Evaluation of the efficacy and safety of β-D-mannuronic acid in patients with ankylosing spondylitis: A 12-week randomized, placebo-controlled, phase I/II clinical trial

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ABSTRACT

Objective: To evaluate the efficacy, safety and tolerability of β-D-mannuronic acid (M2000) in the treatment of ankylosing spondylitis (AS).

Methods: The study was a 12-week randomized, double-blind, placebo-controlled, phase I/II clinical trial with 3 treatment arms: placebo, β-D-mannuronic acid and naproxen. Patients who had AS according to the modified New York criteria, with active disease at baseline were eligible for study. Primary outcome measure was the Assessment of SpondyloArthritis international Society (ASAS) 20 response rate at week 12.

Results: Of the 85 randomized patients, 27 were allocated to receive placebo, 28 naproxen, and 30 β-D-mannuronic acid. There were no statistically significant differences between treatment groups at baseline. Of the patients receiving β-D-mannuronic acid, 57.7% achieved an ASAS20 response at week 12, compared with 59% of the patients in the naproxen group (P > 0.05) and 19% of the patients in the placebo group (P = 0.007). In comparison with patients receiving placebo over the 12-week treatment period, those receiving β-D-mannuronic acid and naproxen demonstrated statistically significantly greater improvement in all secondary endpoints. Interestingly, β-D-mannuronic acid reduced some parameters associated with inflammation more effectively than naproxen and placebo. The incidence of gastrointestinal and other adverse events were higher on naproxen than on β-D-mannuronic acid and placebo.

Conclusion: The present study demonstrated similar efficacy, but with a more favorable safety profile for β-D-mannuronic acid than naproxen and, therefore, suggest that β-D-mannuronic acid is suitable for the management of AS.

Trial registration: Iranian registry of clinical trials; www.irct.ir; IRCT2013062213739N1.

1. Introduction

Ankylosing spondylitis is an inflammatory and debilitating disease which is the prototype of the spondyloarthritides (SpA). It is characterized by inflammation of the sacroiliac joints, loss of spinal mobility and the absence of rheumatoid factor [1]. Over time, chronic spinal inflammation can cause a complete fusion of the vertebrae, a process known as ankylosis and may form a 'bamboo spine' [2]. To date, the etiology of the disease remains unknown [3,4]. Studies have shown a major role for genes in the pathogenesis of AS. The most important

genetic association is with human leukocyte antigen-B27 (HLA-B27). There is a close correlation between the frequency of several subtypes of HLA-B27 and the prevalence of AS in populations [5,6]. AS affects predominantly men between the ages of 18 to 45 years, leading to significant loss of work productivity and quality of life [1,7].

Although, disease modifying antirheumatic drugs (DMARDs) such as methotrexate and sulfasalazine, have high efficacy in the treatment of rheumatoid arthritis (RA) and are considered as the preferred treatment for active forms of RA, there is no evidence that they have any role in the treatment of the axial manifestations of AS [8]. While the tumor necrosis factor-α (TNF-α) inhibitors are highly effective in active AS, their expense, their potential side effects and questionable efficacy to reduce radiographic progression in AS patients, have tempered optimism [9,10]. Until recently, non-steroidal anti-inflammatory drugs (NSAIDs) are first line agents for treatment of axial and peripheral manifestations of spondyloarthritis [11,12]. In spite of their therapeutic efficacy, they cause significant gastrointestinal (GI), cardiovascular and renal toxicities, conditions that limit their use. For several years, scientists have tried to find safer and more effective types of NSAIDs [13].

