Clinical features and current treatments of adult-onset Still's disease: a multicentre survey of 517 patients in China

Q.-Y. Hu[1], T. Zeng[2], C.-Y. Sun[3], C.-N. Luo[4], S. Liu[5], T.-T. Ding[6], Z.-F. Ji[7], A. Lu[8], K. Yimaiti[4], J.-L. Teng[1], X.-B. Cheng[1], J.-N. Ye[1], Y.-T. Su[1], H. Shi[1], Y. Sun[1], H.-H. Chi[1], Z.-C. Zhou[1], L.-J. Chen[6], J. Xu[5], L.-D. Jiang[7], L.-J. Wu[4], J. Lin[3], C.-D. Yang[1], H.-L. Liu[1]

Affiliations: see page S-56.

Qiong-Yi Hu, MD, Ting Zeng, MD**
Chuan-yin Sun, MD, Cai-nan Luo, MD**
Shuang Liu, MD, Ting-ting Ding, MD**
Zong-fei Ji, MD, Anxin Lu, MD**
Kuerbanjiang Yimaiti, MD,
Jia-lin Teng, MD, Xiao-bing Cheng, MD
Jun-na Ye, MD, Yu-tong Su, MD
Hui Shi, MD, Yue Sun, PhD
Hui-hui Chi, MD, Zhuo-chao Zhou, MD
Lin-jie Chen, MD, Jian Xu, MD
Lin-di Jiang, MD, Li-jun Wu, MD
Jin Lin, MD, Cheng-de Yang, MD
Hong-lei Liu, MD

**These authors contributed equally to this work.*

Please address correspondence to:
Dr Cheng-De Yang and Dr Hong-Lei Liu,
Department of Rheumatology and Immunology,
Shanghai Jiao Tong University School of Medicine,
Affiliated Ruijin Hospital,
No. 197 Ruijin Second Road,
Huangpu District,
Shanghai 200025, China.
E-mail: yangchengde@sina.com,
hong-lei-liu@163.com

Received on October 21, 2018; accepted in revised form on March 25, 2019.

Clin Exp Rheumatol 2019; 37 (Suppl. 121): S52-S57.

Key words: adult-onset Still's disease, glucocorticoids, retrospective study

Funding: This study was supported by the National Natural Science Foundation of China (81502016 and 81671589).

Competing interests: none declared.

ABSTRACT

Objective. *As a rare systemic autoinflammatory disease, adult-onset Still's disease (AOSD) has heterogeneous clinical manifestations, response to treatment and outcome. This study tried to assess the clinical characteristics, laboratory tests, and treatments of Chinese AOSD patients, and make a retrospective analysis.*

Methods. *From 7 hospitals in China we collected a total of 517 Chinese patients with AOSD who satisfied the Yamaguchi criteria. We retrospectively evaluated their clinical features, laboratory tests, treatments and compared them with published data from different studies. All the data in this study were from medical records and further statistic analyses.*

Results. *We evaluated a total of 517 AOSD patients, 72% female, average age of onset was 37.7; spiking fever, rash and arthralgia occurred in 472 (91.3%), 413 (79.9%), 378 (73.1%) cases, respectively. There were 439/513 (85.6%) cases with leukocytosis and 456/476 (95.8%) cases with raised serum ferritin. The highest frequently used medications and regimens for remission were glucocorticoids (498/517, 96.3%), methotrexate (273/517, 52.8%) and hydroxychloroquine (174/517, 33.7%). 84.4%. 357/423 of AOSD cases were able to achieve initial remission with different regimens, mostly including glucocorticoids, methotrexate or hydroxychloroquine. 47.2% of them (244/517) received 30<D≤60 mg/d of prednisone to reach final clinical remission. Further analysis indicated that risk factors, such as skin rash, pericarditis, splenomegaly and delayed diagnosis, are highly related to the dosage of prednisone for remission.*

Conclusion. *Glucocorticoids are mostly selected to induce remission in China and half of them required ~0.5-1mg/kgbw prednisone. In patients with skin rash, pericarditis, splenomegaly or delayed diagnosis, a higher dosage of prednisone was needed to obtain remission.*

