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Original Article

Effectiveness of methylprednisolone in ankylosing spondylitis patients with acute anterior uveitis

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Abstract: Purpose: Through observing the effect of high-dose methylprednisolone treatment on active AS with acute anterior uveitis (AAU) to evaluate the influence of methylprednisolone on the serological cytokines IL-23 and IL-17 in AS patients with AAU. We try to explore the clinical effect and possible mechanism of high-dose methylprednisolone treatment on AS with AAU. Methods: The present study included 40 AS patients who were recruited according to the 1984 revision of the AS classification standards in New York. The clinical characteristics of the patients were assessed. Of the 40 AS patients, 4 had AAU. The patients were administered methylprednisolone at a dose of 3-4 mg/kg/d through the vein for 3 days, and a total of 3 courses were administered with an interval of 4 days. We observed the degree of eye inflammation before and after the treatment. Additionally, the levels of the cytokines IL-23 and IL-17 were measured. Results: In the 4 AS patients with AAU, the eye symptoms and visual acuity improved after treatment with high-dose methylprednisolone. Additionally, the serum levels of IL-23 and IL-17 declined significantly. Conclusion: High dose methylprednisolone had a distinct curative effect in active AS patients with AAU, especially for local therapy incompletely response or ineffective AAU. Additionally, high dose methylprednisolone can significantly reduce the levels of IL-23 and IL-17 in AS patients with AAU.

Keywords: Ankylosing spondylitis, acute anterior uveitis, IL-23/IL-17, methylprednisolone

Introduction

Ankylosing spondylitis (AS) is a chronic progressive rheumatic disease, which mainly involves the joint axis and can affect organs and other tissues. The incidence of AS has been reported to be approximately 0.1%-1.4%, and it mainly starts at the age of 20-30 years, especially in young men. The incidence has been reported to be 2 times higher in men than in women [1]. AS is a gradually progressive disease, and it can affect joint function and cause loss of movement, resulting in major disability in affected young adults. Acute anterior uveitis (AAU) is the most common extra articular manifestation in AS patients. It has been reported to occur in approximately 20-30% of AS patients, and the incidence of AS on long-term follow-up has been reported to be 40% [2]. In our department, short-term high-dose methylprednisolone treatment was found to have a positive effect on refractory AS. Some basic research shows that this treatment is highly effective in the majority of patients with active AS and well tolerated [3]. The present study aimed to determine the effect of high-dose methylprednisolone treatment on active AS with AAU and to evaluate the influence of methylprednisolone on clinical characteristics and the serological cytokines IL-23 and IL-17 in AS patients with AAU.

Patients and methods

Patients

The study included 40 patients (32 men and 8 women) with AS from the Department of Rheumatology of the Second Hospital of Shanxi Medical University. The mean age of the patients was 34.7 years (range, 18-56 years). All patients had a Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) score ≥ 4 points. The inclusion criteria were based on the 1984 revision of the AS classification standards in New York. The criteria were aged 18-60 years, bilateral sacroiliac joint classification ≥ II, BASDAI score ≥ 4 points, and erythrocyte sedi-

Table 1. Comparison of characteristics between the HLA-B27-positive and HLA-B27-negative groups

Characteristic	HLA-B27-positive group	HLA-B27-negative group
Patients	25	15
Age (years)	36.5 ± 10.3	36.2 ± 13.9
Disease duration (years)	9.2 ± 6.3	5.0 ± 4.4#
Onset age (years)	27.2 ± 8.2	32.0 ± 12.3
Sex (male/female)	20/5	6/9
Sacroiliac joint grading	3.36 ± 0.76	2.08 ± 0.29#

Upaired student' t test; Compared to the HLA-B27-positive group, #P < 0.05.

mentation rate (ESR) ≥ 30 mm/h. The exclusion criteria were presence of severe diseases of the cardio-cerebral vascular, liver, kidney, or other important organs; involvement of the blood and endocrine systems; and presence of other rheumatic disease, malignant tumor, and acute or chronic infection. The study was approved by the ethics committee of our institution and was performed in accordance with the rules for clinical trials. All patients signed an informed consent form before participation.

Treatment

Methylprednisolone was administered at a dose of 3-4 mg/kg/d through the vein for 3 days, and a total of 3 courses were administered with an interval of 4 days.

