring (GSS) system was used instead of the modified Sharp/van der Heijde score (SHS) method, since the maximum score of GSS and SHS is 290 [26] and 448, respectively, and the GSS system is easy to read [25] and reliable [25-28].

Erosion score (ERS), joint space narrowing score (JSNS) and total GSS of hands/wrists and feet at week 0 and at week 104 were calculated. Intraclass correlation coefficients [25,26,29,30] for ERS, JSNS and total GSS, at week 0 and at week 104, respectively, were computed by an analyst, AY, MSc (PPD-SNBL K.K., Tokyo). The smallest detectable change (SDC) [31] for GSS was computed based on the observed standard deviation of difference between the two x-ray readers. No radiographic progression was defined as total GSS $\leq$ SDC.

Safety assessment

Adverse events (AEs) were reported in 213 patients who were administered at least one tablet (25 mg) of IGU. Laboratory examinations were performed every 2 weeks until week 8 and subsequently every 4 weeks. Severity of AEs was classified according to the Rheumatology Common Toxicity Criteria [32].

Statistical analysis

In estimating the DAS28-ESR, SDAI score and EULAR DAS response, the last observation carried forward (LOCF) imputation method was used to account for missing data. Changes of DAS from baseline to week 104, predictors of a good response and characteristics of patients with AEs were analyzed using *t*-test, paired *t*-test, Wilcoxon signed-rank test or Fisher's exact test. The difference of variables was assessed using the least square means with a 95% confidence interval (95% CI).

P-Values of 0.05 or less were considered to indicate a statistical significance.

Results

Baseline demographics and clinical characteristics

Data for the 213 patients enrolled in this study have been previously reported in the Modern Rheumatology [17]. Data for the 142 active RA patients (DAS28-ESR ≥ 3.2) at baseline and who were treated with IGU continuously for more than 12 weeks are shown in Table 1.

Concomitant medication

Concomitant use of drugs with IR at baseline included csDMARDs (methotrexate (MTX), injectable gold: sodium aurothiomalate, bucillamine [33], salazosulphapyridine (SASP), leflunomide, mizoribine [34] and tacrolimus [35]), bDMARDs (infliximab, etanercept, tocilizumab and abatacept), oral prednisolone ≤ 10 mg/day and NSAIDs (Table 1).

Patient withdrawal

In total, 71 (33%) of the 213 patients were withdrawn from the IGU treatment within 12 weeks of treatment onset. Reasons for being withdrawn were as follows: (1) AEs (35 patients), (2) protocol violation including irregular or no hospital visit, poor adherence by the patient and insufficient data (21 patients), and (3) patients choice because of no perceptible efficacy (15 patients). Furthermore, 91 patients

(43%) had the treatment discontinued in $12 \leq$ to $104 <$ weeks. Reasons for being withdrawn were similar to the patients who discontinued the treatment within 12 weeks (85 patients), and patient's choice because of remission (6 patients).

Efficacy

DAS28-ESR and SDAI scores in 142 active RA patients (DAS28-ESR ≥ 3.2) at baseline treated with IGU for more than 12 weeks showed a statistically significant decrease at week 4, respectively ($P < 0.01$), and a progressive and sustained improvement until week 104 (LOCF). The states of DAS and SDAI remission (REM) and low disease activity were achieved at endpoint in 24% patients and in 16% patients, and in 27% and in 37% of patients, respectively [17].

Radiographic outcome

Radiographs of hands/wrists and feet were obtained for 47 patients at week 104, but radiographs at baseline was obtained for only 31 of the 47 patients, since the initial protocol of this clinical study did not include radiographic evaluation. Therefore, the GSS of hands/wrists and feet at baseline and at week 104 were calculated for 31 patients.

Mean (SD) of age and duration of disease in the 31 patients were 63.1 (12.4) years old and 11.2 (11.7) years, respectively (Table 2). Intra-class intra-reader correlation coefficients for GSS in the 31 patients at baseline and at week 104 were 0.999 and 0.998, respectively. The SDC was 0.84 (Table 2).

Mean changes (95% CI) from baseline to week 104 in ERS, JSNS and total GSS in the 31 patients were -0.7 (-2.8~1.4), 3.5 (0.6~6.4) and 2.8 (-1.8~7.4), respectively. Improvement or no progression in total GSS (≤ 0.84) was seen in 16 (52%) patients (Figure 1) and the mean change (95% CI) of total GSS was -4.3 (-8.1~-0.5) ($P < 0.05$) (Table 2).