Introduction

Adult-onset Still's disease (AOSD) is classified as an autoinflammatory disease with high spiking fever, evanescent skin rash, arthralgia and leukocytosis (1). In 1897, Sir George Still first reported 22 children with symptoms alike to systemic onset of juvenile idiopathic arthritis (SOJIA) (2). Bywaters described 14 adult patients and named the condition adult-onset Still's disease (AOSD) (3). However, the causes of AOSD are mainly unknown. As a systemic condition, AOSD symptoms are varied and characterised by fever, rash, arthralgia or arthritis, sore throat, lymphadenopathy, hepatomegaly or splenomegaly, myalgia, pericarditis or pleuritis. Laboratory test results also differ and include leukocytosis, raised serum ferritin, elevated erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels and liver function abnormality. Patients may have several of these characteristics but generally not all of them simultaneously. The complexity and heterogeneity of AOSD requires excluding infections, malignancies and other rheumatic diseases when making the diagnosis.

The therapy of AOSD is also empirical and dependent on health insurance coverage to a certain extent. Before diagnosis of AOSD, there is usually a period of delay. Antibiotic treatments might be used because of the symptoms, including fever, sore throat, leukocytosis and abnormal CRP levels, which mimic infections. Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used to control fever and pain, however,

covering up infections by reducing fever is a major concern since this limits their application on relapsed patients and those especially with long-term exposure to glucocorticoids and immunosuppressant. Treatments of AOSD were generally based on glucocorticoids and/or conventional disease-modifying anti-rheumatic drugs (cDMARDs), then biological disease-modifying anti-rheumatic drugs (bDMARDs) were introduced in the case of relapse or even in first-line treatment. An Italian group reported ~23.7% using bDMARDs as first-line treatment (4), however, only 7.6% of Turkish AOSD patients received first-line bDMARDs treatment in regimen and 5.4% when they relapsed (5). Relapsing and poor response to treatments is a usual case scenario and may mean that longer term or high doses of medicines are required, which may subsequently result in complications (such as infections). Although AOSD is a rare disorder and poorly understood, improved awareness, early diagnosis and proper treatment could improve prognosis.

Several groups have reported their retrospective studies on AOSD patients from different countries (5-10). These data indicated that it usually differs with clinical features, treatment options, disease course and study size. The published data on Chinese AOSD patients are commonly from single rheumatic departments (6, 7), and a larger multicentre study in China is absent. Here we involved 7 hospitals to collect patients' history records and make a retrospective study.

Patients and methods

Study population

The Department of Rheumatology and Immunology at Ruijin Hospital affiliated to Shanghai Jiaotong University together with 6 other large hospitals collected the clinical and laboratory data, and disease and treatment information of Chinese AOSD patients. All the patients fulfilled Yamaguchi's diagnostic criteria (11). Each centre collected the data using a standardised form, created for AOSD case evaluation. All medical records were recorded by a rheumatologist and finally pooled together.

Ethics approval

This study was approved by the Clinical Ethics Committee of Ruijin Hospital affiliated to Shanghai Jiao Tong University School of Medicine, The First Hospital Affiliated to Zhejiang University, People's Hospital of Xinjiang Uygur Autonomous Region, Xinhua Hospital Chongming Branch, First Affiliated Hospital of Kunming Medical University, Zhongshan Hospital affiliated to Fudan University, and the First Affiliated Hospital of Bengbu Medical College.

Data collection

The patient's clinical characteristics were obtained by retrospectively reviewing inpatient and outpatient data. Demographics include age, gender, age at onset and delayed diagnosis time. Clinical symptoms include fever, maculopapular salmon-pink evanescent skin rash, arthritis/arthralgia, sore throat, myalgia, lymphadenopathy, hepatomegaly, splenomegaly, pericarditis, etc.

Together with the demographics and clinical characteristics, laboratory tests were reported including blood cell counts, serum ferritin, ESR, CRP, liver functions, rheumatoid factor (RF) and anti-nuclear antibody (ANA). Microbiological examination, radiographical reports were made, and bone marrow or lymph node biopsies were partly performed. All the above clinic data were acquired during first onset of AOSD and the laboratory data before the initial treatment. Treatment information was recorded, including the initial treatment, dosage and response to treatment. The dosage for different types of glucocorticoids were converted into prednisone.