The β-D-mannuronic acid (M2000) (DE-102016113018.4), a novel NSAID with immunosuppressive property, is a safe agent without any toxicity on the GI tract and kidney function [14]. It has shown therapeutic benefits with the greatest tolerability, safety and efficacy in various animal disease models such as experimental autoimmune encephalomyelitis (EAE), adjuvant induced arthritis (AIA), acute glomerulonephritis and nephrotic syndrome [15–18]. Recently, studies have shown β-D-mannuronic acid inhibitory effect on Toll-like receptor (TLR) 2, 4 signaling in human embryonic kidney (HEK) 293 cell lines with no evidence of cytotoxicity [19]. This data might supply new insights into the possible role of this drug in order to introduce it as a TLR signaling pathway inhibitor. Selective blockade of TLR signaling have been developed as a new approach for treatment many inflammatory diseases [19]. The present study was a part of phase I/II clinical trial to assess the safety and preliminary efficacy of β-D-mannuronic acid in Iranian patients with AS.

2. Patients and methods

2.1. Patients

85 patients with ankylosing spondylitis fulfilling the modified New York criteria that had active disease, defined as a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 on a 0–10 numerical rating scale (NRS) and Bath Ankylosing Spondylitis Functional Index (BASFI) score ≥ 4 were examined. Other relevant eligibility criteria were an age range of 18–45 years, the presence of axial involvement, no peripheral involvement (apart from hips and/or shoulders) and the need for daily treatment with NSAIDs. Exclusion criteria were history of fever and infectious diseases, positive pregnancy test or lactation, history of other concomitant (Hepatic, renal, cardiovascular, autoimmune, neurological, psychiatric, endocrinologic) diseases or malignancies. In addition, patients were excluded if they required the use of concomitant methotrexate > 15 mg/week, prednisolone > 10 mg/d. TNF-inhibitor treatment was not allowed before and during the study. Washout periods of ≥ 3 days for NSAIDs were required before baseline. Written informed consent was obtained from all patients. All of the patients were enrolled from 3 medical centers in Iran, including the outpatient rheumatology clinic of Rheumatology Research Center (Shariati Hospital), Iran Rheumatology Center (Tehran, Iran) and the Iranian AS Society, a member of the Ankylosing Spondylitis International Federation (ASIF).

2.2. Study design

Our study was a part of phase I/II (IRCT2013062213739N1)

randomized, multicenter, placebo-controlled trial conducted between 20 April 2014, and 20 April 2015. The study was designed for the comparison of the efficacy and safety of β-D mannuronic acid with that of naproxen and placebo over 12 weeks in the patients with active AS. Patients were randomly assigned to one of the three treatment arms using block randomization method. As well, this study was a double-blinded trial that patients and outcomes assessors remained unaware of the intervention assignments throughout the study. The protocols were reviewed and approved by regulatory authorities and the ethics committee of Tehran University of Medical Sciences (Tehran, Iran) and the study was conducted in accordance with the principles of the Declaration of Helsinki, the International Conference on Harmonisation guidelines for Good Clinical Practice. Medical history, physical examinations and clinical outcome assessments were performed at baseline, weeks 4 and 12. For safety assessment, samples were collected for hematology, clinical chemistry, routine urinalysis and fecal occult blood test at baseline, weeks 4 and 12. In addition, at each visit, patients were examined and questioned about adverse events (AEs).

2.3. Study treatment

After confirmation that the patients fulfilled the defined criteria, they were randomly assigned at a 1:1:1 ratio to receive either β-D mannuronic acid 500 mg 2 times a day, naproxen 500 mg twice daily or matching placebo orally for 12 weeks.

2.4. Outcome measures

The primary efficacy measure was a 20% improvement according to the ASAS criteria (ASAS 20) after 12 weeks. The ASAS20 improvement criteria needs an improvement of ≥ 20% and ≥ 1 unit in at least 3 of 4 domains (patients' global assessment, pain, function and inflammation) on a scale of 10 and no worsening of ≥ 20% and ≥ 1 in remaining domain on a scale of 10.

Secondary efficacy endpoints were the following parameters, BASDAI score, BASFI score, Ankylosing Spondylitis quality of life (ASQoL), patients' and physicians' global assessment (0–10 NRS), duration of morning stiffness and CRP (C-reactive protein) level.