There were no statistically significant differences in the changes of GSS between the patients with DAS good response and moderate response at week 104, and with RF positive and negative, and with MDA and HDA at baseline (Table 2). Concomitant use of drugs with IR at baseline including MTX, injectable gold, etanercept and prednisolone did not cause statistically significant changes in the GSS at week 104 (Table 2). The effects of concomitant use of drugs with IR at baseline, including bucillamine, SASP, infliximab, tocilizumab and abatacept, were not analyzed since these drugs had been discontinued in almost every patient by

week 16, because of IR and patient's choice.

Figure 1: Radiographs showing improvement of total GSS at week 104 in a 65 years old female patient with disease duration of 9.6 years.

Safety

A total of 143 AEs were reported in 111 (52%) of the 213 patients enrolled. Frequent AEs were as follows: 54 (25%) gastrointestinal disorders, 38 (18%) hepatic disorders and 17 (8%) dermatologic disorders including 5 alopecia/hair losses. Other AEs included 4 (2%) herpes zoster or herpes simplex, and massive peculiar subcutaneous hemorrhage, gingival bleeding, positive fecal blood, or acute severe anemia in two (1%) female patients in their 60s with concomitant use of IGU and warfarin potassium.

A total 130 (91%) AEs were classified mild or moderate based on the classification of Rheumatology Common Toxicity Criteria [32]. Severe AEs included one gastric ulcer bleeding necessitating two units of blood transfusion and eight elevated liver enzymes of $> 3.0 \times$ upper limit of normal (ULN). Life-threatening AEs were reported in two patients as follows: an octogenarian female patient had gastric ulcer bleeding on 55 days of 25 mg/day IGU treatment. In addition, another female patient in her 50s had gastric ulcer on 62 days of 25 mg/day IGU treatment. The patient was admitted to a general hospital and was

diagnosed to have gastric perforation. The patient had pan-peritonitis and sepsis after gastrectomy and died 146 days after the onset of gastric ulcer. A total of 65 (31%) of the 213 patients discontinued the treatment because of AEs, although 53 (82%) of 65 patients had only mild or moderate AEs. All of the AEs in 110 of 111 patients fully recovered afterwards.

Discussion

Radiographic non-progression has been reported in RA patients treated with various DMARDs such as csDMARDs including MTX plus etanercept [36], sulphasalazine (SSZ) [37,38], leflunomide [38], IGU [17] and combinations of csDMARDs [39,40], bDMARDs including infliximab [41], rituximab [42-44], abatacept [26,27], etanercept [36], adalimumab [45,46], tocilizumab [28,47,48] sarilumab [49], golimumab [50], certolizumab pegol [51] and tsDMARDs, tofacitinib [52,53] and baricitinib [54].

Significantly less progression for both erosion and joint space narrowing scores has been reported in patients treated with rituximab [43], tocilizumab [47], sarilumab [49], certolizumab pegol [51], tofacitinib [52] and baricitinib [54].

Good radiographic outcomes by DMARDs have been reported not only in patients with a short disease duration (≤ 3 years) [36,39,46,47] but also in patients with a long disease duration (mean ≥ 8 to ≤ 12 years) [28,41,45,49,52,54]. Disease duration (mean $\pm$ SD) in the 31 patients treated with IGU was 11.2 ± 11.7 years (Table 2), which indicates that good radiographic outcomes can be achieved with csDMARDs for RA patients of long-standing [17].

The pathophysiological mechanisms of radiographic non-progression in RA patients treated with various DMARDs remain uncertain. A csDMARD, IGU, inhibits the production of proinflammatory cytokines including TNF- α , IL-1B, IL-6, IL-8, IL-17, MCP-1 [2-9], and the MMP-1 and MMP-3 [11,12] which play a pivotal role in the structural destruction in RA. Also, antirheumatic actions and prevention of structural damage have been reported in RA patients treated with bucillamine [39], SSZ [37,38], leflunomide [38], bDMARDs [26-28,36,41-51] and ts DMARDs [52-54]. Furthermore, reduction in serum concentrations of RF, IgG, IgA and IgM have been reported in patients treated with IGU for 24 to 28 weeks [13-15]. These antirheumatic actions by IGU and other DMARDs suggest they play some role in the prevention of inflammation, immune reactions and structural damage in RA patients.

Table 1: Demographics and clinical characteristics at baseline in the 142 patients*1.