The patients initiated the treatment regimens when the diagnosis was made, and the dosages and responses (if initial remission was achieved) were also recorded. Remission was defined as a good response to treatment and the disappearance of all acute manifestations based on laboratory tests and physical examinations.

Statistical analysis

Descriptive statistics are represented as mean values±standard deviation (SD), compared using Chi-square tests. A simple comparison with other published studies was performed. The logistic regression analysis was made to identify certain factors related to higher dosages of glucocorticoids required to induce remission. *p*-value statistics from the multinomial logistic regression model with R2:0.239 and 51.7% correct classification. $p<0.05$ was considered statistically significant. Statistical analyses were performed using the SPSS 17.0 software.

Results

Demographic and clinical features

We selected in total 517 AOSD patients, 372 of whom were female (72%). The median age at onset was 37.7 years and the median delayed diagnosis was 4.6 months (range 0.5–96). All patients experienced fever and 472 (91.3%) of them reported spiking fever (≥39°C). 413 (79.9%) cases presented with a typical skin rash, predominantly found on the proximal limbs and trunk. The reticulo-endothelial system (mononuclear phagocytic system) involvements included sore throat in 313 cases (60.5%), lymphadenopathy in 264 cases (51.1%), splenomegaly in 178 cases (34.4%), and hepatomegaly in 34 cases (6.6%). Serositis that affects the pleura and pericardium was found in 124 (24%) and 73 (14.1%) patients, respectively. Arthralgia, one of the most common symptoms, was present in 378 patients (73.1%). Joint involvement was recorded in detail in 276 cases, and presented predominantly at wrists (179/64.9%), knees (199/72.1%), ankles (133/48.2%) and proximal interphalangeal joints (PIPs) (104/37.7%) as shown in Table III.

Laboratory tests

As presented in Table II, leukocytosis occurs in 439/513 patients (85.6%) and white blood cell count $\geq 15\times10^9$/L in 312/513 patients (60.8%). Neutrophils were increased in 316 patients (78.4%). ESR was elevated in 374/407 patients (91.9%) and CRP was elevated in 391/417 patients (93.8%), livel function abnormality occurred in 303/492 patients (61.6%), high serum ferritin presented in 456/476 (95.8%), and

Table I. Comparison of clinical features of AOSD patients.

	This study	Zeng 2009[6]	Kong 2010[7]	Kalyoncu2016[5]	Paolo 2016[8]	Asanuma 2016[9]	Pouchot1991[10]
Case number	517	61	104	356	245	169	62
Nationality	China	China	China	Turkey	Italy	Japan	Canada
Female	372 (72)*	45 (73.8)	78 (75)	210 (59)	116 (47.3)	121 (72)	28 (45.9)
Average age at onset	37.7	29 (47.5)	32.5	30	38.8	46	24
Delay of diagnosis#	4.6	NA	NA	NA	1.5	1.5	NA
Fever ≥39° C	472 (91.3)	61 (100.0)	100 (96.2)	341 (95.8)	226 (92.6)	152 (91.6)	62 (100.0)
Rash	413 (79.9)	54 (88.5)	95 (91.3)	238 (66.9)	166 (67.7)	102 (62.2)	54 (87.1)
Arthralgia	378 (73.1)	50 (82.0)	90 (86.5)	338 (94.9)	228 (93)	138 (83.1)	58 (93.5)
Sore throat	313 (60.5)	44 (72.1)	81 (77.9)	188 (52.8)	152 (62)	96 (59.3)	57 (91.9)
Lymphadenopathy	264 (51.1)	32 (52.5)	66 (63.5)	100 (28.1)	148 (60.4)	72 (44.7)	46 (74.2)
Hepatomegaly	34 (6.6)	8 (13.1)	NA	89 (25)	102 (41.7)	NA	7 (43.5)
Splenomegaly	178 (34.4)	23 (37.7)	NA	89 (25)	NA	52 (32.3)	34 (54.8)
Pericarditis	73 (14.1)	15 (24.6)	NA	22 (6.2)	42 (17.3)	5 (3.1)	23 (37.1)
Myalgia	168 (32.5)	17 (27.9)	NA	NA	NA	42 (25.9)	52 (83.9)

(N)*: %; #: months; NA: not available.

Table II. Comparison of laboratory testing of AOSD patients.

