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The Efficacy of Imrecoxib and Celecoxib in Axial Spondyloarthritis and Their Influence on Serum Dickkopf-Related Protein 1 (DKK-1) Levels

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF 1 **Guan-Min Gao**
ABCDEF 1 **Yan-Min Li**
ABCDEF 1 **Xiao-Long Zheng**
ABC 1 **Dong-Bin Jiang**
ABCDE 1 **Lei-Lei Zhang**
ABCDE 2 **Peng-Hui Xu**
ABCDEF 1 **Sheng-Yun Liu**
ABCDF 1 **Zhao-Hui Zheng**
ABCDE 3 **Quan-Cheng Kan**

1 Department of Rheumatology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, P.R. China
2 Department of Pharmacology, First Affiliated Hospital of PLA General Hospital, Beijing, P.R. China
3 Department of Pharmacology, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, Henan, P.R. China

Corresponding Author: Guan-min Gao, e-mail: guanmingao12@sina.com

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Background: To observe and demonstrate therapeutic effects and side effects of two selective COX-2 inhibitors, imrecoxib and celecoxib, on patients with axial spondyloarthritis (axSpA) and observe the correlation between imaging scores and serum DKK-1 levels.





Material/Methods: Sixty patients with axSpA were randomly assigned to receive 200 mg imrecoxib or 200 mg celecoxib twice daily. Fifty-one patients who completed follow-up were included in the study. At baseline, week 4, and week 12, the clinical parameters, inflammatory markers (ESR, CRP), and adverse reactions were recorded. Serum DKK-1 levels were investigated by enzyme-linked immunosorbent assay. Radiographic scores were calculated by sacroiliac joint SPARCC (Spondyloarthritis Research Consortium of Canada) score method at baseline serum DKK-1 levels and week 12.

Results: Patients in the imrecoxib group (n=25) and patients in the celecoxib group (n=26) were improved at week 4. At week 12, all clinical parameters and inflammatory markers were improved in the two groups and the differences was not statistically significant. Serum DKK-1 levels were decreased and the differences were not statistically significant. Serum DKK-1 levels in patients in the imrecoxib group at baseline were negatively correlated with all study parameters, while those in the celecoxib group had correlations with BASFI ($r=-0.048$, $p=0.027$) and Schober test ($r=0.437$, $p=0.048$), without any correlation with other clinical parameters or inflammatory markers.

Conclusions: Patients experienced significant improvement in disease activity, functional parameters, and inflammatory markers when treated with selective COX-2 inhibitors for 12 weeks, and the efficacy of imrecoxib was not inferior to celecoxib. Selective COX-2 inhibitors imrecoxib and celecoxib had no obvious effects on serum DKK-1 levels.

MeSH Keywords: **Cyclooxygenase 2 Inhibitors • Molecular Mechanisms of Pharmacological Action • Spondylitis, Ankylosing**

Full-text PDF: <http://www.medscimonit.com/abstract/index/idArt/901727>

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Background

Spondyloarthritis (SpA) is a group of chronic inflammatory rheumatic diseases with similar clinical manifestations, pathophysiology, and genetic characteristics. SpA is categorized into axial SpA and peripheral SpA on the basis of clinical manifestations. Axial spondyloarthritis (axSpA) mainly involves the spine and sacroiliac joints, including ankylosing spondylitis (AS), a non-radiographic axial spondyloarthritis (nr-axSpA) [1]. The ossification of the joint attachment site is the main reason leading to disability in patients. Wnt proteins are essential in the bone remodeling process, and Dickkopf-related protein 1 (DKK-1) is a natural inhibitor of the Wnt signaling pathway. SpA ossification is associated with the Wnt signaling pathway, and DKK-1 expression has been reported to be imbalanced in AS patients. Prostaglandin E2 (PGE2) can downregulate the level of DKK-1, and is a negative regulator of Wnt signaling and sclerostin levels, thus it upregulates the Wnt signaling pathway, initiating osteogenesis. Celecoxib (Celebrex), a selective COX-2 inhibitor, has been shown to delay progression as seen on AS spine imaging changes, which may be related to the regulation of DKK-1 [2,3]. Imrecoxib is a novel, moderately selective COX-2 inhibitor with action similar to celecoxib; it was developed by Chinese pharmaceuticals group and approved in 2011. This study was established in order to observe the efficacy and side effects of imrecoxib in treatment of axSpA and determine the influence of imrecoxib on serum DKK-1 levels.