The safety endpoints included incidence and type of AEs, serious AEs (SAEs), infection and changes in clinical laboratory (hematological and biochemical) parameters from baseline to week 12. All parameters were recorded at all visits. Additionally, findings on urinalysis, stool exam, blood pressure, heart rate, weight and height were obtained at each visit.

2.5. Statistical analysis

Data were represented as means and standard deviations (SD), or as least square means (LSM) and standard error of means (SE) for numerical variables and frequencies or percentages for categorical variables. The intention-to-treat (ITT) analysis approach was performed for analyzing missing values and comprised all patients who were randomized, received at least one dose of study treatment and had at least one efficacy evaluation after baseline. For the primary efficacy analysis, patients who withdrew before week 4 were categorised as not achieving the ASAS20 improvement. ASAS 20 responses were analyzed between treatment groups by the chi-square test and logistic regression. Treatment group differences in continuous variables were evaluated with analysis of covariance, with baseline values as covariates. The safety population included all patients who received at least one dose of study treatment. The frequency of patients reporting adverse events in each treatment group was compared using Fisher's exact test. All statistical tests were two-sided, and a P-value < 0.05 was considered to be statistically significant. The data were analyzed using SPSS software Version 20 (IBM Corporation, Armonk, New York, USA).

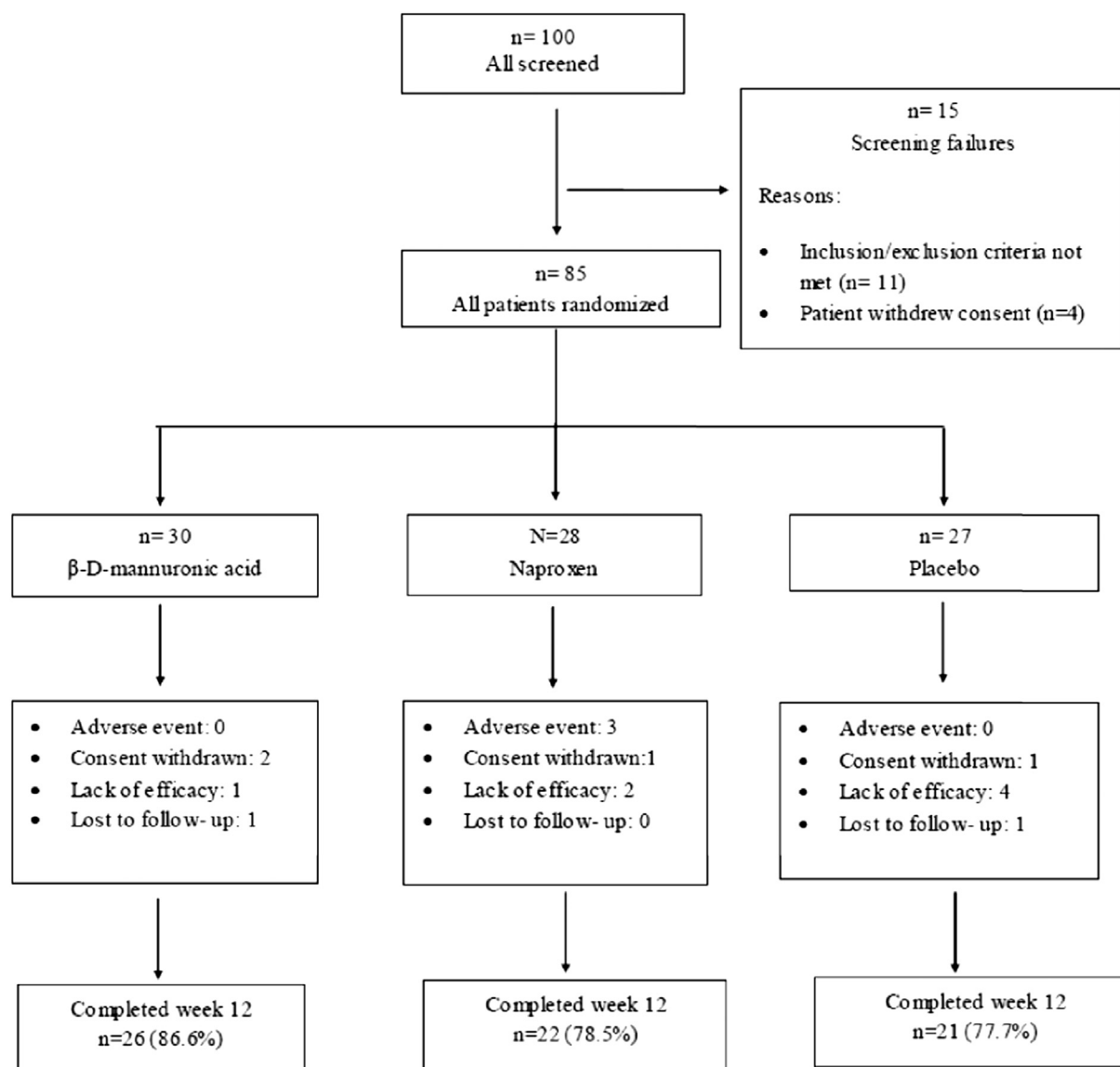For the primary endpoint, a sample size of 28 patients in each group