	This study	Zeng 2009[6]	Kong2010[7]	Kalyoncu 2016[5]	Paolo2016[8]	Asanuma 2016[9]	Pouchot 1991[10]
WBC≥10,000/mm^3	439/513 (85.6)*	51 (83.6)	103 (99)	297/350 (84.9)	198 (81)	134 (79.4)	58 (93.5)
WBC≥15,000/mm^3	312/513 (60.8)	31 (50.8)	NA	NA	NA	NA	50 (80.6)
Neutrophils >80%	316/403 (78.4)	NA	102 (98.1)	241 (66.7)	172 (70.3)	118/165 (71.5)	NA
Haemoglobin ≤10g/dl	108/396 (27.3)	9 (14.8)	28 (26.9)	233 (65.4)	NA	68/169 (40.2)	42 (67.7)
Raised ESR[A]	374/407 (91.9)	61 (100.0)	100 (96.2)	338/344 (98.2)	213 (87)	116 (68.9)	62 (100.0)
Raised ALT and/or AST	303/492 (61.6)	14 (23.0)	65 (62.5)	174/345 (50.4)	131 (53.5)	125 (73.9)	47 (75.8)
Raised LDH	318/390 (81.5)	NA	NA	128/271 (47.2)	NA	NA	NA
Ferritin ≥1×normal	456/476 (95.8)	NA	103 (99)	334/356 (96.7)	138 (56.4)	150 (88.5)	NA
Ferritin ≥5×normal	375/476 (78.8)	43/54 (79.6)	91 (87.5)	NA	196 (80.1)	101 (60)	NA
Negative ANA ANANAANA /titre <1/100	422/465 (90.8)	54 (88.5)	104 (100)	333/340 (97.9)	221 (90.4)	125 (74.2)	55 (88.7)
Negative RF	423/450 (94)	54 (88.5)	99 (95.2)	335/338 (99.1)	235 (96.2)	135 (79.9)	58 (93.5)
Raised CRP[B]	391/417 (93.8)	47/59 (79.7)	86 (82.7)	337/343 (98.2)	NA	155 (91.5)	NA

(N)*: %, [A]: ≥20mm/h, [B]: ≥8mg/L
NA: not available; WBC: white blood cell; ESR: erythrocyte sedimentation rate; LDH: lactate dehydrogenase; AST: aspartate transaminase; ALT: alanine transaminase; ANA: antinuclear antibody; RF: rheumatoid factor; CRP: C-reactive protein.

above five times the normal value was observed in 375/476 patients (78.8%). 423/450 patients (90.8%) were RF negative, 422/465 patients (90.8%) were ANA negative. Only 108/396 (27.3%) of Chinese patients had anaemia (haemoglobin ≤10g/dl). Elevated LDH was found in 318/390 (81.5%).

Treatment regimen and medication options

As reported in Table IV, 423 of cases recorded the initial treatment regimens, of whom 357/423 (84.4%) achieved clinical remission. Among them, 272/423 (64.3%) patients were treated with regimens, including glucocorticoids, methotrexate and/or hydroxychloroquine, to obtain initial remission. 84 patients received all three drugs, 66 patients were given glucocorticoids plus methotrexate, 18 patients, were treated with glucocorticoids plus hydroxychloroquine, while glucocorticoids only were given to 104 patients. 85/423 (20.1%) patients were treated with regimens that included other DMARDs (such as leflunomide (LEF), azathioprine (AZA), etc.) to achieve initial remission (Table IV). As for all 517 patients, 498/517 (96.3%) received glucocorticoids in their last regimen, 341/517 (66%) were given one or more cDMARD (Table V). Among them, methotrexate (273/517, 52.8%) and hydroxychloroquine (174/517, 33.7%) were most frequently selected. Traditional Chinese medicine (TCM) is sometimes used as DMARDs, and 7.6% of patients had TCMs in their regimens. For some reason, only 21/517 (4.1%) patients took biological agents (tocilizumab or etanercept) as additional DMARDs only as second-line treatment.

Glucocorticoids are commonly used to induce remission in China, so we further analysed the dosage distribution of corticosteroids needed to achieve remission (Table VI). 244 (47.2%) patients treated with corticosteroids at a dosage of 30–60mg/d (~0.5-1 mg/kgbw/d) prednisone achieved remission, 129 (24.9%) received a dosage of 0–30mg/d, while 60–120mg/d and more than 120mg/d was needed in 115 (22.2%) and 29 (5.6%) patients, respectively.

