



Original article

The safety and efficacy of Guluuronic acid (G2013) in ankylosing spondylitis: A randomized controlled parallel clinical trial



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ABSTRACT

Background: To assess the therapeutic efficacy, safety and tolerability of Guluuronic acid (G2013) in patients with ankylosing spondylitis (AS) patients.

Methods: This investigation was a 12-week randomized, placebo-controlled, phase I/II clinical trial involving 75 AS patients that were randomly divided into 3 groups: 25 as placebo, 25 Guluuronic acid and 25 naproxen groups. Patients who had AS with active disease at baseline according to the modified New York criteria were considered for this trial. The primary consequence measure was the Appraisal of Spondyloarthritis International Society (ASAS) 20 response-rate at week 12.

Results: There were no statistically significant differences between groups at the entry. ASAS20 response at week 12 was achieved (60.8%) in patients receiving Guluuronic acid compared with – (68.4% of) – patients in the naproxen group ($p > 0.05$) and (21.0%) of patients in the placebo group. In comparison with the placebo group from the baseline to week 12, patients who received Guluuronic acid and naproxen showed significantly greater improvement in all secondary endpoints. Moreover, Guluuronic acid decreased some inflammatory parameters more dramatically than naproxen and placebo group. Patients in the naproxen group had more incidence of gastrointestinal and others adverse events in comparison with Guluuronic acid and placebo groups.

Conclusion: The present research indicated that Guluuronic acid and naproxen are similar in terms of efficacy. However, Guluuronic acid had more notable safety characteristics identifying information than naproxen. Accordingly, it is proposed that Guluuronic acid could be appropriate for management of AS. Clinical trial identifier; IRCT2016091813739N4.

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Introduction

One of the chronic inflammatory diseases is ankylosing spondylitis (AS) which is related to the axial skeleton and relevant to spondyloarthritis (SpA), such that the inflammation of the sacroiliac joints, peripheral inflammatory arthropathy and lack of rheumatoid factor are the only major aspects of AS [1,2]. Some of AS symptoms consist of progressive stiffness of the spine, enthesitis, arthritis, inflammatory back pain and acute anterior uveitis [3]. Most of AS patients are basically male, aged between 18

to 45 years old, who suffer from insufficient productivity in their workplace as well as in their daily casual life activities [1]. The combination of genetic and environment factors affects the level of risk for this complicated AS disease [1]. For males above 40 years, HLAB-27 is the most effective gene cause of AS [1,4,5]. The Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) are the most important option for treatment of AS [6]. Meanwhile NSAIDs are the most common drugs for the treatment of acute and chronic pain but they show adverse events (AEs) affecting the gastrointestinal (GI) tract and cardiovascular system. They also exacerbate the inflammatory bowel disease that often accompanies spondyloarthropathies [3,7]. Despite the evidence and approved record of treatment for axial manifestations of AS, the Disease-Modifying Anti-Rheumatoid Drugs (DMARDs), such as sulfasalazine and methotrexate, are prescribed as a second choice after NSAIDs for

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AS treatment [2,8]. Although the tumor necrosis factor- α (TNF- α) inhibitors have been shown to be effective treatment for the signs and symptoms of AS, their expense, however, as well as the inconvenience of administration, along with the disputable approach to decrease radiographic progression in AS patients, may limit their use to refractory form of this disease [9,10].

Taking into account the high safety and also the lack of evidence pertaining to kidney disorder or toxicity on the GI tract in animal models, the G2013 (G2013), patented (DE-102016113017.6) was considered as a safe novel NSAID with immunomodulatory property for trial study. G2013 has shown its positive effects in experimental autoimmune encephalomyelitis (EAE) model and anti-aging [1,11]. The severity reduction, the delay on disease onset and the lower incidence on EAE were all the result of consuming G2013 [11]. Other experiment findings demonstrate that G2013 is capable to reduce miR-155 expression dramatically following the stimulation by Lipopolysaccharides (LPS) [13]. Study showed that G2013 is able to induce SH-2 containing inositol 5' polyphosphatase 1 (SHIP1), Suppressor of cytokine signaling 1 (SOCS1) and - on the other hand - cause decrease in TLR4, Myeloid differentiation primary response 88 (MYD88) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) at the level of gene expression while reducing IL-1 β as a pro-inflammatory cytokine, which might suggest decrease in inflammatory reactions [12,14]. Fard et al., showed that the G2013 is a safe agent with no side effects on differentiation, maturation and function of dendritic cells. Therefore, it could be a new immunosuppressive agent with no side effect in increasing the risk of infectious and cancers [14].

