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Add-On Effects of Conventional Synthetic Disease-Modifying Anti-Rheumatic Drugs in Ankylosing Spondylitis: Data from a Real-World Registered Study in China

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: The aim of this study was to investigate the effects of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) on patients with ankylosing spondylitis (AS) using real-world data, and to analyze patients' choices of csDMARDs and reasons for discontinuation.

Material/Methods: This observational study included 320 patients satisfying the modified New York criteria for AS. Patients were grouped according to medication: Group 1: 122 patients receiving non-steroidal anti-inflammatory drug (NSAID) monotherapy; Group 2: 198 patients receiving csDMARDs and NSAIDs. Patients were followed for 18 months at 6-month intervals. The change in AS Disease Activity Score and C-reactive protein (ASDAS-CRP) at each visit was the primary outcome. Secondary outcomes were based on validated disease activity questionnaires, clinical assessment, and acute-phase biomarkers (CRP and erythrocyte sedimentation rate [ESR]). Inter-group relationships were assessed across the 18-month follow-up period using generalized additive mixed models.

Results: Sulfasalazine and thalidomide were the most commonly used csDMARDs, with cumulative use times of 8.9±4.1 months and 9.1±4.7 months, respectively. In Group 2, 56 patients discontinued or switched csDMARDs during the follow-up period, with lack of efficacy being the primary reason. The ASDAS-CRP was found to decrease significantly in both groups; however, improvements in many parameters (including ASDAS-CRP, disease activity questionnaires and ESR) were greater in Group 2.

Conclusions: Use of csDMARDs can improve disease activity in terms of ASDAS-CRP. The addition of csDMARDs may provide increased benefits compared with NSAID monotherapy, particularly in the reduction of AS disease activity, in the Chinese population.

MeSH Keywords: Antirheumatic Agents • Spondylitis, Ankylosing • Sulfasalazine • Thalidomide

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Background

Ankylosing spondylitis (AS) is a chronic inflammatory disease that leads to functional impairment and a decreased quality of life (QOL). AS damages the axial skeleton resulting in inflammatory based back pain, bone fusion and formation of new spinal bone [1,2] The inflammation can also impair the entheses, peripheral joints, heart, lungs, eyes, and bowel. The prevalence of AS varies greatly across the world [3]. Amongst the Western population, the prevalence is 0.6%, with an estimated annual incidence of 3–7 per 100 000 people.[4–6]. In China, AS afflicts approximately 0.3%–0.5% of the population [7,8], and the disease affects more than 4 million Chinese people, mainly young and middle-aged males. In China, the high incidence of AS causes a heavy medical burden on the limited economic resources.

The use of conventional synthetic disease-modifying anti-rheumatic drugs (csDMARD) therapy for patients with AS is a matter of continuous debate. At present, the effectiveness of csDMARDs in the treatment of AS remains unclear. In previous recommendations or guidelines, sulfasalazine was only recommended for AS/spondyloarthritis (SpA) peripheral arthritis patients. In 2015, the guidelines for the treatment of AS and non-radiographic axial SpA patients were jointly issued by the American College of Rheumatology (ACR), Spondylitis Association of America (SAA) and Spondyloarthritis Research and Treatment Network (SRARTAN) [9]. Their recommendations for csDMARDs involved conditional recommendations for specific indications. For example, they provide the conditional recommendation of csDMARDs for patients with AS who were contraindicated for tumor necrosis factor inhibitors (TNFIs). Sulfasalazine has been intensively investigated for AS therapy with existing guidelines now established by the Assessment of Spondyloarthritis International Society (ASAS) and the European League against Rheumatism (EULAR) advocating its use in peripheral arthritis patients [10]. However, the efficacy of sulfasalazine in AS patients with axis involvement or axial SpA remains undefined. Methotrexate is extensively used in cases of rheumatoid arthritis (RA) and has been touted as a potential anti-AS therapeutic. In a meta-analyses of randomized trials, methotrexate showed some benefits for peripheral and axial disease, though these were largely limited [11]. To-date, the evidence for the effectiveness of csDMARDs for AS are limited. The updated recommendations of the Asia Pacific League of Associations for Rheumatology (APLAR) for the treatment of axial SpA (2018) suggest that csDMARDs may be appropriate for patients with axial SpA and peripheral arthritis, extra-articular manifestations or limited access to drug resources, seemingly indicating a relaxation in the recommendation of csDMARDs [12]. This is the first time that health economics have been taken into account in treatment recommendations. In fact; in daily practice, about 40% of patients with AS receive csDMARD therapy [13]. This leads us to question whether csDMARDs should be used to treat AS; are they significantly effective or is their use simply "psychological comfort" or a "cheap choice"?