Assessment methods

The ESR and C-reactive protein (CRP) level are common inflammatory indicators for AS disease activity; however, their specificity is not high. In our study, we used a CRP level ≥ 20 mg/L and ESR ≥ 30 mm/h as references. The BASDAI score was used to assess the activity level. With regard to the eye disease index [4]: markedly improved criteria for vision were returned to the previous score or a significant improvement in vision (0.2), negative aqueous humor cells, and disappearance of symptoms; however, there can be aqueous flare. Improved criteria for vision were reduction in the number of aqueous humor cells or disappearance of the cells, relief of symptoms, and aqueous flare reduced. The invalid criteria were no improvement in eyesight, no relief of symptoms, and presence of complications, such as secondary glaucoma and cataract.

ELISA

The ELISA method was used for the detection of cytokines. All samples were extracted using tube without anticoagulant tube and were centrifuged at 3000 rpm for 5 minutes at room temperature. The supernatant was frozen at -80°C until use. The ELISA kits were obtained from Shanghai Multi Sciences Biotech Company, and the procedures were performed in accordance with the kit instructions. The IL-23 kit has a minimum detectable level of 16.35 pg/mL, and the IL-17 kit has a minimum detectable level of 4.09 pg/mL.

Statistical analysis

Quantitative data were presented as mean ± standard deviation (SD). The paired student' t test and unpaired student' t test were performed. All analyses were performed using the SPSS software (version 17.0, IBM Corp., Armonk, NY). *P*-value < 0.05 was considered statistically significant.

Results

Clinical features

The patients were divided into a HLA-B27-positive group (n = 25) and HLA-B27-negative group (n = 15). The disease duration and sacroiliac joint classification were significantly different between the groups (P = 0.03 and P = 0.00). However, age and sex were not different between the groups (P > 0.05) (**Table 1**).

Comparison of variables in the HLA-B27-positive and HLA-B27-negative groups before and after treatment

In the HLA-B27-positive group, the ESR (t = 6.73, P = 0.00), CRP level (t = 4.39, P = 0.00), occiput-to-wall distance (t = 4.98, P = 0.00), finger-to-floor distance (t = 6.23, P = 0.00), thoracic mobility (t = -8.21, P = 0.00), Schober test result (t = -6.04, P = 0.00), BASDAI score (t = 13.91, P = 0.00), Bath Ankylosing Spondylitis Metrology Index (BASMI) score (t = 7.89, P = 0.00), and Bath Ankylosing Spondylitis Functional Index (BASFI) score (t = 12.17, P = 0.00) were significantly different before and after treatment (**Table 2**).

In the HLA-B27-negative group, the ESR (t = 4.52, P = 0.001), CRP level (t = 3.46, P = 0.005),

Table 2. Comparison of variables in the HLA-B27-positive and HLA-B27-negative groups before and after treatment

	HLA-B27-positive group		HLA-B27-negative group	
	0 weeks	3 weeks	0 weeks	3 weeks
ESR (mm/h)	44.90 ± 29.40	7.16 ± 4.73#	29.40 ± 17.72	7.67 ± 3.39#
CRP level (mg/L)	31.50 ± 23.83	3.14 ± 1.91#	27.83 ± 25.50	3.12 ± 1.62#
Occiput-wall distance (cm)	6.36 ± 5.62	3.16 ± 3.02#	2.50 ± 2.65	0.92 ± 1.08#
Finger-floor distance (cm)	27.56 ± 22.25	11.32 ± 11.86#	13.33 ± 14.82	6.67 ± 7.85#
Thoracic mobility (cm)	2.55 ± 1.26	3.72 ± 1.55#	3.38 ± 1.15	3.96 ± 0.86
Schober test result	3.60 ± 1.76	4.72 ± 1.72#	4.42 ± 1.42	5.00 ± 0.95#
BASDAI score	4.51 ± 0.45	1.61 ± 0.77#	4.29 ± 0.33	2.23 ± 0.58#
BASMI score	5.80 ± 2.26	3.00 ± 1.03#	5.56 ± 1.82	3.06 ± 1.34#
BASFI score	5.15 ± 1.04	2.85 ± 0.56#	3.46 ± 0.45	1.96 ± 0.38#

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; BASMI, Bath Ankylosing Spondylitis Metrology Index; BASFI, Bath Ankylosing Spondylitis Functional Index Paired student' t test; Compared to 0 weeks, #P < 0.05.