Materials and methods

Study design

This investigation was a phase I/II, randomized, multicenter, placebo-controlled trial "Clinical trial identifier; IRCT2016091813739N4". The AS patients were administrated at Rheumatology Shariati Hospital (Teheran, Iran), Rheumatology Research Center and Iran Rheumatism Center. This study started on April 2015 and perfected on August 2016. The protocol for this research was approved by the Ethics Committee of Teheran University of Medical Sciences (Tehran, Iran) and all patients participated in this study with full consent and satisfaction. The trial was organized according to the principles of the Declaration of Helsinki (International Conference on Guidelines Harmonization for Good Clinical Practice.) The propose of this study was to evaluate the therapeutic effect and safety of G2013 (DE-102016113017.6) compared with naproxen and placebo in patients with active AS over a 12 weeks period. The patients were randomized according to block randomization method (modified Zelen's design) to one of the three treatment arms [15]. Patients were randomly allocated into three groups of Treatment (G2013), Control (naproxen) and Placebo, at first, 5 blocks of 15, marked by the letters T, C and P (The letters indicating respectively "treatment", "control" and "placebo" groups). The groups were created so that 5 patients belonged to the treatment group, 5 patients to the control group and 5 patients to placebo group. The blocks were then randomly selected and arranged to obtain a sequential combination of 75 letters. Each letter was placed in a sealed packet according to the obtained sequence.

In order to assess the physical condition and clinical consequences, patients were examined at baseline, week 4 and week 12.

Also in this research, we measured samples gathered for hematology, clinical chemistry, routine urinalysis and fecal occult blood as safety parameters, at baseline, weeks 4 and 12. It should be noted that all patients were checked for adverse events (AEs)

such as GI bleeding, abdominal pain, diarrhea and drug related AEs at each visit.

Patients

According to the modified New York criteria, 75 patients entered in this trial that had the status of active AS, with Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 on a 0–10 cm VAS and Bath Ankylosing Spondylitis Functional Index (BASFI) score ≥ 4 . Based on the criteria for the eligibility of patients, all patients (in the range of 18–45 years) who entered in the trial had AS denotation with an axial involvement without peripheral involvement (apart from hips and/or shoulders). Other criteria of exclusion of patients from the study included a history of fever and infectious diseases, positive pregnancy test or lactation and history of other concomitant (hepatic, renal, cardiovascular, autoimmune, neurological, psychiatric, endocrinologic) diseases or malignancies. The enrolled population in this trial were the healthy set of patients with active AS, since our aim was to evaluate the efficacy along with the precise assessment of safety of this novel drug in the young participants suffering from the AS. Patients were ruled out from the study if they had received concomitant methotrexate >15 mg/week, prednisolone >10 mg/d (and other corticosteroids). In addition, patients who were treated with TNF-inhibitor before and during the study were not included in the study. Washout periods of ≥ 3 days for NSAIDs were needed before baseline. In the baseline characteristics of patients, the medication history was balanced across three different group. Mandatory signed written informed consent was obtained from all participants. All patients that participated in the study were enrolled from 3 medical centers in Iran, consisting of the outpatient rheumatology clinic of Rheumatology Research Center (Shariati Hospital), Iran Rheumatology Center (Teheran, Iran) and the Iranian AS Society, a member of the Ankylosing Spondylitis International Federation (ASIF).

Treatment protocol

Patients were randomized on the basis of 1:1:1 ratio to take either G2013 (500 mg) twice a day, naproxen (500 mg) 2 times daily and matching placebo orally for 12 weeks period. Blinding of investigational drugs were matched on the basis of a similar appearance. The investigational product, G2013 was manufactured according to Good Manufacturing Practice (GMP) criteria, announced by WHO, under supervision of Ethics Committee Teheran University of Medical Sciences.