In recent years, the development of TNFIs has greatly improved the prognosis of AS, although many patients are unable to use this therapy [14]. China has the lowest rate of biological DMARD (bDMARD) use. In many countries and regions (including China), economic constraints and/or lack of drug resources mean that the rate of TNFI (a bDMARD) use is suboptimal. According to the data of 3370 patients with SpA from 22 countries, the average use of bDMARDs ranged from 5% (China) to 74% (Belgium) [14]. The high cost of these drugs is a significant obstacle to their use, resulting in a considerable number of patients with AS receiving the – much cheaper – csDMARDs. Here, we analyzed patient data during screening and follow-up, to assess the treatment of AS patients and provide insight into the status of treatment, efficacy, compliance, side effects of drugs, and the reasons for switching or discontinuing csDMARD treatment.

Material and Methods

Patient population and inclusion criteria

This was an observational study of Chinese patients with AS using real patient data with or without interventions. Because of the limited cohort data relating to AS in China, we enrolled patients with unrestricted age and disease duration. All questionnaires were collected by the General Hospital of the Chinese People's Liberation Army (PLA), a prominent tertiary referral hospital in the capital of China. This is one of the largest hospitals in China, receiving referral patients with AS from all over the country. Most patients are transferred to our center after being transferred to the Department of Orthopedics and Rheumatology of the local primary hospital. Almost all patients have used NSAIDs administered by themselves or by doctors; few are NSAID naive. Patients were admitted to the hospital from the rheumatology clinic continuously, regardless of whether or not their condition was accompanied by psoriasis, acute anterior uveitis (AAU), or inflammatory bowel disease (IBD). AS patients were continuously recruited from the outpatient clinic between April 2016 and May 2018.

Radiographic evaluations were performed to identify sacroiliitis in either the lumbar or sacroiliac joints. Blood samples were taken to determine serum levels of human leukocyte antigen B27 (HLA-B27), C-reactive protein (CRP), as well as erythrocyte sedimentation rate (ESR).

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Inclusion criteria were as follows: 1) AS defined using the modified New York criteria [15], 2) receiving NSAIDs (either starting NSAIDs during the study period or previous use) and with complete medication records, 3) definite starting time of csDMARDs, and 4) completion of at least 1 follow-up visit within the follow-up window (18 months) after the baseline visit. Exclusion criteria were treatment with bDMARDs or other oral corticosteroids, lack of informed consent, invalid questionnaires, or incomplete data.

Enrollment process

Figure 1 shows the enrollment process. Group 1 included patients receiving NSAID monotherapy, while Group 2 included patients who received NSAIDs along with csDMARDs. The latter included both patients who began csDMARD therapy and NSAIDs simultaneously, and those who started csDMARDs when they were already receiving NSAIDs.

Baseline was defined as the time at which csDMARD therapy was initiated in Group 2 (either the first use of csDMARDs or the time of re-starting following a cessation of more than 3 months). Group 1 served as the control group for which the baseline was defined as the time of enrollment.

"First csDMARDs" were defined as the initial combinations of csDMARDs at baseline. "Second csDMARDs" were defined as the combinations of csDMARDs that were administered after failure of first csDMARD treatment.