Factors related to higher glucocorticoids dosage required

Because high initial dosage of glucocorticoids required for remission usually means high disease activity, response to treatment, and also a longer term of glucocorticoid exposure, it is important that we know the differential

Table III. Joint involvement among different case series.

Joint affected	This study n=276	Zeng 2009[6] n=61	Kalyoncu 2016[5] n=356	Pouchot 1991[10] n=62
PIPs	104 (37.7)*	27 (44)	65 (18.3)	29 (47)
MCPs	94 (34.1)	26 (43)	89 (25)	22 (35)
Wrists	179 (64.9)	37 (61)	153 (42)	45 (73)
Elbows	111 (40.2)	30 (49)	43 (12.1)	27 (44)
Shoulders	108 (39.1)	30 (49)	31 (8.7)	25 (40)
Hips	34 (12.3)	6 (10)	8 (2.2)	7 (11)
Knees	199 (72.1)	42 (69)	120 (33.7)	51 (82)
Ankles	133 (48.2)	30 (49)	87 (24.4)	34 (55)
Feet	20 (7.2)	3 (5)	N/A	2 (3)

(N)*: %, NA: not available.
PIPs: proximal interphalangeal joints; MCPs: metacarpophalangeal joints.

Table IV. Remission rate of initial treatment comparing with Turkish data.

Regimens	This study	Turkish data[5]
Glucocorticoids only	104/142	52/60
Glucocorticoids + Hydroxychloroquine	18/21	35/37
Glucocorticoids + Hydroxychloroquine+ other DMARDs	6/8	N/A
Glucocorticoids + Methotrexate	66/72	85/97
Glucocorticoids + Methotrexate + other DMARDs	28/33	N/A
Glucocorticoids + Methotrexate + Hydroxychloroquine	84/89	68/81
Glucocorticoids + Methotrexate + Hydroxychloroquine + other DMARDs	23/26	N/A
Glucocorticoids + other DMARDs	28/32	13/26
NSAIDs	N/A	5/19
Total	357/423 (84.4%)*	254/306 (83%)*

DMARDs: disease-modifying anti-rheumatic drugs; other DMARDs: Thalidomide, Cyclosporine, Leflunomide, Azathioprine, Cyclophosphamide, Mycophenolate mofetil, Sulfasalazine, Total glucosides of paeonia, tripterygium glycosides, Tocilizumab, Etanercept; NSAIDs: nonsteroidal anti-inflammatory drugs.

Table V. Medication used in AOSD patients in our study.

Medications	Numbers (%)
Glucocorticoids	498 (96.3)
DMARDs	341 (66)
Methotrexate	273 (52.8)
Hydroxychloroquine	174 (33.7)
Thalidomide	21 (4.1)
Cyclosporine	20 (3.9)
Leflunomide	22 (4.3)
Azathioprine	9 (1.7)
Cyclophosphamide	7 (1.4)
Mycophenolate mofetil	6 (1.2)
Sulfasalazine	4 (0.8)
Traditional Chinese medicine	
Total glucosides of paeonia	33 (6.4)
tripterygium glycosides	6 (1.2)
Biologic agents	
Tocilizumab	15 (2.9)
Etanercept	6 (1.2)
Intravenous Immunoglobulin	8 (1.5)

DMARDs: disease-modifying anti-rheumatic drugs.

risk factors related to the initial dosage of glucocorticoids. Therefore, we investigated the related factors for different dosages in patients with AOSD (Table VI). 517 patients were split into 4 groups of 0<D≤30 mg/d (129), 30<D≤60 mg/d (244), 60<D≤120 mg/d (115), >120 mg/d (29) according to their GCs treatment. The features to be analysed are shown in Table VI. Our univariate analysis showed that most of our concerned features highly related to higher dosage of prednisone needed as initial remission, but in multivariate model, the presence of skin rash, pericarditis, splenomegaly and delayed diagnosis (both more than 3 months and more than 6 months) are significantly associated with higher dosage of prednisone for remission.