Outcomes

The primary endpoint was measured by the proportion of patients who achieved 20 improvement, based on the ASAS criteria (ASAS20) response at week 12. An improvement of ≥ 20 and ≥ 1 unit in at least 3 of 4 domains (patient's global assessment, pain, function and inflammatory) on a scale of 10 and no worsening of ≥ 20 and ≥ 1 in remaining domain on a scale of 10 was necessary in the ASAS20 improvement. The secondary endpoints were the change from the baseline at month 1 and 3 in the BASDAI score, BASFI score, Ankylosing Spondylitis quality of life (ASQOL), patient's and physician's global assessment (0–10 cm VAS), duration of morning stiffness and CRP (C-reactive protein) level.

At each baseline, after 4 and 12 weeks visit, safety endpoints consisting of serious AEs (SAEs), change in hematological and biochemical parameters, were filed.

Besides, findings on urinalysis, blood pressure, weight and other adverse events were recorded at each visit.

Statistical analysis

The numerical variables were indicated as least square mean \pm standard error. Least square means are less sensitive to missing data and they are better estimates of the true population mean. They were also reported as N (%) for the categorical variables. Primary efficacy between treatment groups with ASAS20 response was evaluated by the chi-square test. For continuous variables, reported measure one-way ANOVA was used to measure the differences between the groups. Also, the baseline values were adjusted by analysis of covariance with baseline values as covariates condition. All statistical tests were two-sided, and a p -value <0.05 was considered as statistically significant. SPSS software version 20 (IBM Corporation, Armonk, New York, USA) was used to analyze all data. For primary endpoint, a sample size of 25 patients in each group was required to prepare 90% statistical power to find a difference of 40% in the ASAS20 response between the Guluuronic acid and placebo-treated groups at the 5% significance level adjusted for a drop-out rate of 8%.

Results

Disposition and characteristics of the patients

75 patients were randomly assigned to this study, 25 of them were defined placebo group, 25 of them in treatment group with naproxen and 25 in the treatment group with Guluuronic acid (Fig. 1). The randomized presence of patients in this investigation was determined according to the criteria for inclusion and

exclusion criteria. It should be noted that, the three parallel treatment groups (Guluuronic acid, naproxen and placebo) were matched based on the baseline demographic and disease characteristics items. There were no significant differences between treatment groups for the detectable characteristics were observed (Table 1). 90% of patients in the Guluuronic acid group, 76% of patients in the Naproxen group and 76% of patients in the placebo group were completed 12 weeks period of treatment. High disease activity according to (BASDAI score ≥ 4 [0–10 cm NRS] and BASFI score ≥ 4 [0–10 cm NRS]) was observed in all patients under this trial. In this research, 73.9% of randomized selected patients were male and 86.9% of patients had HLA-B27 allele. The mean age of the patients was 33.06 ± 7.17 years (range 18–45 years), and the mean duration of disease was 5.5 ± 3.9 years.

Efficacy

ASAS20 response at week 12 was achieved in 14 of 23 (60.8%) of patients among the group that was taking Guluuronic acid, compared with 13 of 19 (68.4%) of the patients in the naproxen group ($p = 0.853$) and 4 of 19 (21.0%) of the patients in the placebo group ($p = 0.022$ and $p = 0.009$, respectively). The ASAS20 responses in the Guluuronic acid group compared to the naproxen group were not statistically significant as early as week 4 and at each visit until week 12. A significant increase in ASAS20 responses in the naproxen group and the Guluuronic acid group than the placebo group was shown as early as week 4 and at each visit until week 12. Measures of disease activity (BASDAI score) as the secondary endpoints in patients who received Guluuronic acid and naproxen