142 patients	
Sex Female, n(%): Male, n (%)	113 (80): 29 (20)
Age (years), mean $\pm$ standard deviation (SD) (range)	63.8 $\pm$ 11.3 (33-90)
Body weight (kg), mean $\pm$ SD (range)	52.6 $\pm$ 10.0 (33-80)
Disease duration (years), mena $\pm$ SD (range)	13.9 $\pm$ 10.7 (0.3-53)
Rheumatoid factor (RF) positive, n (%) negative, n (%)	109 (77) 33 (23)
Stage I, II, III, IV	23, 30, 28, 61
Class I, II, III, IV	27, 97, 18, 0
Tender joint count-28 joints, mean $\pm$ SD	6.9 $\pm$ 4.9
Swollen joint cout-28 joints, mean $\pm$ SD	8.7 $\pm$ 4.8
Patient's global assessment (VAS*2), mean $\pm$ SD	44.5 $\pm$ 18.3
Physician's global assessment (VAS), mena $\pm$ SD	40.0 $\pm$ 18.0
ESR*3 (mm/hour), mean $\pm$ SD	41.7 $\pm$ 30.3
C-reactive protein (mg/dl), mean $\pm$ SD	1.3 $\pm$ 1.9
DAS 28-ESR*4, mean $\pm$ SD (range)	5.2 $\pm$ 1.0 (3.3-8.5)
Remission DAS<2.6 n (%)	0
Low disease activity DAS $\geq$ 2.6to<3.2 n (%)	0
Moderate disease activity DAS $\geq$ 3.2to $\leq$ 5.1 n (%)	67 (47)
High disease activity DAS>5.1 n (%)	75 (53)
SDAI score*5, mean $\pm$ SD (range)	25.4 $\pm$ 11.2 (8.9-70.2)
Remission SDAI score $\leq$ 3.3 n (%)	0
Low disease activity SDAI score>3.3to $\leq$ 11.0 n (%)	7 (5)
Moderate disease activity SDAI score>11.0to $\leq$ 26 n (%)	82 (58)
High disease activity SDAI score>26 n (%)	53 (37)
Concomitant medications	
MTX*6 plus folic acid 5mg/week n (%)	83 (58)
Cs DMARDs*7 except for MTX n (%)	87 (61)
B DMARDs *8 n (%)	19 (13)
Oral prednisolone ($\leq$ 10mg/day) n (%)	94 (66)
Non-steroidal anti-inflammatory drugs n (%)	80 (56)

*1 The 142 patients who had DAS $\geq$ 3.2 at baseline and were treated with iguratimod for more than 12 weeks.

*2 VAS=visual analogue scale (DAS 0-100, SDAI 0-10). *3 ESR= erythrocyte sedimentation rate/hour. *4 DAS 28-ESR=disease activity score 28 joints using ESR. *5 SDAI score=the simplified disease activity index score. *6 MTX=methotrexate, weekly MTX dose in 83 of 142 patients, mean $\pm$ SD (range): 7.7 $\pm$ 1.8mg (4.0-12.0). *7 Cs DMARDs = conventional synthetic disease modifying antirheumatic drugs. *8 B DMARDs=biological DMARDs

NF- κ B induced by TNF- α [55-58] translocate to the nucleus and binds to the NF- κ B sites in target genes such as IL-6, IL-8 and MCP-1, and activates their transcription. Various DMARDs such as IGU [5-7], MTX [57-59], leflunomide [57], SSZ [59], gold compounds [34,55] and bDMARDs including infliximab [59] inhibit the activation and transcription of NF- κ B and decrease the production of various proinflammatory cytokines such as IL-1 β , IL-6, IL-17 and TNF- α [5-7]. Suppression of NF- κ B activity by DMARDs causes anti-inflammatory, antiproliferative, and immunosuppressive effects in RA patients [56,57].

The RANKL system is an important osteoclast

differentiation factor which promotes RANKL-dependent osteoclastogenesis and causes structural damage in RA [12,43,44,60,61]. The RANKL expression is induced by various factors such as IL-1 β , TNF- α , IL-17 [12,43,44,60], and IL-6/soluble IL-6 receptor (sIL-6R) mediated by the Janus kinase/signal transducer and activator of transcription (STAT) [60]. RANKL is also expressed by activated synovial B cells [62] and switched memory B cells (CD27+IgD-) [42] in RA patients. B cell depletion therapy with rituximab has been demonstrated to reduce not only active inflammation but also structural joint damage [43,44]. Furthermore, rituximab decreases RANKL expression both in the synovium and serum and increases in the

Table 2: Radiographic outcome at week 104 in the 31 patients*1.