Discussion

AOSD is a rare heterogeneous autoinflammatory disease that is difficult to diagnose (15). The diagnosis of AOSD depends on clinical manifestations and laboratory test reports, excluding infections, malignancies and other similar diseases. Manifestations of AOSD varies in different ethnical groups and regions, although it occurs worldwide (5-10, 14-17). In the present study, AOSD usually affects young adults (16~40); female patients are more often affected than male with a ratio of 2.57:1. Most of the flares presented the main manifestations (fever, typical skin rash, arthralgia) and inflammatory laboratory tests (leukocytosis, raised ESR, CRP, LDH, ferritin level) as acute phase responses. In these features, there is a much lower presence of hepatomegaly (6.6%) in our study, compared to the Turkish (25%) and Canadian data (43.5%). Another published study also shows much less hepatomegaly in the Chinese population (6, 18), although liver abnormalities are unexpectedly similar in each group. The most possible explanation might be due to ethnic differences; another reason could be that all the data on liver evaluation are made by ultrasound tests and slight changes in liver size may not be reported because of the sensitivity and examiners. Moreover, fewer chronic destructive changes and joint erosions occurred than in the published data (data not shown). We recently performed a relatively detailed study of evaluation on joint involvement and destructive changes in Chinese patients.

The cDMARDs mostly selected were combined with glucocorticoids, methotrexate and/or hydroxychloroquine. Biological agents, such as tumour necrosis factor-α (TNF-α) blockers and interleukin-6 (IL-6) receptor antagonists, were rarely used in first-line or even second-line treatments. Interleukin-1 (IL-1) inhibition drugs have not yet been approved by the CFDA (China Food and Drug Administration). Biological DMARD application on AOSD in China is much less frequent than in Italy, where 23.7% of patients may receive bDMARDS as a first line treatment (8). Most of the patients had a good response to conventional treatments, however, bDMARDs are still an important option for relapsed patients or also as a first-line regimen, which may help to reduce the dosage in terms of glucocorticoid and other cDMARD exposure (19, 20).

Table VI. Factors related to higher GC dosage required for induction of remission.

Clinical features	0<D≤30#	30<D≤60	60<D≤120	>120	*p* (univariate)	*p* (multivariate)*
Rash	88/129 (68.2)	202/244 (82.8)	96/115 (83.5)	27/29 (93.1)	[a] <0.001,[b] <0.001,[c] 0.001	[a] 0.003,[b] 0.002,[c] 0.02
Splenomegaly	30/129 (23.3)	85/244 (34.8)	48/115 (41.7)	15/29 (51.7)	[a] 0.019,[b] 0.002,[c] 0.003	[a] 0.01,[b] 0.009,[c] 0.014
Pericarditis	15/129 (11.6)	28/244 (11.5)	17/115 (14.8)	13/29 (44.8)	[c] <0.001,[e] <0.001,[f] <0.001	[c] 0.003,[e] 0.002, [f] 0.004
Delayed diagosis (>3mo)	50/129 (38.8)	129/244 (52.8)	80/115 (69.6)	26/29 (89.7)	[a] 0.007,[b]<0.001,[c]<0.001,[e]0.001	[b] 0.005,[c] 0.003,[e] 0.022
Delayed diagosis (>6mo)	21/129 (16.2)	46/244 (18.9)	24/115 (20.9)	10/29 (34.5)	[b] 0.005,[c]<0.001,[e]0.001,[f] <0.001	[c] 0.001,[e] 0.005, [f] 0.002
WBC≥15,000/mm^3	65/127 (51.2)	152/242 (62.8)	75/115 (65.2)	20/29 (69.0)	[a] 0.023,[b] 0.011,[c] 0.016	NS
Raised ESR	91/101 (90)	166/182 (91.2)	94/99 (94.9)	23/25 (92)	[b] 0.028,[d] 0.025	NS
Raised CRP	97/103 (94.2)	171/186 (91.9)	97/101 (96)	26/27 (96.3)	[d] 0.034,[e] 0.022	NS
Ferritin≥5×normal	76/109 (69.7)	178/229 (77.7)	96/109 (88.1)	25/29 (86.2)	[a] 0.001,[b] <0.001,[c] 0.001,[d] 0.032	NS
Liver dysfunction	59/123 (48)	149/229 (65.1)	75/111 (67.6)	20/29 (69)	[a] 0.004,[b] 0.001,[c] 0.002	NS
Raised LDH (%)	64/84 (76.2)	152/183 (83.1)	78/95 (82.1)	24/28 (85.7)	[a] 0.028,[b] 0.021,[c] 0.008	NS
GC distribution	129/517 (24.9)	244/517 (47.2)	115/517 (22.2)	29/517 (5.6)		