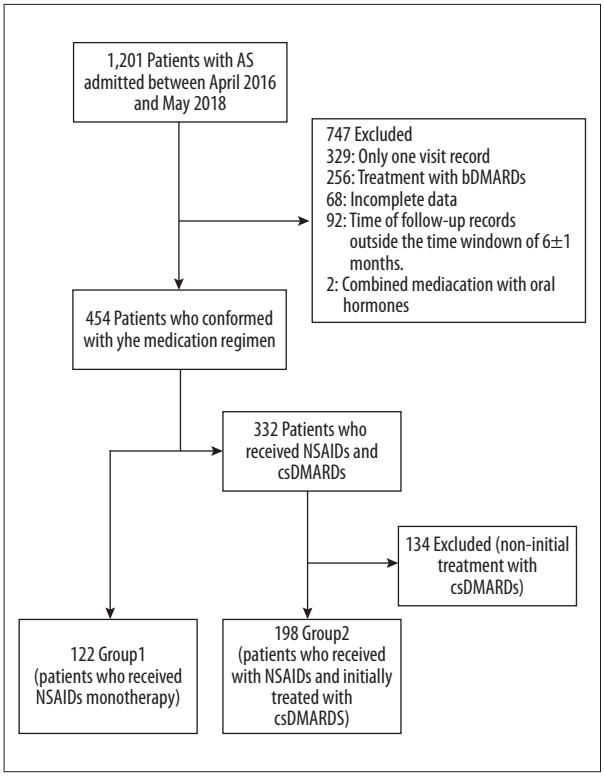

Figure 1. Flow chart of participant enrollment. AS – ankylosing spondylitis; bDMARDs – biological disease-modifying anti-rheumatic drugs; csDMARDs – conventional synthetic disease-modifying anti-rheumatic drugs; NSAID – non-steroidal anti-inflammatory drug.

Drug exposure

NSAIDs included oral acemetacin (90 mg once daily, 90 mg per tablet), oral meloxicam (15 mg once daily, 7.5 mg per tablet), oral diclofenac sodium (75 mg twice per day, 75 mg per tablet), oral loxoprofen sodium (60 mg 3 times per day, 60 mg per tablet), oral celecoxib (200 mg once daily, 200 mg per tablet) and 6-hourly oral ibuprofen (100 mg, 100 mg per tablet). Conventional synthetic DMARDs included oral methotrexate (10 mg once weekly, 2.5 mg per tablet), oral sulfasalazine (1000 mg twice daily, 250 mg per tablet), oral leflunomide (20 mg once daily, 10 mg per tablet) and oral thalidomide (100 mg every night, 50 mg per tablet).

Study protocol, selection of follow-up time interval and follow-up time window

The main drugs of interest in this study were csDMARDs, which usually take effect within 3 months. Efficacy should be evaluated after 6 months.[16] Therefore, the follow-up interval was set at 6 months. Because the curative effects of csDMARDs are relatively stable after onset, the follow-up window was defined as within 1 month of each follow-up point. Patients were followed up for 18 months, every 6 months.

Drug selection

Drug dosages were recorded at baseline. Usage, dosage and any reasons for switching or discontinuation were recorded at each follow-up visit.

Drug compliance and safety evaluations

At each follow-up, patients' medication use was recorded in terms of whether the drugs were taken on time and at the prescribed doses, and the use of other drugs. Safety assessments were carried out at each follow-up appointment to identify any adverse reactions.

Outcomes

We recorded the patient demographics including age, sex, smoking status, onset date of back pain initiation, onset age, disease duration, HLA-B27 status, enthesitis, peripheral arthritis, family history of AS, comorbidities, past medical history, and AS characteristics (AAU, psoriasis and IBD). Full blood counts, ESR, CRP and biochemical profiles of creatinine and liver biomarkers were measured at baseline and at each follow-up

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visit. Any occurrences of AAU, psoriasis or IBD were recorded. The validated questionnaires (Bath AS Disease Activity Index [BASDAI] [17], Bath AS Metrology Index [BASMI] [18], and Bath AS Functional Index [BASFI] [17]) were assessed at each clinical visit.

Efficacy evaluations

AS disease activity scores (ASDASs) were the primary outcome and were recorded at each visit, using published formulas in AS patients [19,20]. The ASDAS presented included CRP, but the ASDAS with ESR is shown as an alternative. CRP at 2 mg/L was used as the cutoff to calculate the ASDAS-CRP [21].