	Change at	No. of Patients	At baseline	At week 104	week 104*11 95% CI*12	P value*13
Erosion score		31	8.6 ± 10.5	7.8 ± 8.7	-0.7(-2.8~1.4)	P=0.478
Joint space narrowing score		31	30.8 ± 33.3	34.3 ± 33.9	3.5(0.6~6.4)	P=0.018
GSS*2		31	39.3 ± 39.6	42.1 ± 39.6	2.8(-1.8~7.4)	P=0.221
No progression*3 in total GSS		16(52%)	38.2 ± 41.2	33.9 ± 39.7	-4.3(-8.1~-0.5)	P<0.05
Progression in total GSS*3		15(48%)	40.6 ± 39.1	50.9 ± 38.8	10.4(3.4~17.3)	P<0.01
Total GSS in patients with						P value*14
DAS good response		16(52%)	29.9 ± 33.0	32.1 ± 30.8	2.2(-4.5~8.9)	P=0.780
DAS moderate response		15(48%)	49.3 ± 44.5	52.8 ± 45.9	3.5(-3.6~10.5)	
DAS no response		0(0%)	-	-	-	
RF*4 positive at baseline		23(74%)	43.7 ± 43.4	46.1 ± 43.9	2.4(-1.6~6.4)	P=0.840
RF negative at baseline		8(26%)	26.8 ± 23.3	30.7 ± 21.1	3.9(-12.5~20.4)	
MDA*5 at baseline		11(35%)	30.3 ± 29.3	31.1 ± 34.9	0.8(-8.7~10.3)	P=0.513
HDA*6 at baseline		20(65%)	44.3 ± 44.1	48.2 ± 41.5	3.9(-1.5~9.3)	
Concomitant drugs MTX*7	Yes*8	17(55%)	42.3 ± 36.1	45.4 ± 37.1	3.1(-4.2~10.4)	P=0.877
	No	14(45%)	35.7 ± 44.5	38.1 ± 43.5	2.4(-3.7~8.5)	
b DMARD*9 (Etanercept)	Yes	5(16%)	33.8 ± 33.7	33.5 ± 33.0	-0.3(-1.8~1.3)	P=0.193
	No	26(84%)	40.4 ± 41.1	43.8 ± 41.1	3.4(-2.1~8.8)	
Prednisolone	Yes*10	16(52%)	45.8 ± 49.0	45.8 ± 48.5	0.0(-5.3~5.4)	P=0.217
	No	15(48%)	32.4 ± 26.1	38.2 ± 28.3	38.2 ± 28.3	
Injectable gold	Yes	22(71%)	35.7 ± 39.2	38.3 ± 38.6	2.6(-2.9~8.1)	P=0.907
	No	9(29%)	48.1 ± 41.4	51.4 ± 42.8	3.2(-6.9~13.4)	

*1 Age and duration of disease (mean ± SD) of 31 patients were 63.1 ± 12.4 years old and 11.2 ± 11.7 years, respectively. Intraclass correlation coefficients for GSS at baseline and at week 104 were 0.999 and 0.998, respectively. *2 GSS= Genant modified Sharp score. *3 No progression was defined in total GSS≤SDC (smallest detectable change, 0.84). *4 RF= rheumatoid factor. *5 MDA=moderate disease activity, see Table 1. *6 HDA=high disease activity, see Table 1. *7 MTX=methotrexate with inadequate response at baseline. *8 Mean dose 6.1 mg/w. *9 b DMARD=biological disease modifying antirheumatic drug. *10 Mean dose 4.1 mg/day. *11 Change at week 104=at week 104-at baseline. *12 95% confidence interval. *13 P value: difference of score change at week 104 in each group using paired t test. *14 P value: difference of score change in each group using t test.

osteoprotegerin (OPG)/RANKL ratio in serum [44]. Also, a human monoclonal antibody to RANKL (denosumab [63-65]), and various DMARDs such as MTX [12,59], IGU [12], SSZ [59], infliximab [59,61], tocilizumab [60], sarilumab [49], etanercept [66], tofacitinib [52,53] and baricitinib [67], suppress the production of RANKL and inhibit structural damage in RA patients.

Denosumab significantly suppresses the progression of bone erosion but shows no protective effects for joint space narrowing [64,65]. Various DMARDs have protective effects both on joint-space narrowing and bone erosion. The different outcomes with denosumab and DMARDs may be explained by that DMARDs having some antirheumatic function whereas denosumab does not. Additionally, since denosumab markedly increases bone mineral density of the whole hip and lumbar spine [64], prevention of

osteoporotic fracture in RA patients by denosumab can be expected [65].

Recently, possible RANKL-independent osteoclastogenesis has been reported by combinations of IL-6 and IL-11 [68], and TNF-α and IL-6 [69], and by lysyl oxidase (LOX) [70]. However, several investigators indicate that there is no clear evidence of RANKL-independent osteoclastogenesis or factor that replaces RANKL [71,72].

One limitation of this study is that the number of patients treated with IGU and evaluated by the GSS method was not very large. Further studies including more RA cohorts and research investigations are necessary to fully determine the findings described.

Conclusions

Various DMARDs, including IGU, perform various anti-inflammatory, antiproliferative and immunosuppressive actions, have inhibitory effects on the NF- κ B activation which produces various proinflammatory cytokines, and the drugs suppress the expression of the RANKL mechanism that causes osteoclastogenesis.

These antirheumatic effects might be indicating how DMARDs could prevent the progression of proliferative inflammation and bone/cartilage destruction in RA patients.

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Conflict of interest

None

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