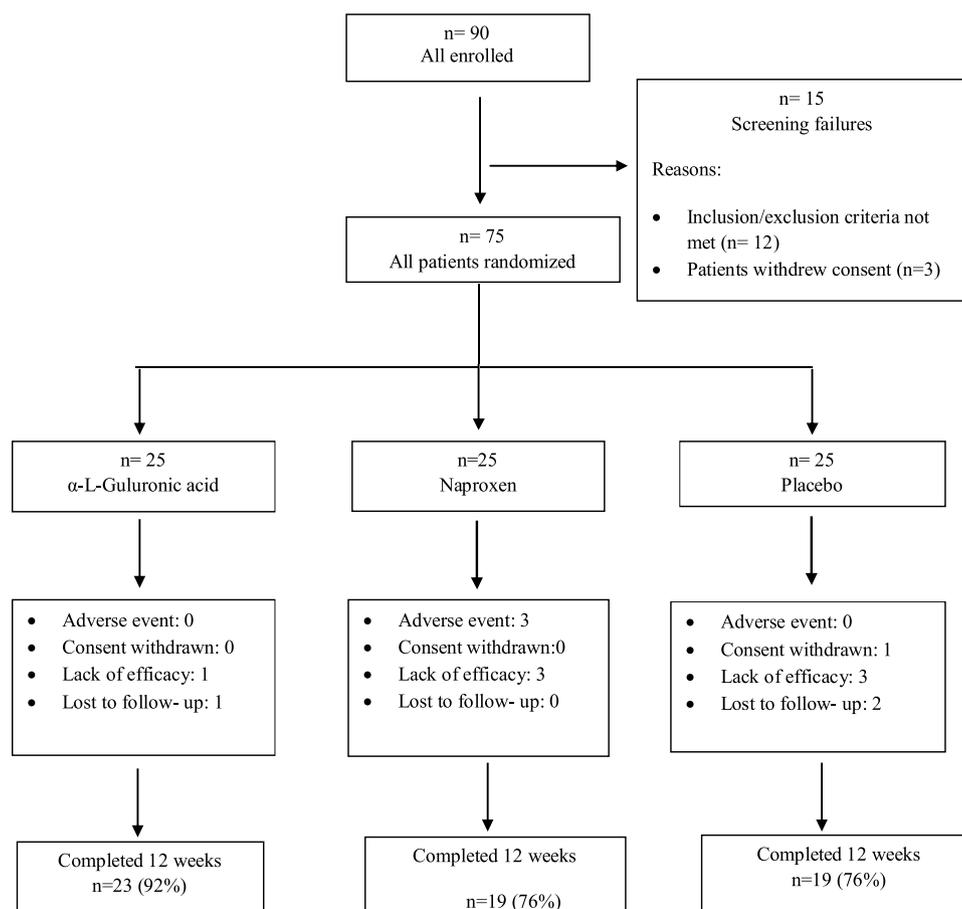


Fig. 1. Trial profile. All of 90 patients were screened and 15 patients were excluded due to meeting exclusion criteria. All randomized patients were included in the full analysis set (FAS) and the safety set.

Table 1
Baseline demographic and disease characteristics.

	Guluronic acid n=23	Naproxen n=19	Placebo n=19	p-value
Age (Year)*	34.1 ± 2	32.6 ± 8.5	32.1 ± 6.9	0.613
Male*	17 (73.9)	13 (68.4)	16 (84.2)	0.516
Disease Duration (Year)*	6.4 ± 6.8	4.8 ± 3.07	5.3 ± 2.7	0.077
Weight (kg)*	78.7 ± 10.8	77.6 ± 10.1	81.4 ± 12.3	0.583
Body mass index (kg/m ²)*	22.2 ± 2.7	22.4 ± 2.5	23.2 ± 3.7	0.409
HLA-B27 Positivity*	20 (86.9)	16 (84.2)	15 (78.9%)	0.781
Total back Pain (0–10 cm VAS)*	5.3 ± 2.4	6.2 ± 2.0	6.5 ± 2.4	0.194
BASDAI (0–10 cm VAS)*	6.1 ± 1.5	5.7 ± 1.4	5.9 ± 1.5	0.684
BASFI (0–10 cm VAS)*	5.0 ± 1.0	4.2 ± 1.8	4.7 ± 1.8	0.316
ASQoL Score (range 0–18)*	9 ± 4.1	9.1 ± 4.0	9.2 ± 4.8	0.964
Physician's global assessment of disease activity (0–10 cm VAS)*	5.1 ± 1.07	6.1 ± 1.7	6.3 ± 2.2	0.066
CRP (mg/L)*	6.8 ± 1.7	6.8 ± 2.6	7.0 ± 3.2	0.978
Patient's global assessment of disease activity (0–10 cm VAS)*	6.3 ± 1.8	6.5 ± 2.1	5.8 ± 2.7	0.657

*Indicated as least square mean ± SE, * indicated as N (%).