Fig. 1. Summary of patient disposition. A total of 100 patients were screened and 15 patients were excluded mostly due to meeting the exclusion criteria. All patients randomized were included in the full analysis set (FAS) and the safety set.

was needed to provide 90% statistical power to detect a difference of 40% in the ASAS20 response between the β-D-mannuronic acid and placebo-treated groups at the 5% significance level adjusted for a drop-out rate of 10%.

3. Results

3.1. Disposition and characteristics of the patients

Of the 85 randomized patients, 30 were assigned to β-D-mannuronic acid, 28 to naproxen and 27 to placebo group (Fig. 1). Baseline demographic and disease characteristics were similar in the three treatment groups (Table 1), and there were no clinically meaningful differences between the treatment groups for any of the evaluated characteristics. The majority of patients completed the study through week 12 (86.6% in the β-D-mannuronic acid group, 78.5% in the Naproxen group and 77.7% in the placebo group). All of patients had high disease activity (BASDAI score ≥ 4 [0–10 NRS] and BASFI score ≥ 4 [0–10 NRS]). The majority of patients enrolled in this study were male (70.5%), and positive for the HLA-B27 allele (69.4%) (The overall

prevalence of HLA-B27 in AS patients is around 90% worldwide, but such prevalence is much lower in Iranian population) [20]. The mean age at diagnosis in the patients was 30.4 years (range 18–45 years), and the mean disease duration was 11.4 ± 7.1 years.

3.2. Efficacy

Of the patients receiving β-D-mannuronic acid, 57.7% achieved an ASAS20 response at week 12, compared with 59% of the patients in the naproxen group (P > 0.05) and 19% of the patients in the placebo group (P = 0.007) (Fig. 2). The ASAS20 responses in the β-D-mannuronic acid group compared to the naproxen group were not statistically significant as early as week 4 and at each visit until week 12. The greater ASAS20 responses in the β-D-mannuronic acid group and the naproxen group than the placebo group were statistically significant as early as week 4 and at each visit until week 12 (Fig. 2).

In comparison with patients receiving placebo over the 12-week treatment period, those receiving β-D-mannuronic acid and naproxen demonstrated statistically significantly greater improvement in all secondary endpoints. Baseline mean values for the secondary endpoints

Table 1
Baseline demographic and disease characteristics.