The ASDAS was based on back pain, peripheral pain and swelling, nocturnal back pain, the length of morning stiffness, ESR, CRP, and disease and fatigue assessments. ASDAS were defined as: <1.3 "inactive disease", ≥1.3 and <2.1 "low disease activity", ≥2.1 and ≤3.5 "high disease activity" and >3.5 "very-high disease activity" [22].

Secondary outcomes included the BASDAI, BASFI, general evaluations and CRP and ESR.

Statistical analysis

Categorical data are reported as number (%). Continuous data are the mean±standard deviation (SD). Fisher's exact test and the Kruskal-Wallis test were used for statistical analyses of categorical variables and quantitative variables, respectively. A general additive mixed model with smooth curve fitting [23] was used to explore the non-linear relationship between follow-up duration and ASDAS through drug regimen stratification. A generalized additive mixed model was used to study the potential linear relationship between drug treatment and ASDAS trajectory during follow-up. An additive mixed model was used to analyze repeated measurements. Intercept and time were considered as random terms in this study. In these models; ASDAS was the dependent variable, which was assessed at baseline and all follow-up visits. All models used the same set of fixed effects, which have been widely used in research on drugs and disease outcomes [24]. Disease activity, gender and age were calculated at the baseline and entered into the adjusted model. The interaction between follow-up times and drug treatment was also evaluated.

$P<0.05$ (2-tailed) indicated significant differences. Data were analyzed using Empower and R statistics.

Ethical considerations

Our local review board of the PLA approved the study (S2016-049-02). Informed consent was provided by all study participants.

Results

Baseline characteristics

Table 1 shows the characteristics of all included patients. We enrolled 320 AS patients (Group 1: 122; Group 2: 198). At baseline, 93 out of 122 patients in Group 1 were being administered NSAIDs for disease control prior to the commencement of the study. Group 2 included 4 patients who had started csDMARD and NSAID therapy simultaneously, all of whom had stopped NSAID therapy more than a year ago due to the poor efficacy of the drug. Group 2 contained more male patients than Group 1. The ASDAS in Group 1 was significantly higher than in Group 1 at baseline. The indices of total back pain, night back pain, patient's global assessment (PGA), CRP level, ESR, BASDAI, ASDAS, ASAS Health Index (ASAS HI), physician's global assessment (PhGA), and BASMI were all significantly higher in Group 2 than Group 1, and the number of patients with periarthritis was also higher in Group 2. Age, age at onset, BMI, course of disease, positive family history, smoking, HLA-B27-positive rate, enthesitis or AS-related symptoms (uveitis, IBD, psoriasis) were similar between Groups 1 and 2 at baseline.

Group 2 drug selection

Table 2 shows the csDMARDs administered to Group 2. During the initial treatment regimen, 168 patients (84.8%) received csDMARD monotherapy, with sulfasalazine accounting for the largest proportion. We found that 29 patients (14.6%) received 2 csDMARDs and 1 patient received triple-csDMARD therapy. Sulfasalazine and thalidomide were the most commonly selected csDMARDs, and their cumulative use time was 11.2±5.7 months and 10.7±5.7 months, respectively, during the whole follow-up period (range: 5–19 months).

Follow up rate

Patients with AS were followed-up in order to evaluate the response rate to different treatment regimens. All patients were followed approximately every 6 months (range: 5–7 months, median: 6 months), for a total of 3 follow-up visits. The final follow-up was therefore carried out around 18 months (range: 17–19 months). The numbers of completed follow-up visits of the 2 groups are shown in Table 3.

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Table 1. Baseline characteristics of patients.