Material and Methods

Objects of the study

A total of 60 axSpA patients who met the Assessment of Spondyloarthritis International Society (ASAS) classification criteria for axial SpA (2009) were selected from patients treated at the Division of Rheumatology, the First Affiliated Hospital of Zhengzhou University seen from October 2014 to March 2015 [4]. A parallel randomized, double-blind approach was used. Group select was done using a simple randomized grouping method and statistical software package SAS 9.2 to generated randomized groups and serial numbers. Random cards were made according to randomized groups and serial numbers, and were put in a sealed envelope (corresponding to the appropriate drug numbers). Patients were given twice daily treatment: imrecoxib (HRH) or celecoxib (Pfizer) 0.2 g at one time, twice daily, based on their selection to a group.

Inclusion criteria

- 1) Patients 18–50 years of age, and who were cognitively alert and able to fully cooperate with researchers were selected.

Female patients of childbearing age could not be pregnant or lactating during the study period.

- 2) Patients who met the ASAS classification criteria for axial SpA (2009).
- 3) No long-term use of aspirin or glucocorticoids; no intra-articular injection of drugs used within six months.
- 4) No cardiovascular diseases occurred within six months, including unstable angina, acute myocardial infarction, acute cerebral ischemia, infarction, a stable hypertension (blood pressure <140/90 mm Hg) controlled by drugs and other diseases.
- 5) Patients with gastrointestinal symptoms agreed to receive endoscopy before participating in the trial.
- 6) Patients had signed the informed consent document before any procedures of the study.

Exclusion criteria

- 1) Patients with rheumatoid arthritis, arteritis, relapsing polychondritis, systemic lupus erythematosus and other diffuse connective tissue diseases, primary fibromyalgia syndrome (secondary fibromyalgia which researchers believe not to interfere with the assessment of pain in patients can be selected) and a history of inflammatory bowel disease (such as ulcerative colitis and Crohn disease).
- 2) Patients in which myocardial infarction, angina pectoris or coronary artery bypass occurred within six months prior to the SpA treatment were excluded. Patients in which following cardiovascular events occurred: patients with coronary heart disease in which ECG showed myocardial ischemia; congestive heart failure patients (NYHA grade III–IV grade) of which symptoms occurred at rest or after slight exercise.
- 3) Patients who used anticoagulants (such as warfarin, low molecular weight heparin, etc.) and anti-platelet aggregation drugs.
- 4) Patients who had evidence of active upper gastrointestinal ulcers within 30 days prior to screening, or gastric and duodenal perforation and a history of upper gastrointestinal bleeding within one year prior to screening.
- 5) Patients who had any history of gastric surgery (such as gastrectomy or vagotomy), except simple ulcer suture and fundoplication, within six months prior to the SpA treatment.
- 6) Patients with a history of upper gastrointestinal cancer.
- 7) Patients with complications of diverticulitis (such as inflammation, pain, bleeding).
- 8) Patients with a history of bleeding disorders.
- 9) Patients with abnormal liver function and/or renal dysfunction and/or coagulation abnormalities and/or anemia (hemoglobin was less than 20 g/L, the normal lower limit).
- 10) Patients who were known to be allergic to pain medication, Celebrex or other non-steroidal anti-inflammatory drugs.

- 11) Patients who had any history of organ malignant lesions in the past five years.
- 12) Patients with significant diseases, including uncontrolled hypertension, type 2 diabetes, thyroid disease, active hepatitis within two years, and known HIV seropositive.
- 13) Patients with nonadherence to medical regimens.
- 14) Patients with a history of drug, alcohol abuse, and mental illness.
- 15) Patients who were litigating with the hospital.
- 16) Patients who used any kind of study drugs or were still within the 10 half-lives within one month prior to screening.