	β-ᴅ-Mannuronic acid	Naproxen	Placebo
	(n = 30)	(n = 28)	(n = 27)
Age, mean ± SD	31.4 ± 9.1	29.3 ± 5.9	30.6 ± 6.1
Male n (%)	22 (73.3%)	20 (71.4%)	18 (66.6%)
Disease duration in years, mean ± SD	11.8 ± 8.6	11.5 ± 9.1	11.0 ± 6.0
Weight (kg), mean ± SD	72.5 ± 13.6	70.5 ± 12.8	72.0 ± 14.1
Body mass index (kg/m^2), mean ± SD	26.9 ± 5.2	26.4 ± 5.1	27.0 ± 5.3
HLA-B27 Positivity n (%)	21 (70%)	19 (67.8%)	19 (70.3%)
Total back pain (0–10 NRS), mean ± SD	5.8 ± 1.4	6.2 ± 2.0	6.5 ± 2.4
BASDAI (0–10 NRS), mean ± SD	5.8 ± 1.3	5.7 ± 1.4	5.9 ± 1.5
BASFI (0–10 NRS), mean ± SD	4.4 ± 2.0	4.2 ± 1.8	4.7 ± 1.8
ASQoL Score (range 0–18), mean ± SD	9.8 ± 4.5	9.1 ± 4.0	9.2 ± 4.8
Physician's global assessment of disease activity (0–10 NRS), mean ± SD	6.4 ± 1.8	6.3 ± 1.5	6.7 ± 2.5
Patient's global assessment of disease activity (0–10 NRS), mean ± SD	6.5 ± 2.0	6.5 ± 2.1	5.8 ± 2.7
CRP (mg/L), mean ± SD	8.3 ± 6.7	8.0 ± 4.7	8.1 ± 4.8
Duration of morning stiffness (0–10 NRS), mean ± SD	4.8 ± 2.5	5.0 ± 1.8	5.6 ± 2.7

All values are expressed as mean ± SD unless otherwise indicated. ASQoL, Ankylosing Spondylitis quality of life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C-reactive protein; HLA- B27, Human leukocyte antigen-B27; NSAID, Non-steroidal anti-inflammatory drug; NRS, numerical rating scale.

were generally similar among the 3 treatment groups (Table 1). Measures of disease activity (BASDAI score) and physical function (BASFI score) during 12 week study were significantly improved in the β-ᴅ-mannuronic acid and naproxen groups compared with the placebo group. The LSM ± SE change from baseline at week 12 in BASDAI score was − 1.8 ± 0.3 in the β-ᴅ-mannuronic acid group and − 2.1 ± 0.3 in the naproxen group (P = 0.9) compared with − 0.3 ± 0.4 in the placebo group (P = 0.009) (Table 2). The LSM ± SE change from baseline at week 12 in BASFI score was − 1.1 ± 0.3 in the β-ᴅ-mannuronic acid group and − 1.5 ± 0.3 in the naproxen group (P = 0.8) compared with 0.1 ± 0.3 in the placebo group (P = 0.021). Total back pain decreased similarly between baseline and week 12 in β-ᴅ-mannuronic acid (LSM ± SE change from baseline − 2.1 ± 0.2) and naproxen (LSM ± SE change from baseline − 2.3 ± 0.4) groups (P = 0.87). These values were statistically significant compared with values in placebo (LSM ± SE change from baseline − 0.56 ± 0.5) group (P = 0.03).

A similar result was seen for the duration of morning stiffness with improvements by − 2.3 ± 0.2 (LSM ± SE change from baseline) on β-ᴅ-mannuronic acid group and − 1.9 ± 0.3 (LSM ± SE change from baseline) on naproxen group (P = 0.59) versus − 0.3 ± 0.3

(LSM ± SE change from baseline) on placebo group (P < 0.001). There was a numerically decrease in the CRP level over the 12 weeks in β-ᴅ-mannuronic acid − 1.3 ± 0.9 (LSM ± SE change from baseline) and naproxen − 1.1 ± 1.1 (LSM ± SE change from baseline) treatment groups (P = 0.7) compared with the placebo 0.19 ± 1.1 (LSM ± SE change from baseline) group (P = 0.6) (Table 2).

In addition, similar improvements from baseline to week 12 were observed in β-ᴅ-mannuronic acid and naproxen groups for Patient's Global Assessment of Disease Activity, Physician's Global Assessment of Disease Activity and ASQol score that were statistically significant compared with placebo group (Table 2).