	All patients Group 1+Group 2 N=320	Group 1 NSAID n=122	Group 2 NSAID+DMARD n=198	*P* value
Age (years)	30.6±8.7	29.8±8.8	31.1±8.7	0.215
Total back pain (vas0~10)	2.6±2.0	2.1±1.9	2.9±2.0	<0.001*
Night back pain (vas0~10)	2.6±2.2	2.2±2.1	2.8±2.2	0.013*
PGA	2.9±2.2	2.3±1.9	3.3±2.2	<0.001*
BASDAI	2.3±1.7	1.9±1.5	2.5±1.8	<0.001*
BASFI	1.4±1.5	1.0±1.2	1.6±1.6	<0.001*
ASAS HI	5.3±4.2	4.4±4.0	5.9±4.2	0.002*
BMI	23.4±3.9	23.2±3.5	23.6±4.1	0.410
PhGA	2.2±1.3	1.8±1.2	2.5±1.3	<0.001*
ESR	17.2±19.8	12.7±14.5	19.9±22.0	0.003*
CRP (mg/L)	11.8±16.1	7.0±9.0	14.6±18.6	<0.001*
BASMI	1.6±2.1	1.1±2.0	1.8±2.2	0.010*
Onset age (years)	22.3±7.5	22.0±7.3	22.5±7.6	0.546
Disease duration (years)	8.5±6.0	7.8±5.4	8.8±6.3	0.199
ASDAS	2.1±1.0	1.7±0.8	2.3±1.0	<0.001*
Male gender	260 (81.2)	89 (73.0)	171 (86.4)	0.003*
Family history of AS	89 (28.2)	34 (27.9)	55 (28.4)	0.926
Smoking habits				0.101
Never	225 (71.2)	95 (77.9)	130 (67.0)	
Now	74 (23.4)	21 (17.2)	53 (27.3)	
Ever	17 (5.4)	6 (4.9)	11 (5.7)	
HLA-B27 positive	268 (87.0)	100 (87.0)	168 (87.0)	0.982
Presence of comorbidities				
Enthesitis	60 (24.6)	16 (19.5)	44 (27.2)	0.190
Arthritis (current)	34 (13.9)	5 (6.1)	29 (17.9)	0.012*
TB	21 (6.8)	4 (3.5)	17 (8.8)	0.077
HBV	10 (3.2)	3 (2.6)	7 (3.6)	0.641
Uveitis	70 (22.4)	22 (18.6)	48 (24.7)	0.211
IBD	31 (9.9)	12 (10.2)	19 (9.8)	0.914
Psoriasis	9 (2.9)	2 (1.7)	7 (3.6)	0.327
ASDAS Condition				<0.001*
ID	62 (21.2)	38 (35.2)	24 (13.0)	
LDA	101 (34.6)	37 (34.3)	64 (34.8)	
HDA	105 (36.0)	31 (28.7)	74 (40.2)	
VHDA	24 (8.2)	2 (1.9)	22 (12.0)	

Continuous data are presented as mean±standard deviation, categorical data are presented as number (%). * *P*<0.05.

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Table 2. Treatment regimens of various drug combinations of csDMARDs at baseline in Group 2.

Combination	Number of patients (total n=198)		Disease activities by ASDAS			
			ID+ILD (ASDAS <2.1)		HAD+VHDA (ASDAS ≥2.1)	
SSZ	82	(41.4)	49	(59.8)	33	(40.2)
SSZ+LEF	9	(4.5)	2	(22.2)	7	(77.8)
Tha	57	(28.8)	19	(33.3)	38	(66.7)
SSZ+Tha	15	(7.5)	7	(73.3)	8	(26.7)
LEF	23	(11.6)	18	(78.3)	5	(21.7)
MTX	6	(3.0)	5		1	
MTX+Tha	1	(0.5)	1		0	
MTX+LEF	1	(0.5)	0		1	
MTX+SSZ	1	(0.5)	1		0	
LEF+Tha	2	(1.0)	1		1	
SSZ+LEF+Tha	1	(0.5)	0		1	

Data are presented as number (%). csDMARD – conventional synthetic disease-modifying anti-rheumatic drug; ASDAS – ankylosing spondylitis disease activity score; LEF – leflunomide; MTX – methotrexate; SSZ – sulfasalazine; THAL – thalidomide.

Table 3. Number of completed follow-up visits.

	Baseline N=320		Visit 1 at 5–7 months		Visit 2 at 11–13 months		Visit 3 at 17–19 months	
Group 1	122	(100)	109	(89.3)	72	(59.0)	42	(34.4)
Group 2	198	(100)	181	(91.4)	123	(62.1)	75	(37.9)

Data are presented as number (% of group).