Research methods

According to the group orders, axSpA patients who met the inclusion criteria were given randomly assigned to received 200 mg (0.2 g) of imrecoxib or celecoxib packed in the same type of package twice daily after meals. The study participants underwent a washout period (without using any NSAIDs or analgesics) two weeks before taking imrecoxib or celecoxib. They could continue taking disease-modifying anti-rheumatic drugs (DMARDs) MTX, SASP, and thalidomide if they did in the past. All study participants signed an informed consent document. The study was approved by the research/drug clinical trials ethics committee of the First Affiliated Hospital of Zhengzhou University, and registered in Chinese Clinical Trial Register (registration number: ChiCTR-TRC-14004718). The clinical evaluation of patients included Bath ankylosing spondylitis disease activity index (BASDAI) scores, which were used to evaluate disease activity in patients. BASDAI scores were composed of the average scores of the following five items in the past one week: a – degree of fatigue and drowsiness; b – spinal pain; c – peripheral joint pain; d – enthesopathy (enthesitis); e – degree of morning stiffness; and f – duration of morning stiffness. $BASDAI=0.2 \times [a+b+c+d+0.5 \times (e+f)]$ (the total score range was 0–10); the higher the score was, the more active the disease. Points less than 4 indicated disease inactivity. Bath ankylosing spondylitis functional index (BASFI): this score is used to evaluate the functional status of patients with AS. BASFI score is an average of 10 questions. Eight questions were related to functional anatomy and two were related with daily living ability. For a patient's global assessment, VAS scores 0–10 were used to evaluate the current overall situation of disease. An examination of spinal mobility included tragus-to-wall distance, lumbar side flexion, the Schober test, finger to floor distance and intermalleolar distance. Laboratory tests included routine blood tests, routine urine tests, renal function and liver function tests (including alanine aminotransferase, aspartate aminotransferase, creatinine and uric acid), infectious diseases (hepatitis B virus, hepatitis C virus, syphilis and HIV) serology, WBC surface-associated antigens (HLA-B27), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Data were input into a study database.

At baseline and at week 12, a 5 mL sample of peripheral venous blood was taken from axSpA patients. After letting stand for 1–2 hours, the serum was centrifuged at 3,000 rpm for 10 minutes. The separated serum was dispensed to EP tubes, and stored at -80°C . Serum DKK1 levels were investigated by enzyme-linked immunosorbent assay. Reagents were purchased from RayBiotech, Inc., USA. Imaging was done using A 3.0T MRI (German Siemens.); a 16-channel body coil was used to obtain a coronal oblique scan of sacroiliac joints. MRI was performed on a 3.0T MRI scanner using the following sequences: T2_tirm_cor: pulse repetition interval TR 3800 ms, echo time TE 79 ms, FOV 420 mm, 18 layers, thickness of 5.0 mm; T2_tirm_tra: pulse repetition interval TR 5000 ms, echo time TE 75 ms, FOV 400 mm, 22 layers, layer thick 5.0 mm; T1_tse_cor_p2_384: pulse repetition interval TR 5000 ms, echo time TE 22 ms, FOV 400 mm, 18 layers, thickness of 3.0 mm; T2_tse_cor: pulse repetition interval TR 3000 ms, echo time TE 87 ms, FOV 400 mm, layer number 18, the thickness of 3.0 mm; T2_tirm_cor: pulse repetition interval TR 3900 ms, echo time TE 84 ms, FOV 400 mm, 18 layers, thickness of 3.0 mm. Two experienced radiologists read films independently, using SPARCC scoring system to calculate MRI scores and averages. The SPARCC scoring method mainly refers to MRI imaging features on T2 sequences on the plane of the coronal oblique scan. A normal signal is 0 points while a signal enhancement is 1 point. On bilateral sacroiliac joints, each quadrant (lower and upper parts of iliac and sacrum) were evaluated. Scoring included three aspects: 1) the presence or absence of bone marrow edema according to the sacroiliac joint surface: 1 point was scored for the presence in each quadrant; the total score of six levels was 48 points; 2) depending on the depth of bone marrow edema: 1 point was added when the length of edema lesions in the sacroiliac joint from the surface of cartilage was equal to or higher than 1 cm; the total score of six levels was 12 points; 3) according to the intensity of bone marrow edema: when the intensity of bone marrow edema was equal to or higher than the presacral vessels signal, regardless of the number, 1 point was scored at the unilateral joint; the total score of six levels was 12 points. The total score could be up to 72 points [5].