*p-value statistics from the multinomial logistic regression model with R2:0.239 and 51.7% correct classification.
a: 0 <D≤30 *vs*. 30 <D≤60; b: 0 <D≤30 *vs*. 60 <D≤120; c: 0 <D≤30 *vs*. >120; d: 30 <D≤60 *vs*. 60 <D≤120; e: 30 <D≤60 *vs*. >120; f: 60 <D≤120 *vs*. >120, D: dosage. #mg per day.

Although fewer bDMARDs were used, even as second line treatment, most of the patients (84.4%) were able to achieve clinically remission initially, which is similar to the result of the Turkish data (83%). Glucocorticoids and cDMARDs are still a frequent option to Chinese AOSD patients and those in several other countries. However, in some western countries, bDMARDs may be used as a first-line treatment option for AOSD patients. The high costs of bDMARDs are probably the reason for their limited use in some countries like China and Turkey. However, this should be improved in the future because of the advantages of biological reagents.

Glucocorticoids are still the most commomly used medicine for Chinese AOSD patients. In the present study, most patients initially received a regimen involving a varied dose of corticosteroids to obtain clinical remission, almost half ranged from ~0.5mg/kgbw to ~1mg/kgbw of predinose. About a quarter of the patients needed ~1 to ~2mg/kgbw of predinose, and 5.6% received even higher than ~2mg/kgbw when in initial remission. Although the starting dosage of glucocorticoids is commonly empirical, higher doses (≥~1mg/kgbw) of prednisone are usually not the first choice as initial treatment. Patients who require a higher dose of glucocorticoids to induce remission usually had a poor response to treatment and more exposure to glucocorticoids in duration and total dose, which means being at high risk of infections or glucocorticoid-induced osteoporosis (GIOP) and probably a refractory or poor outcome.

However, no factors were identified that could guide physicians as to an accurate dose of glucocorticoids when the patient is first diagnosed. Patients who present an acute flare at peak, highly active mononuclear phagocyte system and important organ involvements may require a higher dose of glucocorticoids after diagnosis. Initially high-dose glucocorticoid administrations may help to control the disease activity and achieve remission for those patients. However, clinical features and the genetic background of each patient may play a central role in manifestations, treatment response, prognosis and outcome. A further genetic analysis may benefit the understanding of AOSD and may subsequently be needed.

Because it is a rare disease, there is an obvious limitation for AOSD patient collection. For this reason, we tried to analyse and report on larger population of Chinese AOSD patients. This present study retrospectively surveyed the baseline information of manifestations, treatments and tried to identify several factors statistically associated with higher glucocorticoid administration.

Conclusion

We conducted a multicentre survey of AOSD to retrospectively study important features of clinical manifestations, laboratory tests, therapeutic responses and factors related to relapse and prognosis. Steroids, methotrexate and hydroxychloroquine are used mostly in the initial regimen, however, bDMARDs are rarely used for first-line treatment for AOSD in China. The presence of skin rash, pericarditis, splenomegaly and delayed diagnosis are highly related to the dosage of prednisone for remission.

Acknowledgements

We express our gratitude to the participants for the data collection. We appreciate the precious suggestions for revision in our study.

Affiliations

[1]Department of Rheumatology and Immunology, Shanghai Jiao Tong University School of Medicine Affiliated Ruijin Hospital, Shanghai;
[2]Xinhua Hospital Chongming Branch Affiliated to Shanghai JiaoTong University School of Medicine, Shanghai;
[3]Department of Rheumatology, First Affiliated Hospital of the Medical School, Zhejiang University, Hangzhou;
[4]Department of Rheumatology and Immunology, People's Hospital of Xinjiang Ugyur Autonomous Region, Urumqi;
[5]Department of Rheumatology and Immunology, First Affiliated Hospital of Kunming Medical University, Kunming;
[6]Department of Rheumatology and Immunology, First Affiliated Hospital of Bengbu Medical College;
[7]Department of Rheumatology, Zhongshan Hospital, Fudan University, Shanghai;
[8]Shanghai Jiao Tong University School of Medicine, Shanghai, China.

