

A retrospective analysis of colchicine in combination with NSAIDs therapy in patients with systemic form of adult-onset Still's disease with serositis

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Abstract

Objective

Adult-onset Still's disease (AOSD) is increasingly viewed as autoinflammatory disease associated with the so-called inflammasomopathy. Proinflammatory cytokines, such as IL-18 and IL-1 β , processed through the inflammasome machinery, play an important role in the pathogenesis of AOSD. AOSD is heterogenous, therefore there are two subtypes of the disease, systemic and articular, which probably imply different approaches for the treatment. Over 20% of patients with systemic AOSD have serositis. Recently, colchicine in combination with non-steroidal anti-inflammatory drugs (NSAIDs) has become the "gold standard" for recurrent pericarditis treatment. However, data on this combination therapy in AOSD are scarce.

Methods

In this retrospective case series study, we assessed the medical history of 20 patients with a systemic form of AOSD. All patients had pericarditis and received a combination of NSAIDs (in most cases ibuprofen 600-800 mg x3 daily) and colchicine (1 mg daily) for treatment.

Results

13/20 (65%) of patients responded to this combination of anti-inflammatory drugs. Of note, not only pericarditis, but also other manifestations were improved such as arthritis, rash, hepatomegaly, acute phase reactants, and abnormal liver tests.

Conclusion

The low cost, safety and wide availability of such therapy make this option relevant and determine the need for further study.

Key words

systemic adult-onset Still's disease, colchicine, serositis, pericarditis, treatment

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Introduction

The group of complex autoinflammatory diseases (AID) is under rapid reassessment by inclusion of new pathologies or reclassification of well-known diseases. Recently, adult-onset Still's disease (AOSD) and idiopathic recurrent pericarditis (IRP) have been classified as AIDs. AOSD is a rare systemic autoinflammatory disease, the genetics of which are currently undetermined (1). Although the main symptoms include fever, sore throat, rash, and arthritis, clinical manifestations may differ from patient to patient, and the absence of specific and highly sensitive markers explain the several sets of diagnostic criteria (2-4). AOSD is a heterogeneous disease. Many authors support the concept of dividing the disease into 2 subtypes, systemic and articular (5). The prevalence of serositis varies from 21 to 53%. In earlier descriptions, serositis (pericarditis and/or pleuritis) was assessed as one of the main symptoms of AOSD. Cush *et al.*, Bywaters *et al.* and Pouchot *et al.* stressed the importance of this symptom (2, 6, 7). In Cush's proposed criteria, pericarditis was included as one of the minor criteria. Pouchot *et al.* proposed a systemic score for AOSD where pericarditis was also included. According to his data, serositis was detected in 53% of cases. In later review articles, the prevalence of serositis was estimated at 21% (8). In some cases, serositis can be the leading manifestation, thereby mimicking idiopathic recurrent pericarditis (9-11). The differential diagnosis between these pathologies is complex, since no specific markers and symptoms exist, especially in case when systemic AOSD occurs without any sign of joint or skin involvement (12).

The current therapeutic recommendations for AOSD are not evidence-based and there are no accepted treatment guidelines due to the lack of randomised controlled trials. Some authors recommend NSAIDs for mild AOSD variant as the first line therapy. The use of glucocorticoids (GCs) is a common second line option. Usually, a clear treatment response can be observed after systemic administration of medium to high GSc doses. However,

in many cases, reduction of the dose of GCs results in disease relaps. Moreover, steroid resistance, dependence and long-term side effects occur frequently. Methotrexate (MTX) is widely administered as a steroid-sparing drug, which has been confirmed to be effective in a number of case series. However, no randomised clinical trials have been carried out. The results concerning effectiveness of biologic agents such as anti-IL-1 (13) and anti-IL-6 (14, 15) have recently been published. However, the biologic treatment is still considered to be a last line therapy, with the exception of life-threatening systemic manifestations. Although in two clinical trials the primary endpoint was not achieved, treatment with canakinumab and tocilizumab led to an improvement of several outcome measures in AOSD (16, 17).

IRP is usually treated by colchicine (COL), which, in most cases, can help to avoid GCs. The first line therapy for IRP is a combination of NSAIDs and colchicine, which has shown high efficiency in clinical trials CORP (18) and CORP-2 (19), thus being included in the latest recommendations of the European Society of Cardiology for IRP (20). On the other hand, colchicine has been successfully used not only for IRP, but also for secondary pericarditis in systemic lupus erythematosus, post-pericardiotomy syndrome, and also in AOSD (21-25). Furthermore, COL is frequently administered to patients with pericarditis of unknown origin. In this retrospective cohort study, we describe the safety and treatment effects of COL in patients with serositis related to AOSD.