were associated with significantly greater improvement compared with placebo in 12 weeks period of examination. LSM (SE) change from baseline at week 12 in BASDAI score was -1.8 (2.7) in the Guluronic acid group and -2.1 (1.7) in the naproxen group compared with 0.15 (1.4) in the placebo group, ($p = 0.007$). However, these differences for physical function (BASFI score) were not significant, so that the LSM (SE) change from baseline at week 12 in BASFI score was -1.6 (3.0) in the Guluronic acid group and -1.4 (1.6) in the naproxen group compared with 0.04 (1.3) in the placebo group ($p = 0.052$). Total back pain reduced similarly between baseline and week 12 in Guluronic acid [LSM (SE) change from baseline -0.89 (2.8)] and naproxen [LSM (SE) change from baseline -2.4 (1.7)] groups. These differences were statistically significant compared with values in placebo [LSM (SE) change from baseline 0.36 (1.6)] group ($p = 0.037$).

A similar result was seen for the duration of morning stiffness with improvements by -0.91 (2.8) [LSM (SE) change from baseline] in Guluronic acid group and -1.7 (2.2) [LSM (SE) change from baseline] in naproxen group and 0.21 (1.5) [LSM (SE) change from baseline] versus placebo group ($p = 0.04$). There was a reduction in the CRP level over 12 weeks in Guluronic acid [-2.7 (2.9) LSM (SE) change from baseline] and naproxen [-1.05 (1.8) LSM (SE) change from baseline] treatment groups compared with the placebo [0.02 (1.9) LSM (SE) change from baseline] group ($p = 0.001$) (Table 2).

Moreover, a similar improvement from baseline to week 12 was observed in Guluronic 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).

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

	Guluronic acid (n=23)	Naproxen (n=19)	Placebo (n=19)	Difference in LSM P†	p-value	Difference in LSM P‡	p-value
BASDAI (0–10 cmNRS)	-1.8 ± 2.7	-2.1 ± 1.7	0.15 ± 1.4	(-0.88 ± 2)	0.007	(-3.2 ± -0.4)	0.7
BASFI (0–10 cm NRS)	-1.6 ± 3.0	-1.4 ± 1.6	0.04 ± 1.3	(-1.8 ± 1.5)	0.052	(-3.4 ± 0.01)	0.9
Total Back Pain (0–10 cm NRS)	0.89 ± 2.8	-2.4 ± 1.7	0.36 ± 1.6	(-0.4 ± 2.7)	0.037	(-3.3 ± -0.08)	0.21
ASQoL score (range 0–18)	-1.7 ± 3.7	-3.2 ± 4.6	0.42 ± 3.0	(-1.04 ± 3.7)	0.052	(-4.7 ± 0.01)	0.43
Physician's global assessment of disease activity (0–10 cm NRS)	-1.5 ± 2.3	-2.5 ± 1.8	-0.11 ± 1.7	(-1.04 ± 1.8)	0.002	(-3.6 ± -0.7)	0.87
Patient's global assessment of disease activity (0–10 cm NRS)	-2.0 ± 3.1	-2.5 ± 2.4	-0.02 ± 2.4	(-1.3 ± 1.9)	0.02	(-3.4 ± -0.14)	0.95
Duration of morning stiffness (0–10 cm NRS)	-0.91 ± 2.8	-1.7 ± 2.2	0.21 ± 1.5	(-1.08 ± 2.07)	0.04	(-3.2 ± -0.04)	0.82
CRP (mg/L)	-2.7 ± 2.9	-1.05 ± 1.8	-0.02 ± 1.9	(-3.5 ± -0.04)	0.001	(-4.5 ± -1.05)	0.04

ASQoL, Ankylosing Spondylitis Quality of Life; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASFI, Bath Ankylosing Spondylitis Functional Index; CRP, C reactive protein; least square mean (LSM) ±SE; VAS, visual analog scale.

† α -L-Guluronic acid versus placebo ‡ α -L-Guluronic acid versus naproxen. NS = Non-significant.