3.3. Safety

Overall, β-ᴅ-mannuronic acid was well tolerated. During the study, the incidence of AEs were higher in the naproxen treatment group (39.2%) compared with β-ᴅ-mannuronic acid (16.6%) (P < 0.05) and the placebo (29.6%) groups (P = 0.3). Although 3 patients withdrew from the study because of AEs in the naproxen treatment group, there were no patients in the 12 week β-ᴅ-mannuronic acid and placebo groups who discontinued due to an AE. The most commonly type of AEs
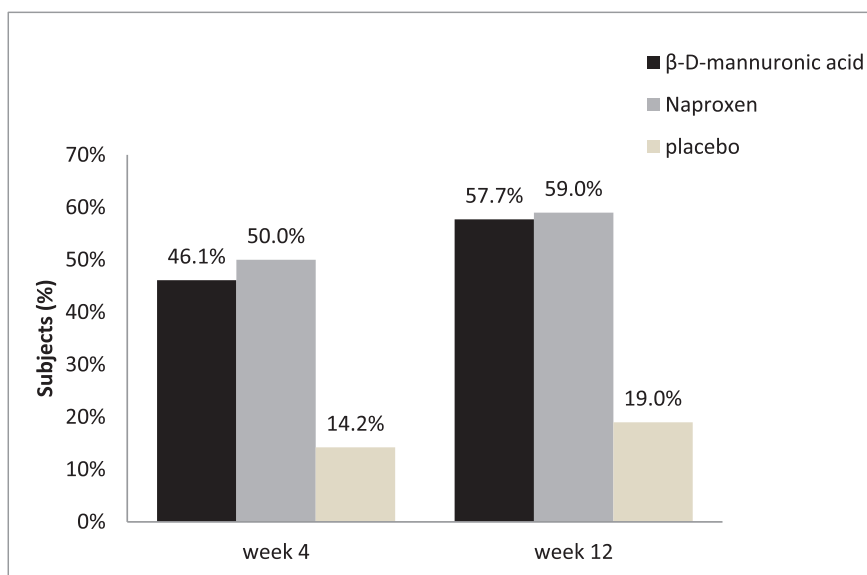

Fig. 2. Patients (%) achieving an Assessment in Ankylosing Spondylitis 20 response at weeks 4 and 12 in three treatment groups.

Table 2
Efficacy outcomes at week 12 in patients with AS.

Assessment	Change from baseline to week 12						
	Placebo	β-D-Mannuronic acid	Naproxen	Difference in LSM	P^a	Difference in LSM	P^b
	(n = 27)	(n = 30)	(n = 28)	(95% CI)[a]		(95% CI)[b]	
BASDAI (0–10 NRS)	− 0.3 ± 0.3	− 1.8 ± 0.3	− 2.1 ± 0.3	− 1.5 (− 2.7 to − 0.3)	0.009	0.4 (− 0.8 to 1.5)	NS
BASFI (0–10 NRS)	0.1 ± 0.3	− 1.1 ± 0.3	− 1.5 ± 0.3	− 1.2 (− 2.4 to − 0.1)	0.021	0.3 (− 0.7 to 1.4)	NS
Total back pain (0–10 NRS)	− 0.5 ± 0.4	− 2.1 ± 0.2	− 2.3 ± 0.4	− 1.5 (− 2.9 to − 0.09)	0.03	0.2 (− 1.2 to 1.6)	NS
ASQoL score (range 0–18)	− 0.5 ± 0.7	− 3.1 ± 0.6	− 3.4 ± 0.7	− 2.5 (− 5.0 to − 0.07)	0.04	0.27 (− 2.2 to 2.7)	NS
Physician's global assessment of disease activity (0–10 NRS)	− 0.08 ± 0.7	− 2.5 ± 0.5	− 2.8 ± 0.60	− 2.4 (− 4.7 to − 0.11)	0.03	0.28 (− 1.8 to 2.4)	NS
Patient's global assessment of disease activity (0–10 NRS)	− 0.4 ± 0.4	− 1.9 ± 0.4	− 2.3 ± 0.4	− 1.5 (− 3.0 to − 0.004)	0.04	0.3 (− 1.2 to 1.8)	NS
Duration of morning stiffness (0–10 NRS)	− 0.3 ± 0.3	− 2.3 ± 0.2	− 1.9 ± 0.3	− 2.0 (− 3.0 to − 0.9)	< 0.001	− 0.5 (− 1.5 to 0.57)	NS
CRP (mg/L)	0.19 ± 1.1	− 1.3 ± 0.9	− 1.1 ± 1.1	− 1.4 (− 5.1 to 2.2)	0.6	− 0.19 (− 3.8 to 3.4)	NS