References

1. GERFAUD-VALENTIN M, JAMILLOUX Y, IWAZ J, SEVE P: Adult-onset Still's disease. *Autoimmun Rev* 2014; 13: 708-22.
2. STILL GF: On a form of chronic joint disease in children. *Med Chir Trans* 1897; 80: 47-60.
3. BYWATERS EG: Still's disease in the adult. *Ann Rheum Dis* 1971; 30: 121-33.
4. YOO DH: Treatment of adult-onset still's disease: up to date. *Expert Rev Clin Immunol* 2017; 13: 849-66.
5. KALYONCU U, SOLMAZ D, EMMUNGIL H *et al*.: Response rate of initial conventional treatments, disease course, and related factors of patients with adult-onset Still's disease: Data from a large multicenter cohort. *J Autoimmun* 2016; 69: 59-63.
6. ZENG T, ZOU YQ, WU MF, YANG CD: Clinical features and prognosis of adult-onset still's disease: 61 cases from China. *J Rheumatol* 2009; 36: 1026-31.
7. KONG XD, XU D, ZHANG W, ZHAO Y, ZENG X, ZHANG F: Clinical features and prognosis in adult-onset Still's disease: a study of 104 cases. *Clin Rheumatol* 2010; 29: 1015-9.
8. SFRISO P, PRIORI R, VALESINI G *et al*.: Adult-onset Still's disease: an Italian multicentre retrospective observational study of manifestations and treatments in 245 patients. *Clin Rheumatol* 2016; 35: 1683-9.
9. ASANUMA YF, MIMURA T, TSUBOI H *et al*.: Nationwide epidemiological survey of 169 patients with adult Still's disease in Japan. *Mod Rheumatol* 2015; 25: 393-400.
10. POUCHOT J, SAMPALIS JS, BEAUDET F *et al*.: Adult Still's disease: manifestations, disease course, and outcome in 62 patients. *Medicine* (Baltimore) 1991; 70: 118-36.
11. YAMAGUCHI M, OHTA A, TSUNEMATSU T *et al*.: Preliminary criteria for classification of adult Still's disease. *J Rheumatol* 1992; 19: 424-30.
12. CUSH JJ, JR MEDSGER TA, CHRISTY WC: Adult-onset Still's disease. Clinical course and outcome. *Arthritis Rheum* 1987; 30: 186-94.
13. WOUTERS JM, VAN DE PUTTE LB: Adult-onset Still's disease; clinical and laboratory features, treatment and progress of 45 cases. *Q J Med* 1986; 61: 1055-65.
14. PAY S, TÜRKÇAPAR N, KALYONCU M *et al*.: A multicenter study of patients with adult-onset Still's disease compared with systemic juvenile idiopathic arthritis. *Clin Rheumatol* 2006; 25: 639-44.
15. LOUTHRENOO W, ARAMSAREEWONG T, SUKITAWUT W: Adult onset Still's disease: clinical features and outcome in 16 Thai patients. *J Clin Rheumatol* 2001; 7: 301-7.
16. AL-ARFAJ AS, AL-SALEH S: Adult-Onset Still's disease in Saudi Arabia. *Clin Rheumatol* 2001; 20: 197-200.
17. APPENZELLER S, CASTRO GR, COSTALLAT LT, SAMARA AM, BÉRTOLO MB: Adult-onset Still disease in southeast Brazil. *J Clin Rheumatol* 2005; 11: 76-80.
18. ZHU GH, LIU G, LIU YX, XIE QB, SHI GX: Liver abnormalities in adult onset Still's disease: a retrospective study of 77 Chinese patients. *J Clin Rheumatol* 2009; 15: 284-8.
19. ZHOU S, QIAO J, BAI J, WU Y, FANG H: Biological therapy of traditional therapy-resistant adult-onset Still's disease: an evidence-based review. *Ther Clin Risk Manag* 2018; 24: 167-71.
20. RUSCITTI P, URSINI F, CIPRIANI P, DE SARRO G, GIACOMELLI R: Biologic drugs in adult onset Still's disease: a systematic review and meta-analysis of observational studies. *Expert Rev Clin Immunol* 2017; 13: 1089-97.