Table 3. Clinical characteristics of the 4 ankylosing spondylitis patients with acute anterior uveitis

Characteristic	Case 1	Case 2	Case 3	Case 4
Sex	Male	Male	Female	Male
Age (years)	41	38	56	39
Disease duration (years)	5	20	10	10
Peripheral joint involvement	No	Yes	Yes	Yes
Eye involvement	Left	Right	Left	Eyes alternate
HLA-B27	Positive	Positive	Negative	Positive
Sacroiliac joint grading	IV	IV	II	IV
ESR (mm/h)	35	45	29	30
CRP level (mg/L)	5.54	20.20	10.00	9.02
BASDAI score	4.60	4.40	4.05	4.80

ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index.

occiput-to-wall distance (t = 3.83, P = 0.006), finger-to-floor distance (t = 2.82, P = 0.017), Schober test result (t = -2.24, P = 0.046), BASDAI score (t = 13.96, P = 0.00), BASMI score (t = 11.18, P = 0.00), and BASFI score (t = 12.83, P = 0.00) were significantly different before and after treatment. However, thoracic mobility was not significantly different (t = -1.63, P = 0.13) (**Table 2**).

Clinical characteristics and therapy efficacy of the 4 ankylosing spondylitis patients with acute anterior uveitis

Among the 40 AS patients, 4 patients had AAU (3 men and 1 woman). Three patients had peripheral joint involvement. Monocular uveitis was noted in 3 patients, and both eyes were involved in 1 patient. The characteristics of the 4 patients are presented in **Table 3**.

In the 4 patients, we evaluated the curative effect according to the visual acuity and eye inflammation changes before and after treatment. In 3 of the patients, symptoms, such as red eyes, eye pain, tears, and blurred vision, disappeared. The visual acuity improved, aqueous humor cells were negative, and curative effect evaluation was markedly improved. In 1 of the patients, the clinical symptoms significantly reduced, eyesight increased by 0.5, and curative effect evaluation was improved.

IL-23 and IL-17 levels of the 4 ankylosing spondylitis patients with acute anterior uveitis before and after treatment

The levels of both IL-23 and IL-17 were higher than the minimum detectable levels of the kits. The mean IL-17 level significantly decreased from 36.14 ± 19.26 pg/mL before treatment to 8.09 ± 5.75 pg/mL after treatment (t = 3.27, P = 0.047), and the mean IL-23 level significantly decreased from 66.97 ± 27.05 pg/mL before treatment to 19.52 ± 13.05 pg/mL after treatment (t = 3.27, P = 0.047) (**Table 4**).

Table 4. Comparison of the IL-23 and IL-17 levels of the 4 ankylosing spondylitis patients with acute anterior uveitis before and after treatment

	Before treatment IL-17 (pg/mL)	After treatment IL-17 (pg/mL)	Before treatment IL-23 (pg/mL)	After treatment IL-23 (pg/mL)
Case 1	30.98	9.37	62.94	29.87
Case 2	49.70	15.66	38.30	3.50
Case 3	11.11	3.99	63.24	14.23
Case 4	52.75	4.32	103.60	30.45

Adverse reactions

The most common adverse reaction of short-term high-dose methylprednisolone treatment was upper respiratory tract infection (10%), followed by sleep disorders (5%) and stomach problems (5%). The other adverse reactions were rise in liver enzyme levels, and changes in the blood glucose level and blood pressure. The above-mentioned adverse reactions were treated symptomatically. There was no impact on the methylprednisolone treatment, and no stomach bleeding, severe water sodium retention, or cardiovascular events were noted.

Discussion

AS is a common autoimmune disease and mainly involves tendons, tendon ends, synovial joints, and the surrounding areas. The characteristic pathological change is chronic inflammation of the tendon and ligament attachment points. Some AS patients have different degrees of lesions in the eyes, lungs, cardiovascular organs, renal organs, and other organs during the course of the disease. Chronic inflammation can lead to ligament fibrosis and osteophyte formation in the spinal vertebral body edge, which can further cause spine stiffness. A previous study showed that HLA-B27 is closely related to AS and that the onset characterizations of AS differs between HLA-B27-positive and HLA-B27-negative patients [1]. In this study, we found that the proportion of men was higher, onset age was lower, disease course was longer, and the degree of sacroiliac joint grading and radiographic classification were greater in HLA-B27-positive patients than in HLA-B27-negative patients. The wall distance and ground distance were positively correlated with radiographic classification.