Drug discontinuation and drug compliance between the groups

Drug compliance in Group 1

In Group 1, drug compliance was 94.3% with 7 patients discontinuing voluntarily for unknown reasons with no definite adverse effects.

Reasons for discontinuation of csDMARDs in Group 2

In Group 2, 56 patients discontinued treatment or switched csDMARDs during the follow-up period. The reasons for discontinuation included lack of efficacy, effective/stable condition, adverse effects, planning a family and unknown reasons (Table 4). Adverse effects included gastrointestinal symptoms (2 patients), infection (1 patient), hematuria under the microscope (1 patient), leucopenia (1 patient), rash (1 patient), edema (1 patient) and abnormal liver function (1 patient).

Table 4. Reasons for discontinuation of csDMARDs in Group 2.

Primary reason for discontinuation	Group 2 (n=56)	
	n	%
Lack of efficacy	21	37.5%
Effective/stable condition	12	21.4%
Adverse effects	8	14.3%
Planning a family	9	16.1%
Missing data	6	10.7%

csDMARD – conventional synthetic disease-modifying anti-rheumatic drug.

Second combinations of csDMARDs in Group 2

In the second csDMARD regimens in Group 2, the rate of single drug use was 37.5%, with sulfasalazine and methotrexate

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Table 5. Drug combinations used in the second conventional synthetic disease-modifying anti-rheumatic drug regimens Group 2.

Drug combinations	Second csDMARD combinations	
	(n)	(%)
SSZ	15	37.5
SSZ+LEF	5	12.5
Tha	5	12.5
SSZ+Tha	0	0.0
LEF	1	2.5
MTX	10	25
MTX+Tha	2	5.0
MTX+LEF	1	2.5
MTX+SSZ	0	0.0
LEF+Tha	1	2.5
SSZ+LEF+Tha	0	0.0

csDMARD – conventional synthetic disease-modifying anti-rheumatic drug; LEF – leflunomide; MTX – methotrexate; SSZ – sulfasalazine; THAL – thalidomide.

being the most common choices (Table 5). The rate of combined drug use was 22.5%, which was higher than in the first csDMARD regimens.

Efficacy

Intra-group comparison

The mean ASDAS-CRP decreased significantly at each follow-up visit for both groups (Figure 2, Table 6). A clinical response was observed in both groups. We found that, for both groups, efficacy was increased compared with baseline at all follow-up points both in unadjusted analyses and after adjustment for gender, age and baseline ASDAS.

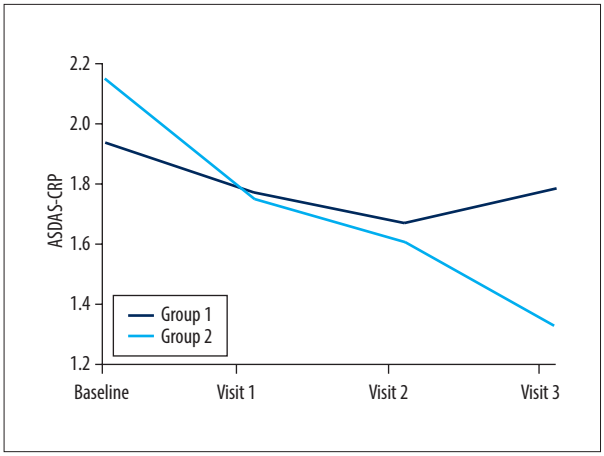

Figure 2. Variation of ASDAS-CRP with follow-up time. ASDAS-CRP – ankylosing spondylitis disease activity score and C-reactive protein.

Inter-group comparison

Multivariate analysis of intergroup continuous variables

Comparing the primary and secondary efficacy indices between Group 1 and Group 2 revealed significantly greater improvements in ASDAS-CRP, BASDAI, ESR, CRP, PGA, PhGA and BASFI in Group 2 compared with Group 1 (Table 7).

Table 6. Changes of the primary outcome, ankylosing spondylitis disease activity score, during follow-up.