Safety

To perform safety assessments, the evaluation of physical status of patients, checking of AEs, consideration of vital symptoms and various clinical laboratory tests such as hematological and biochemical measurements were assessed. It should be mentioned that neither any serious AEs nor any death were observed during this study. Significantly higher incidence of AEs was observed in the patients who received naproxen (57.8%) compared with patients who received Guluronic acid (17.3%) and the placebo group (20.9%) ($p = 0.005$). In placebo group and Guluronic acid treated group, none of the patients were excluded from the study due to AEs; But in naproxen treatment, group 3 patients left the study because of AEs.

The most common types of AEs mentioned in this study were comparable with the identified toxicities of NSAIDs. The most common reported clinical AEs in Guluronic acid, naproxen and placebo treatment groups were abdominal pain (0%, 5.2% and 5.2%, respectively), heartburn (4.3, 21% and 0%, respectively), vertigo (4.3%, 15.7% and 0%, respectively) and headache (0, 15.7% and 15.7%, respectively) which were all mild to moderate in intensity. (Table 3). In addition, the hematological and biochemical analysis were performed and displayed consistent treatment-related effects in patients who received Guluronic acid. There were no statistically significant differences in mean of Hb, RBC, HCT, MCV, MCH, MCHC, WBC, monocytes, neutrophils, eosinophils and platelet values at weeks 0, 4 and 12 in Guluronic acid treatment group (Table 4). Collectively, these parameters were within the reference range throughout the study. All means and individual

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

	Guluronic acid n = 23	Naproxen n = 19	Placebo n = 19	p-value
all adverse events	4 (17.3)	11 (57.8)	4 (20.9)	0.005
Headache	0	3 (15.7)	3 (15.7)	0.133
Diarrhea	0	0	0	–
Vertigo	1 (4.3)	3 (15.7)	0	0.125
Nausea	2 (8.6)	0	0	–
Heartburn	1 (4.3)	4 (21.0)	0	0.042
GI bleeding	0	0	0	–
Abdominal pain	0	1 (5.2)	1(5.2)	0.535
Rash	0	0	0	–
Urticarial	0	0	0	–
Nasopharyngitis	0	0	0	–
Pharyngitis	0	0	0	–
Elevated AST/ALT	0	0	0	–
Leukopenia/ thrombocytopenia	0	0	0	–

Results indicated as N (%).

Table 4
Hematological parameters in AS patients treated with Guluronic acid (n=23), 500 mg, 2 times per day.

Parameters	Baseline	Week 4	Week 12	p-value
RBC ($10^6/\mu\text{L}$)	5.4 ± 0.4	5.1 ± 0.4	5.1 ± 0.6	0.861
HB (g/dL)	13.2 ± 1.6	14.2 ± 1.7	14.6 ± 1.3	0.645
HCT (%)	42.1 ± 4.2	40.5 ± 9.2	43.1 ± 2.9	0.385
MCV (fl)	84.0 ± 7.7	83.5 ± 7.6	85.7 ± 6.3	0.401
MCH (pg)	28.4 ± 2.9	28.1 ± 2.9	28.3 ± 2.7	0.221
MCHC (g/dL)	33.8 ± 1.9	34.3 ± 3.9	33.0 ± 1.4	0.284
White blood cells ($10^3/\mu\text{L}$)	7.4 ± 2.2	6.9 ± 1.3	6.9 ± 1.3	0.279
Neutrophils (%)	58.0 ± 10	57.3 ± 6.7	54.8 ± 6.6	0.20
Lymphocytes (%)	32.1 ± 8.1	34.0 ± 5.1	37.4 ± 6.5	0.001
Monocytes (%)	6.3 ± 2.7	5.7 ± 2.8	5.1 ± 2.7	0.66
Eosinophils (%)	2.8 ± 2.1	2.5 ± 2	2.3 ± 2.3	0.29
Platelet ($10^3/\mu\text{L}$)	257 ± 62.5	250 ± 62.9	233 ± 38.8	0.183

Values are expressed as least square mean ± SE. RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; MCV, mean corpuscular volume; MCH, mean corpuscular hemoglobin; MCHC, mean corpuscular hemoglobin concentration.

concentrations of the serum biochemical analyses in Guluronic acid treatment group were within the reference range throughout the study. There were no statistically significant differences in any of these parameters over time points (Table 5).