AAU is one of the most common extra-articular issues associated with AS. It has been shown that the incidence of AAU is high in AS patients with peripheral arthritis symptoms [5], and this might be related with the presence of similar type II collagen. AS with AAU is common in youth and middle-aged men, and in female patients, it might be associated with a reduction in the estrogen level [6]. A previous study showed that estrogen could induce the generation of vascular endothelial nitric oxide synthase, thereby reducing the permeability of the cell membrane and inflammation [7]. In menopausal women, AAU might result from the absence of the protective effects of estrogen. AS with AAU can result in monocular lesions, which can occur repeatedly, and can also cause eye issues. It has been shown that AS patients who are positive for HLA-B27 have high risks of AAU; however, the reason for this remains unclear [1]. A previous study showed that HLA-B27-positive patients were more susceptible to acute anterior uveitis than HLA-B27-negative patients [8]. Factors associated with infection may be the most important factors of the disease. The pathogenesis of infection may be the factor that initiates a bacterial antigen cell-mediated immune response, resulting in an immune reaction to the membrane and eventually causing AAU [9]. A previous study on the interleukin-23 receptor (IL-23R) rs17375018 GG genotype in AS patients with anterior uveitis showed that other genes besides *HLA-B27* might participate in AS with AAU [10]. Another study reported that IL-23/IL-17 participate in the onset of uveitis through Th17 cell differentiation, suggesting that these cytokines play an important role in the pathogenesis of uveitis [11, 12]. High expression of cytokines and inflammatory factors, such as TNF-α, has been reported in acute uveitis patients, and cytokines secreted by Th1 cells have been reported to be predominant [13, 14]. Currently, limited information is available on IL-23 in patients with uveitis, and IL-10 and TNF-α have been previously shown to be highly correlated with IL-23 [14].

The present study suggested that in addition to the existence of T-lymphocytes, there might be a balance disorder with regard to the immune

cells in AS patients. Th17 and various innate immune cells, such as macrophages and dendritic cells, might increase in number, which can result in an increase in the IL-23 level. The increase in the IL-23 level can induce Th17 cells to secrete more IL-17, resulting in the production of more inflammatory mediators and a strong inflammatory response, which can cause delayed eye disorders. In our study of 40 AS patients, there were 4 AS patients with AAU. Of these 4 patients, 3 were young and middle-aged men and 1 was a menopausal woman. There were 3 patients with peripheral joints symptoms, unilateral onset, and HLA-B27 positivity. In only 1 patient, both eyes were involved alternatively. Therefore, we believe that AS with AAU mainly occurs in young or middle-aged men and HLA-B27-positive patients with peripheral joint symptoms. The AS patients with AAU showed high levels of IL-23 and IL-17.

The treatment of AAU associated with AS should be based on the degree of disease severity and the response to drugs. Overall, glucocorticoids are effective for AAU. The routine use of hormones with local injections and a mydriatic agent has been suggested to reduce ciliary muscle spasm and pain [15]. For bilateral acute anterior uveitis with macular edema or optic disc edema, or for a severe condition, prednisone can be orally administered at an initial dose of 30-40 mg (at approximately 8 o'clock), and the dose can be reduced after a week. The general course is for approximately 2-4 weeks. Methylprednisolone is a synthetic glucocorticoid, in which methyl is introduced at the 6th d locus of prednisolone. This modification enhances its anti-inflammatory effects and reduces its breakdown. Short-term high-dose methylprednisolone can effectively treat AS patients. We found that short-term methylprednisolone treatment could alleviate the disease activity and reduce eye inflammation, with a decrease in eye redness and pain, in AS patients with AAU. Additionally, it could improve vision, control inflammation, and reduce the levels of IL-23 and IL-17. We carefully administered methylprednisolone according to the indications and contraindications, and adverse reactions rarely occurred. All adverse reactions were successfully treated, and there was no impact on the treatment course.

In conclusion, short-term high-dose methylprednisolone treatment can quickly control acute inflammation, relieve symptoms, and reduce the levels of IL-23 and IL-17 in AS patients with AAU. Additionally, HLA-B27 positivity might have a negative effect on the outcome. The influence of IL-23 and IL-17 in the pathogenesis of AS with AAU requires further research.

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Disclosure of conflict of interest

None.

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