	Unadjusted						
	Baseline	Visit 1		Visit 2		Visit 3	
	Value (intercept)	Value	*P*	Value	*P*	Value	*P*
Group 1	1.7361	–0.1515	0.0678	–0.3611	0.0005*	–0.0832	0.5658
Group 2	2.2735	–0.4311	<0.0001*	–0.5062	<0.0001*	–0.8492	<0.0001*
	Adjusted						
	Baseline	Visit 1		Visit 2		Visit 3	
	Value (intercept)	Value	*P*	Value	*P*	Value	*P*
Group 1	0.4457	–0.1614	0.0404*	–0.3616	0.0002*	0.1710	0.9117
Group 2	0.8174	–0.4416	<0.0001*	–0.4695	<0.0001*	–1.0486	<0.0001*

* $P<0.05$.

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Table 7. Comparison of outcomes adjusted for gender, age and baseline ankylosing spondylitis disease activity score between Group 1 and Group 2.

	Baseline	Visit 1		Visit 2		Visit 3	
	Value	Value	*P*	Value	*P*	Value	*P*
ASDAS-CRP	0.6387	–0.3415	<0.0001*	–0.4270	<0.0001*	–0.6910	<0.0001*
BASDAI	0.2694	–0.5698	0.0017*	–0.2111	0.3436	–0.8928	0.0081*
ESR	2.9999	–7.084	0.0012*	–7.4551	0.0052*	–14.1504	0.0004*
CRP	1.5936	-1.4816	0.6045	-1.5343	0.6623	-11.7765	0.0228*
PGA	0.3846	–0.8002	0.0020*	–0.1377	0.6610	–1.6172	0.0006*
PhGA	0.5059	–0.5155	0.0068*	–0.4455	0.0500*	–0.5813	0.088
BASFI	0.1925	–0.4871	0.0015*	–0.3681	0.0526	–0.7397	0.0102*

* $P<0.05$.

Discussion

Although there are no clear recommendations in the guidelines, we found that csDMARDs are commonly used to treat AS in daily practice. Furthermore, patients with AS who undergo csDMARD treatment do benefit from this therapy. We observed that patients who received csDMARDs in the current study exhibited significantly greater improvements in ASDAS-CRP, BASDAI, ESR, CRP, PGA, PhGA, and BASFI during the follow-up period compared with patients who received NSAIDs only. Although disease activities and other indicators were different at baseline between the 2 groups (that is, the baseline was not uniform), the main outcomes and ASDAS were significantly reduced in both groups after adjusting for gender, age, and baseline ASDAS with the mixed linear model, and significant differences were detected between the 2 groups. To improve the reliability of our results, we included more patients to minimize the impact of factors such as baseline disease activity on the results. The use of csDMARDs appears to promote the improvement of disease activity and ASDAS.

There are few reports in the literature similar to the present study, and different opinions have been presented on the efficacy and usefulness of csDMARDs. Sulfasalazine is the most extensively studied csDMARD in AS/SpA treatment, and the drug has been used in this context for more than 20 years. The 2 placebo-controlled studies of sulfasalazine revealed no effect on axial symptoms, although peripheral joint symptoms improved [25,26]. However, there is some evidence of the efficacy of the drug for axial symptoms. Braun and colleagues investigated the efficacy of sulfasalazine on undifferentiated SpA induced back pain or during cases of inflammatory <5 years in AS patients [27]. While the authors concluded that the drug was no better than the placebo on the whole, they demonstrated favorable outcomes for the treatment of spinal pain in those lacking peripheral joint symptoms. Furthermore, ASCEND studies in which AS patients were administered etanercept or sulfasalazine for 16 weeks reported improvements from baseline in the ASAS5/6, ASAS40, BASDAI, and BASFI values of both treatment groups [28]. Although no placebo group was presented for comparison, these results suggest that sulfasalazine might have better efficacy than previously believed. A meta-analysis also showed that administration of the drug resulted in some reduction of ESR and spinal stiffness in patients with AS compared with a placebo [29]. The findings from this study suggest that sulfasalazine is efficacious in those in which NSAIDs are ineffective, or with co-existing enteropathic arthritis. However, the alleviation of spinal mobility, enthesitis or physical function by the drug is limited [29]. Thalidomide is widely used in Chinese AS patients with its effectiveness extensively reported in a small samples [30] and long-term (36 months) assessments [31].