ASQoL, Ankylosing Spondylitis quality of life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C reactive protein; LSM, Least square mean; NRS, numerical rating scale.
  [a] β-D-Mannuronic acid versus placebo.
  [b] β-D-Mannuronic acid versus naproxen. NS = Not significant.

Table 3
Adverse events during 12 week period of the study.

	β-D-Mannuronic acid	Naproxen	Placebo
	(n = 30)	(n = 28)	(n = 27)
All adverse events	5(16.6%)	11(39.2%)[†]	8(29.6%)
Drug-related AEs	0(0%)	6(21.4%)[†]	4(14.8%)[‡]
Serious AEs	0	0	0
Drug withdrawn due to AEs	0 (0%)	3(10.7%)	0(0%)
Most common AEs			
Headache	1(3.3%)	3(10.7%)	4(14.8%)
Diarrhea	0	0	0
Vertigo	2(6.6%)	3(10.7%)	2(7.4%)
Nausea	0	0	0
Heartburn	2(6.6%)	4(14.2%)	1(3.7%)
GI bleeding	0	0	0
Abdominal pain	0	1(3.5%)	1(3.7%)
Rash	0	0	0
Urticaria	0	0	0
Nasopharyngitis	0	0	0
Pharyngitis	0	0	0
Elevated AST/ALT	0	0	0
Leukopenia/thrombocytopenia	0	0	0
BUN (mg/dL), mean ± SD	12.8 ± 2.8	13.1 ± 3.6	12.7 ± 3.5
Creatinine (mg/dL), mean ± SD	1.0 ± 0.2	1.0 ± 0.18	0.95 ± 0.15
Sodium (mmol/L), mean ± SD	140.9 ± 3.1	143.0 ± 3.1	138 ± 4.9
Potassium (mmol/L), mean ± SD	4.2 ± 0.42	4.1 ± 0.50	4.5 ± 0.21
Urinalysis	Normal	Normal	Normal

Values are the number (%) of patients. AE, adverse events; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, Blood urea nitrogen.
  [†] P ≤ 0.05 β-D-mannuronic acid versus naproxen.
  [‡] P ≤ 0.05 β-D-mannuronic acid versus placebo.

reported in this study are comparable with the recognized toxicities of NSAIDs. The most commonly reported clinical AEs in β-D-mannuronic acid, naproxen and placebo treatment groups were heartburn (6.6%, 14.2% and 3.7%, respectively), abdominal pain (0%, 3.5% and 3.7%, respectively), headache (3.3%, 10.7% and 14.8%, respectively) and vertigo (6.6%, 10.7% and 7.4%, respectively). All were mild to moderate in intensity. No serious AEs or deaths were detected during this study (Table 3). Moreover, the hematological, biochemical and urinalysis findings in β-D-mannuronic acid group did not show any consistent treatment-related effects. There were no statistically significant differences in mean Hb, RBC, HCT, MCV, MCH, MCHC, WBC and platelet values at weeks 0, 4 and 12 in β-D-mannuronic acid treatment group. These parameters were within the reference range throughout

the study. All of means and individual concentrations of the serum biochemical analyses in β-D-mannuronic acid treatment group were within the reference range throughout the study. There were no statistically significant differences in any of these parameters at any time points.