Statistical methods

SPSS17.0 statistical software was used for statistical data processing. Normality and homogeneity of numeric variables were tested. Measurement data complying with normal distribution were expressed as mean \pm standard deviation. Non-normal variables were expressed in the median and quartile method. For normally distributed measurement data, comparisons adopted the two independent sample *t*-test. For measurement data, correlation analysis used correlation analysis Pearson. A *p* value of less than 0.05 was considered statistically significant, the confidence intervals of the data were set by default at 95%.

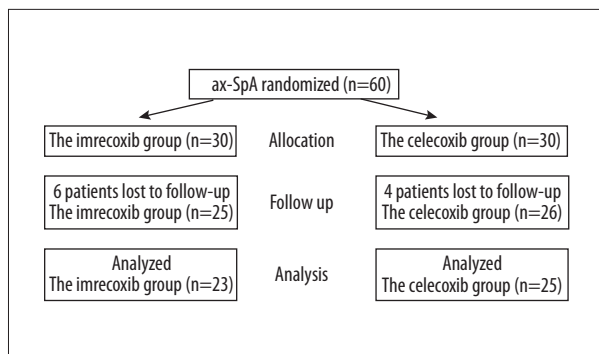


Figure 1. Follow chart of ax-SpA randomized patients.

Results

General information

A total of 51 out of 60 axSpA patients completed the 12-week follow-up. The general features of nine patients were lost to follow-up but were not significantly difference from patients who completed the follow-up. The imrecoxib group was composed of 25 patients, and the celecoxib group was composed of 26 patients (Figure 1). There were 35 male patients and 16 female patients in the overall group. The male to female ratio was 2.2 to 1. The age range was 18 to 48 years. The duration was 0.5 to 22 years. In all, 51 patients underwent HLA-B27 testing, of which 47 cases (92.16%) showed positive results (Table 1).

Week 4 of treatment compared with baseline showed that patients in the imrecoxib group and celecoxib group improved in clinical parameters (BASDAI, BASFI, patient’s global assessment, tragus-to-wall distance, lumbar side flexion, finger to floor distance, intermalleolar distance, and Schober test) as well as inflammatory markers ESR ($p < 0.05$). Differences in indicators of the degree of improvement in the two groups were not statistically significant ($p > 0.05$). On week 4 CRP levels in the celecoxib group decreased compared with baseline, while those in the imrecoxib group increased compared with baseline. However, there was no significant difference ($p > 0.05$). Changes from baseline in the two groups on week 4 were expressed as mean \pm standard deviation (-0.7 ± 13.26 vs. 4.01 ± 11.44 , respectively). The difference was not statistically significant ($p > 0.05$). On week 12 of the treatment, patients in the imrecoxib group and celecoxib group improved in the clinical indicators and inflammatory markers compared with baseline ($p < 0.05$). The differences between the two groups were not statistically significant ($p > 0.05$) (Table 2).

Adverse reactions

No serious adverse events occurred among axSpA patients in the imrecoxib or celecoxib group. The overall incidence of gastrointestinal reactions was 9.81%. Gastrointestinal reactions mainly manifested themselves in abdominal pain and constipation. Cardiovascular adverse events, with the incidence of 5.88%, mainly manifested themselves in increased blood pressure. The following data showed the comparisons

Table 1. Demographic and baseline clinical characteristics of 168 ax-SpA patients (ratio/range/mean \pm standard deviation).