Our study demonstrates that the addition of csDMARDs such as sulfasalazine, thalidomide, methotrexate or leflunomide to NSAID treatment has beneficial effects, not only for the relief of subjective symptoms (PGA), but also for the improvement of disease-activity indices (ASDAS, BASDAI, ESR, and CRP) and functional indices (BASFI) compared with NSAID monotherapy. Although our positive results could be due to a placebo effect, the decrease in ASDAS and BASDAI scores as well as ESR likely result from the ability of the drugs to combat inflammation, suggesting disease-modifying effects of csDMARDs.

Our results provide a foundation for the development of long-term clinical treatment approaches, which will be beneficial to health economics due to the low cost of csDMARDs compared with bDMARDs. Furthermore, our study provides evidence which can be used to promote the use of csDMARDs and drive further research. Although we did not observe any

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changes in imaging findings during follow up, the functional index (BASFI) improved, consistent with their known ability to alleviate rheumatism; however, evidence to support their effectiveness in AS treatment could increase current use and result in the aforementioned clinical and economic benefits.

There were several limitations in this study. The study was performed only in 1 center and the enrolled patients were limited in terms of numbers. However, the General Hospital of the Chinese PLA is the largest hospital in China, with patients from all over the country, and our results can therefore be considered to be representative of all Chinese AS patients. Baseline data of the AS patients were comparable with those of other cohort studies on AS [32] including the GESPIC cohort [33], the DESIR cohort [34], the SCQM cohort [35], and the OASIS cohort [36]. Given the agreement with international studies, our results can be expected to be generalizable to other countries and regions. However, the rate of patients who attended the second and third follow-up visits was low, and due to the limited number of patients, we did not specifically distinguish the treatment group of each csDMARD. Therefore, we were not able to evaluate the efficacy of each csDMARD drug individually. At baseline, 93 out of 122 patients in Group 1 were taking NSAIDs before the start of the study to control their disease. This may have resulted in the reduced improvement in the disease-activity parameters observed in Group 1. Group 2 included 4 patients who began csDMARD therapy and NSAIDs simultaneously, all of whom stopped NSAID use more than a year ago due to the poor efficacy of the drug. Most patients, regardless of grouping, were treated with NSAIDs in this study. Consequently, there was a very small possibility that the greater reduction in AS activity score observed in Group 2 was due to the therapeutic effect of NSAIDs. Regarding the high drop-out rates, patients enrolled continuously into the study with varying baseline starting times. Thus, some patients may have not attended the second and third follow-up visits as they may have joined the study group later in the observation period. This resulted in the seemingly high drop-out rates, particularly in the later parts of the study. However, these patients were still included in the follow-up period of the study. In order to improve the reliability of the results, we included as many patients as much as possible. However, as the reviewer noted, influencing factors cannot be completely controlled in real-world cohorts to the level of randomized controlled trials. In order to solve this problem, we used generalized additive mixed models to control for ASDAS parameters at baseline. In these models, we considered the possible influencing factors and evaluated changes in ASDAS and follow-up times. All models used the same set of fixed effects. The following variables were measured or calculated at baseline and were entered into the adjusted model as fixed effects (including disease activity parameters). The interaction between follow-up times and drug treatment was also evaluated in order to analyze the impact on the results. Good patient education was provided to every patient in the study and information about the disease and self-assessments was deemed to be true and reliable. During outpatient follow-up, the specialists who were responsible for inquiring about records and measurements were relatively consistent. Thus, the information migration in this study can be assumed to be relatively small.

This study provides preliminary results, and we will continue to follow up enrolled patients. Furthermore, we will continue to enroll more patients with AS. In the future, we will be able provide increased data relating to csDMARD treatment for AS.

Conclusions

Use of csDMARDs can improve disease activity in terms of ASDAS-CRP. The addition of csDMARDs may provide increased benefits compared with NSAID monotherapy, particularly in the reduction of AS disease activity among Chinese patients.

Conflicts of interest

None.

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