Methods

We assessed 621 clinical cases of pericarditis among patients hospitalised at the Almazov National Medical Research Centre, St. Petersburg, Russia, from January 2015 to January 2021. The inclusion criteria were: the presence of serositis with pericarditis as the leading symptom, and colchicine in combination with NSAIDs treatment. Secondary causes of pericarditis were excluded: including tuberculosis, autoimmune diseases,

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Table I. General information of 20 systemic AOSD patients receiving combination of COL+NSAIDs treatment.

Age (years old), gender	White blood cells * 10 ⁹ /L	Neutrophil count, * 10 ⁹ /L	CRP (mg/l) (normal range 0-5)	Ferritin (ng/mL) (normal range 30.0-300.0)	GF, % (<20%)	Alanine aminotransferase (U/L 0.00-33)	Aspartate Aminotransferase (U/L 5.0-32)	MEFV gene	TNFRSF1A gene	Presence of ANA, RF	Myalgia	Rash	Fever	Arthritis	Arthralgia	Pericarditis	Pleuritis	Sore throat	Splenomegaly	Lymphadenopathy	Hepatomegaly	Systemic score	Previous treatment before COL	Achieve remission during COL+NSAIDs treatment
44, f	20,3	14,4	267	408	37	57	30	-	-	-	-	-	+	-	+	+	+	-	-	-	-	5	NSAIDs	Yes
*51, m	13,9	10,65	170	643	29	44	26	-	-	-	-	-	+	-	+	+	+	-	-	-	-	4	NSAIDs	Yes
*54, f	11	8	63	352	43	54	29	NA	NA	-	-	-	+	-	+	+	+	+	-	-	-	5	NSAIDs Pulse GCs	Yes
56, f	12	9,7	135	215	50	65	132	-	-	-	+	+	+	-	+	+	+	-	+	-	-	7	NSAIDs	Partial response
68, m	10,3	8,05	104	786	21	162	79	-	-	-	-	-	+	+	+	+	+	-	+	-	+	6	NSAIDs	No
65, f	7,10	6,15	54	15	96	21	20	-	-	-	-	-	+	-	+	+	+	+	-	-	+	5	NSAIDs	Partial response
*56, f	9,2	6,34	172	216	80	81	48	-	-	-	-	-	+	-	+	+	+	-	+	-	+	5	NSAIDs	Yes
21, m	18	14,94	82	5380	18	67	58	-	-	-	-	+	+	-	+	+	+	+	+	+	+	9	NSAIDs Pulse GCs	Yes
25, f	14	11	84	654	28	22	32	-	-	-	+	+	+	+	+	+	+	+	-	+	-	8	GCs MTX	Yes
*28, m	17,4	14	144	NA	NA	75	53	-	-	-	-	-	+	-	-	+	+	+	-	+	+	7	GCs MTX	No
38, f	8,7	6	49	18	98	19	16	-	-	-	-	-	+	+	+	+	+	+	-	-	-	5	GCs MTX	Yes
39, m	12,6	10,7	150	500	30	96	32	NA	NA	-	-	-	+	-	+	+	+	-	-	+	+	5	NSAIDs	Yes
41, m	13	11	238	NA	NA	78	14	-	-	-	-	-	+	+	+	+	+	-	-	-	+	5	NSAIDs GCs	Yes
59, f	11,5	7,9	82	26	95	47	39	G/Z 148E/Q	-	-	-	+	+	-	+	+	+	+	-	-	+	6	NSAIDs GCs	Yes
64, f	13,20	10,90	271	300	56	53	46	-	-	-	-	+	+	+	+	+	+	-	-	+	-	7	NSAIDs GCs	Partial response
***58, f	12	10	460	791	63	15	14	-	-	-	-	-	+	+	+	+	+	-	-	-	+	5	NSAIDs	No
39, f	15,4	10,50	16	NA	NA	47	10	-	-	-	-	+	+	+	+	+	+	+	-	-	+	8	GCs	No
32, f	12,2	10,2	194	NA	NA	48	39	-	-	-	+	+	+	+	+	+	+	+	-	+	-	9	NSAIDs	Yes
32, m	32	25,6	50	450	NA	204	64	-	-	-	-	+	+	+	+	+	+	+	-	-	+	8	GCs MTX	Yes
**37, f	17,6	12,2	88	1400	13	24	28	-	-	-	-	+	+	+	+	+	-	-	+	+	+	7	NSAIDs GCs	Yes

+; persistence of sign; -; absence of sign; f; female; m; male; NA; not available; CRP; C-reactive protein; MEFV; gene of familial Mediterranean fever; TNFRSF1A; gene of tumour necrosis factor (TNF) receptor associated periodic syndrome; GF; glycosylated ferritin; ANA; antinuclear antibodies; RF; rheumatoid factor; COL; colchicine; NSAIDs; non-steroidal anti-inflammatory drugs; MTX; methotrexate; GCs; glucocorticoids.