General characteristics	The imrecoxib group (25)	The celecoxib group (26)	All patients (51)	P values
The average ages (years)	30.4 (18–48)	38.67 (21–38)	29.51 (18–48)	0.84
Numbers of male patients (%)	16 (64%)	19 (73.08%)	35 (68.63%)	0.80
Duration (years)	6.15 (1–13)	7.74 (0.5–22)	6.96 (0.5–22)	0.96
HLA-B27 positive (%)	23 (92%)	24 (92.31%)	47 (92.16%)	0.88
BASDAI scores (0–100)	4.06 \pm 1.88	3.87 \pm 1.84	3.96 \pm 1.84	0.91
BASFI scores (0–100)	2.24 \pm 2.49	1.48 \pm 1.70	1.85 \pm 2.13	0.40
Patient’s global assessment (0–100)	5.65 \pm 1.73	5.48 \pm 1.78	5.56 \pm 1.73	0.61
Tragus-to-wall distance (cm)	14.92 \pm 4.02	15.01 \pm 3.85	15.12 \pm 3.81	0.37
Lumbar side flexion (cm)	13.98 \pm 6.8	13.14 \pm 7.07	13.55 \pm 6.86	0.42
Schober tests (cm)	3.82 \pm 2.09	3.88 \pm 2.20	3.85 \pm 2.12	0.43
Finger to floor distance (cm)	15.48 \pm 15.13	11.64 \pm 11.32	13.51 \pm 13.29	0.42
Intermalleolar distance (cm)	113.48 \pm 29.38	113.3 \pm 31.63	113.4 \pm 30.17	0.94
ESR (mm/h)	619.63 \pm 21.96	19.28 \pm 18.89	19.45 \pm 20.19	0.84
CRP (mg/L)	12.21 \pm 13.28	12.31 \pm 14.31	12.26 \pm 13.64	0.80

Table 2. Changes in clinical indicators and inflammatory markers in the two groups on the 4th week and 12th week of treatment (mean ± standard deviation).

Therapeutic effect indexes	Variation value of 4 weeks in Imrecoxib group	Variation value of 4 weeks in Celecoxib group	P	Variation value of 12 weeks in Imrecoxib group	Variation value of 12 weeks in Celecoxib group	P
BASDAI scores	-0.8±1.67	-0.79±1.20	0.714	-0.82±2.41	-1.51±1.91	0.427
BASFI scores	-0.35±1.72	-0.22±1.23	0.234	-0.57±2.38	-0.12±1.86	0.484
Patient's global assessment	-1.15±1.18	-1.3±1.45	0.210	-2.40±2.58	-2.15±2.16	0.768
Tragus-to-wall distance	-0.51±2.94	-0.85±1.54	0.056	-0.44±3.08	-0.32±2.12	0.407
Lumbar side flexion	0.91±2.82	1.19±1.87	0.145	1.57±3.08	0.98±3.16	0.829
Schober tests	0.68±0.90	0.91±1.16	0.349	0.42±1.17	0.52±1.77	0.193
Finger to floor distance	-2.85±11.23	-1.50±8.29	0.443	-0.79±13.31	-1.86±7.54	0.062
Intermalleolar distance	16.78±18.45	12.18±21.85	0.443	12.09±23.40	9.83±25.70	0.841
ESR (mm/h)	-1.47±10.76	-7.15±11.22	0.977	-6.17±18.20	-10.25±13.58	0.986
CRP (mg/L)	4.01±11.44	-0.7±13.26	0.864	-0.89±12.39	-3.4±12.74	0.734

Table 3. Adverse reactions in a 12-week follow-up.

Adverse reactions	The imrecoxib group Cases (%)	The celecoxib group Cases (%)	Overall adverse reactions Cases (%)	P values	F values
Gastrointestinal reactions	4 (16.0%)	6 (23.08%)	10 (19.61%)	0.41	0.73
Abdominal pains	3 (12.00%)	4 (15.38%)	7 (13.73%)	0.12	1.00
Constipation	1 (4.00%)	2 (7.69%)	3 (5.88%)	0.31	1.00
Cardiovascular adverse events	2 (8.00%)	1 (3.85%)	3 (5.88%)	0.40	0.61
Hypertension	2 (8.00%)	1 (3.85%)	3 (5.88%)	0.40	0.61

between the imrecoxib group and celecoxib group: hypertension (8% vs. 3.85%, respectively); and gastrointestinal adverse reactions (16% vs. 23.08%, respectively) including abdominal pains (12% vs. 15.38%, respectively) and constipation (4% vs. 7.69% respectively). The differences were not statistically significant ($p>0.05$) (Table 3). During the follow-up, three cases with abdominal pain showed mild symptoms three days after taking drugs. The symptoms were relieved and disappeared three days later. Upper respiratory tract infection during the follow-up included one case that showed mildly elevated alanine aminotransferase (ALT) of 59 U/L and aspartate aminotransferase (AST) of 47 U/L. After one week the symptoms were relieved and transaminase levels returned to normal.