Discussion

NSAIDs are currently the main agent for treatment of AS, but evidence demonstrates that these medicines have many side effects, especially in the long time. Most AS patients usually use diclofenac, naproxen and indomethacin. Recent studies have shown that naproxen can be used to control patients with active AS. [16] Also it has been shown that Guluronic acid as a novel

Table 5
Biochemical parameters in AS patients treated with Guluronic acid (n = 23), 500 mg, 2 times per day.

Parameters	Baseline	Week 4	Week 12	p-value
Glucose (mg/dl)	90.6 ± 8.5	87.2 ± 16.8	92.5 ± 8.6	0.760
BUN (mg/dl)	17.7 ± 6.6	16.7 ± 6.0	16.8 ± 6.0	0.377
Creatinine (mg/dl)	0.98 ± 0.18	1.3 ± .16	1.0 ± 0.21	0.489
Uric Acid (mg/dl)	5.8 ± 1.1	5.9 ± 1.0	6.1 ± 1.5	0.666
Calcium (mg/dl)	9.1 ± 0.53	9.2 ± 0	9.0 ± 0.37	0.252
Phosphorous(mg/dl)	3.6 ± 0.63	3.5 ± 0.65	3.7 ± 0.67	0.467
ALT (U/L)	33.3 ± 45.8	34.5 ± 41.0	28.9 ± 22.9	0.284
AST (U/L)	23.6 ± 17.1	22.4 ± 14.1	22.5 ± 16.2	0.738
ALP (U/L)	194.8 ± 78.4	190 ± 74	183.6 ± 60.3	0.084

Values are expressed as least square mean ± SE. BUN, Blood urea nitrogen; ALT, alanine aminotransferase; AST, aspartate aminotransferase; ALP, Alkaline phosphatase.

NSAID has immunomodulatory property. The aim of this study, which was conducted for the first time, was to compare the safety and efficacy of Guluronic acid with naproxen and placebo in patients with active AS.

Guluronic acid and naproxen that were used 500 mg 2 times a day in 12 weeks period of treatment showed similar effects in the treatment of AS. Result of this research has shown that Guluronic acid and naproxen have significant efficacy compared to placebo group [17]. According to the obtained data from the endpoint analysis for ASAS20 response, patients who received Guluronic acid during 12 weeks period had more efficacy than those who received naproxen. Therefore, based on this efficacy, Guluronic acid can be considered as a valuable option for management of the AS disease.

The ASAS20 response in patients receiving Guluronic acid was parallel to other studies which had used different NSAIDs for the treatment of AS [18,19]. It has proved that NSAIDs cause the reduction of inflammation, back pain and stiffness, as well as improvement of physical function, which is the most important aim for treatment AS. In this trial, the pain and determinants reflecting inflammation (CRP and duration of morning stiffness) in patients who consumed Guluronic acid and naproxen were reduced. Also, the administration of Guluronic acid and naproxen was led to an improvement in BASDAI and BASFI scores compared with placebo group during the 12 weeks period. Our findings are comparable with other studies with similar design [18,19]. Based on the result, it was approved that taking 1000 mg per day of Guluronic acid leads to an optimal effect on treatment of AS.

It was found in colleague's studies that Guluronic acid as a novel NSAID has favorable anti-inflammatory effects compared with other commonly used drugs, which indicates that Guluronic acid has more safety in patients [11,20]. It should be mentioned that the result of this study shows that Guluronic acid has a notable safety property for AS disease. Researches have shown that those who use conventional NSAID are at risk of developing cardiovascular and toxicity on GI tract and kidney, while in recent studies conducted in animal models and *in vitro* studies have shown that Guluronic acid - as a very small molecule NSAID - has no toxicity on GI tract and kidney function [11,20]. In this small and short-term study, it was proved that GI and renal tolerance in Guluronic acid treated group was better in comparison to naproxen group. Based on this clinical trial, it is believed that Guluronic acid might be considered as an efficient NSAID for the management of AS, as our findings suggest more favorable effects for Guluronic acid than naproxen [16,21]. In conclusion, Guluronic acid, as a novel NSAID significantly reduced signs and symptoms in patients with AS within 12 weeks and also improved the clinical parameters of AS disease, including the activity of disease, physical activity and inflammation. According to the obtained results in this trial, Guluronic acid is a NSAID that is effective, safe and well tolerated in patients with AS.

Conflict of interest

There is no conflict of interest in this work.

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