4. Discussion

This is the first study comparing the safety and efficacy of β-D-mannuronic acid (M2000) as a novel NSAID with immunosuppressive property versus naproxen and placebo in patients with active AS. This study demonstrated that β-D-mannuronic acid 500 mg two times a day showed similar efficacy to naproxen 500 mg twice daily during the 12-week period of treatment of AS; both β-D-mannuronic acid and naproxen demonstrated significantly superior efficacy when compared with placebo. Naproxen was selected as the active control because it is widely used by patients who have AS [21].

In the primary endpoint analysis, β-D-mannuronic acid showed to be comparable in efficacy to naproxen for ASAS20 response in patients with AS after 12 weeks of treatment, thereby confirming the therapeutic value of β-D-mannuronic acid within the options available for the management of AS. The results concerning the ASAS20 response in patients on β-D-mannuronic acid were consistent with other studies that used other NSAIDs for the treatment of AS [22,23].

The following goals are important in effective treatment of AS: relief of pain and stiffness, reduction of inflammation and improvement in physical function. There was a reduction of pain and improvement in BASDAI and BASFI scores in β-D-mannuronic acid and naproxen groups compared with placebo group with further improvement through to week 12. These results are comparable with those of similarly designed studies in AS using the other comparator treatments [23,24]. Interestingly, there was a decrease in the variables reflecting inflammation (such as CRP level and duration of morning stiffness) in the active treatment (β-D-mannuronic acid and naproxen) groups when compared with placebo group. Based on these results, we conclude that 1000 mg β-D-mannuronic acid is effective in AS.

The favorable anti-inflammatory effect of β-D-mannuronic acid, which can be considered at least comparable with that of conventional NSAIDs, must be evaluated with respect to its high safety profile. Our results confirmed the acceptable short-term safety profile of β-D-mannuronic acid in patients with AS. One of the most important concerns with the use of NSAIDs is the risk of gastrointestinal (GI), cardiovascular, and renal toxicities. The in vitro and animal model studies have shown that the β-D-mannuronic acid (M2000) is a safe NSAID with a low molecular weight and no detectable toxicity on GI tract and kidney

function. This novel NSAID, not only had no any side effect on kidney, but also, it has shown the potent therapeutic effect on experimental models of immune complex glomerulonephritis and nephrotic syndrome [14,17]. In addition, previous studies have shown that β-D-mannuronic acid is highly tolerable and biocompatible with no cytotoxic effect compared with diclofenac, dexamethasone and piroxicam [17]. In our analyses, β-D-mannuronic acid was safe and well tolerated with better GI tolerability than naproxen. The majority of patients in the naproxen group and a few in placebo group received an acid-suppressing medication during study. β-D-Mannuronic acid also demonstrated a favorable renal tolerability profile (Table 3). In the present study, hypertension-related AEs were relatively uncommon and the incidence of these AEs in the β-D-mannuronic acid and naproxen groups was generally similar. However, it should be noted that the number of patients was too small and the period of treatment too short to allow further conclusions. Several studies have shown that continuously applied NSAIDs may have the ability to stop radiological progression in the AS patients, thereby underlining the need for introducing safe NSAIDs that are appropriate for continuous long-term treatment [25,26]. The present study demonstrated similar efficacy, but with a more favorable safety profile for β-D-mannuronic acid than naproxen and, therefore, it could be suggested that β-D-mannuronic acid is suitable for the long-term management of AS.

In summary, β-D-mannuronic acid treatment led to an acceptable reduction in the signs and symptoms of AS and this effect was sustained through week 12. Furthermore, β-D-mannuronic acid provided considerable benefits to patients with AS by also improving multiple disease aspects including disease activity, inflammation and physical function. However, β-D-mannuronic acid has not yet been tested for its effect on radiographic progression of AS. This study demonstrated that β-D-mannuronic acid, is effective, safe and generally well tolerated in patients with AS.

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Conflict of interest

The authors have declared no conflicts of interest.

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