SPARCC score changes

At week 12 weeks, the SPARCC scores in the two groups of patients decrease compared with baseline. The difference was not statistically significant ($p>0.05$) (Figure 2, Table 4).

Serum DKK-1 levels at week 12 of treatment

Serum DKK-1 levels at week 12 are shown in the Table 5. Serum DKK-1 levels in the patients from the two group decreased from baseline after 12 weeks of treatment. The differences were not statistically significant ($p>0.05$) (Figure 3).

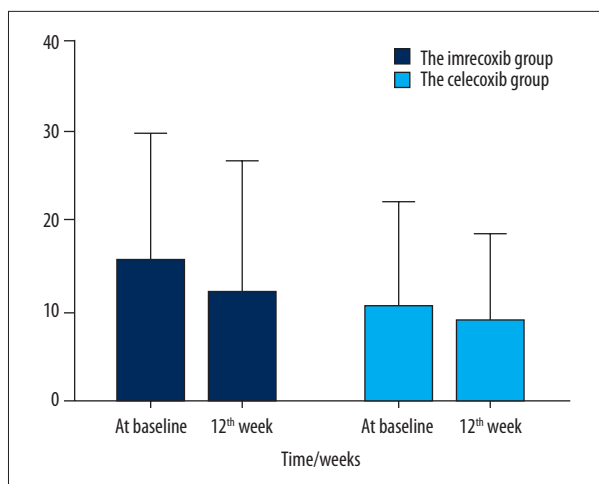


Figure 2. Comparison between SPARCC scores at baseline and week 12 in the imrecoxib group and the celecoxib group.

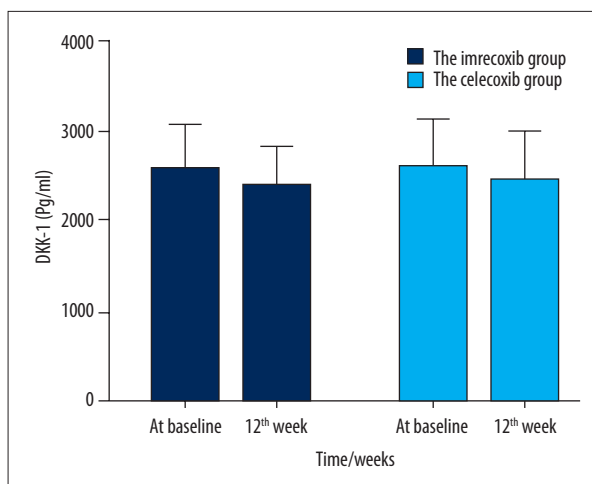


Figure 3. Comparison between serum DKK-1 levels at baseline and at week 12 in the imrecoxib group and celecoxib group.

Table 4. SPARCC scores at baseline and in the 12th week in the imrecoxib group and the celecoxib group.

SPARCC scores	N	Baseline	The 12 th week	p Values
The imrecoxib group	23	13.5±14.19*	11.9±14.73	0.064
The celecoxib group	25	11.71±13.08#	8.09±8.14	0.162

* Compared with 12w SPARCC, t=1.967; # Compared with 12w SPARCC, t=1.451.

Table 5. Serum DKK-1 levels at baseline and in the 12th week in the imrecoxib group and celecoxib group.

Serum DKK-1 levels	N	Baseline	The 12 th week	p Values
The imrecoxib group	25	2537.1±493.0*	2354.9±479.6	0.085
The celecoxib group	26	2573.2±683.9#	2423.5±568.5	0.077

*: Compared with 12w DKK-1, t=1.815; # Compared with 12w DKK-1, t=1.864.

Correlation analyses of serum DKK-1 levels, clinical parameters, inflammatory markers, and radiographic parameters

At baseline, serum DKK-1 levels and clinical parameters (BASDAI, BASFI, patient's global assessment, tragus-to-wall distance, lumbar side flexion, finger to floor distance and intermalleolar distance), inflammatory markers (ESR, CRP), and SPARCC scores did not show any significant correlation in the imrecoxib group ($p > 0.05$). For DKK-1 levels and BASFI and the Schober test was significantly correlated in the celecoxib group ($p < 0.05$). DKK-1 levels were negatively correlated with BASFI ($R = -0.048$, $p = 0.027$), and positively correlated with the Schober test ($R = 0.437$, $p = 0.048$) in the imrecoxib group. DKK-1 levels were not correlated to the remaining indicators (Table 6).

Discussion

Spine arthritis is the most common rheumatic disease, and is also the most common cause of disability in adolescents. For axial spondyloarthritis (axSpA), there is currently no effective treatment. Drugs which have relatively broad clinical application are two major categories: non-steroidal anti-inflammatory drugs (NSAIDs) and tumor necrosis factor (TNF) antagonists. DMARDs drugs such as methotrexate and sulfasalazine, which have been proven to be effective drugs for the treatment of peripheral joints and rheumatoid arthritis, have not been confirmed to have significant effects on axSpA [1,6–8]. Although TNF antagonists are able to better control symptoms and improve function, they do not have affirmative effects on the progress of disease and the formation of osteophytes. Therefore, they cannot indeed improve the prognosis [9]. Although many new biological agents and small-molecule drugs that affect bone metabolism have shown some potential,

Table 6. Correlation analyses of serum DKK-1 levels, clinical parameters, inflammatory markers and radiographic parameters at baseline in ax-SpA patients.

Correlation analyses Indicators	The imrecoxib group		The celecoxib group	
	R values	P values	R values	P values
BASDAI scores	-0.186	0.431	-0.060	0.797
BASFI scores	-0.228	0.334	-0.482	0.027
Patient's global assessment	-0.315	0.177	-0.222	0.333
Tragus-to-wall distance	-0.217	0.358	-0.366	0.103
Lumbar side flexion	-0.093	0.697	0.399	0.073
Intermalleolar distance	0.218	0.355	-0.140	0.545
Schober tests	0.011	0.964	0.437	0.048
Finger to floor distance	-0.341	0.141	-0.330	0.144
ESR (mm/h)	0.062	0.796	-0.343	0.129
CRP (mg/L)	0.035	0.883	-0.374	0.095
SPARCC scores	-0.214	0.351	-0.006	0.979

their clinical applications need to be further studied. Therefore, NSAIDs are still the main drugs for the treatment of ankylosing spondylitis (AS) [10].

NSAIDs are the most widely used drugs in the world and account for the largest market share. The role of NSAIDs in the treatment of AS is becoming increasingly important. Recently, they are believed to have not only anti-inflammatory analgesic effects but also effects on improving function, slowing joint damage, and inhibiting the formation of osteophytes [11,12]. Imrecoxib is a kind of NSAID, which has therapeutic effects and side effects similar to celecoxib. It is one of the few chemicals explored originally by the Chinese. However, there is a lack of clinical evidence of its clinical application in the treatment of other rheumatic diseases [13,14].

This randomized, double-blind, prospective trial showed that both imrecoxib and celecoxib can significantly improve axSpA patient's pain, disease activity and function, and can reduce MRI sacroiliac joint inflammation. These therapeutic effects were significant in week 4 of treatment, and more significant in week 12, indicating that imrecoxib has analgesic and anti-inflammatory effects no less than celecoxib, and it improves patient's function and quality of life, and possibly further delays the progression of the disease as seen on imaging.

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Since the observation time in our study was short, there were no observed statistically significant radiological changes. Despite a downward trend in serum DKK-1 levels, there was no statistically significant difference, which may also be related to the short observation time and the small number of cases. New bone formation in patients takes a long time. To study both of these COX-2 inhibitors and how they inhibit the action of bone destruction through intervention in DKK-1 levels requires larger sample sizes and long-term follow-up studies.

Conclusions

In short, a three-month, randomized, double-blind, positive drug-controlled observational study showed that imrecoxib 0.4 g/d was not inferior to celecoxib 0.4 g/d in the control of symptoms of axSpA, reducing inflammation and disease activities, improving mobility function, and other disease aspects. A larger sample, a more long-term observation, and verification are needed to determine whether the two drugs affect DKK1 levels, a key factor in regulating bone formation and thus inhibit disease process.

Conflict of interest

None.

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