AOSD-related outcome: *cardiac tamponade; **MAS (macrophage activation syndrome); ***thrombosis.

monogenic AID (FMF, TRAPS) and tumours.

Overall, 32 cases were identified meeting the criteria of our search strategy. Among these cases, 20 patients were diagnosed as AOSD in the follow-up. All these patients met the criteria proposed by Yamaguchi *et al.* (3). The clinical feature of the cohort was the presence of polyserositis (pericarditis, pleuritis) as the leading symptom, and a mild articular syndrome: 19 patients had arthralgia, whereas half of them had non-destructive oligoarthritis.

Each patient was assessed by the systemic score proposed as by Pouchot *et al.* (8). All patients were catego-

risied by the presence of AOSD-related complications (26). According to the clinical patterns which was described by Cush *et al.*, all patients were classified as having a polycyclic course (2). Treatment regimens before using the combination NSAIDs + COL were categorised into four groups, *i.e.*, monotherapy with medium dose of glucocorticoids (GCs): 10-20 mg of prednisone; NSAIDs; NSAIDs plus medium dose of GCs; combination therapy with GCs plus MTX. Clinical data, laboratory parameters and systemic scores of AOSD patients before colchicine therapy are presented in Table I.

Since criteria for the remission in

AOSD are not available, we considered remission if the following criteria were met: persistent apyrexia, absence of rash, absence of articular syndrome and sore throat, pericardial effusion less than 7 mm according to transthoracic echocardiography, absence of chest pain, CRP level less than 5 mg/l, normalisation of aminotransferases, leukocyte count and ferritin level. The partial response was defined based on the following conditions: absence or mild elevated body temperature, pericardial effusion less than 7 mm according to transthoracic echocardiography, absence of chest pain, decrease of CRP level more than 50% of baseline,

normalisation of leukocyte count, improvement of clinical symptoms assessed by the patients of at least 50%.

Analysis

Statistical analysis was performed with STATISTICA 10 software. McNemar's test was used to assess the effect of therapy on clinical and laboratory disease manifestations. *p*-values less than 0.05 were considered significant.

Results

Clinical features

The group consisted of twenty patients: 7 men and 13 women; the mean age was 47 years (21-68). The main clinical and laboratory characteristics of patients are shown in Table I. In 13 patients serositis was the first symptom, while in 7 patients serositis developed in the course of the disease. Other symptoms were rash (9 patients), arthralgia (19 patients), oligoarthritis (10 patients) which were non-destructive, 10 patients had sore throat. It was documented that almost all patients had polyserositis manifesting both pericardial and pleural effusion, except one. We suppose that we could not detect this transient pleuritis. According to Ruscitti *et al.* the systemic score of ≥ 7.0 was associated with a more severe outcome (26). In our cohort, the median systemic score was 6 (5-9). There were 6 AOSD-related complications: one patient with MAS, four patients with cardiac tamponade. Also, one patient had central retinal vein thrombosis associated with disease activity and significant thrombocytosis, which was not recognised as an AOSD-related outcome in previous works (27). Only two patients had a score of 7.0, one patient with tamponade and another one with MAS. Patients with AOSD-related outcome are marked in Table I. In our cohort, we did not find a relationship between the systemic score and AOSD-related complications and the response to COL. We suggest that such data was obtained due to the small sample size. The polycyclic pattern was presented in all patients. Patients received different treatments before the fixed combination with NSAIDs and COL. One patient was treated with medium dose of

Table II. The response to combination of colchicine and NSAIDs according the symptoms.

Symptoms and signs	Number (N), %	Before COL treatment, n=20	After COL treatment, n=20	<i>p</i>
Fever	N (%)	20 (100)	0 (0)	<0.001
Sore throat	N (%)	10 (50)	0 (0)	0.002
Arthritis	N (%)	10 (50)	4 (20)	0.008
Arthralgia	N (%)	19 (95)	2 (10)	0.002
Chest pain	N (%)	19 (95)	1 (5)	0.002
Serositis	N (%)	20 (100)	3 (15)	<0.001
Rash	N (%)	9 (45)	1 (5)	0.008
Splenomegaly	N (%)	5 (25)	1 (5)	0.14
Lymphadenopathy	N (%)	7 (35)	1 (5)	0.031
Hepatomegaly	N (%)	13 (65)	3 (15)	<0.001
Elevated CRP	N (%)	20 (100)	6 (30)	<0.001
Elevated Ferritin	N (%)	13 (65)	2 (10)	<0.001
Leukocytosis	N (%)	17 (85)	1 (5)	<0.001
Abnormal liver tests	N (%)	16 (80)	3 (15)	<0.001
Adverse events	N (%)		6 (30)	
Diarrhoea CTCAE v5.0 grade 1	N (%)		3 (15)	
Elevated transaminase level CTCAE v5.0 grade 1	N (%)		1 (5)	
Neutropenia CTCAE v5.0 grade 1	N (%)		2 (10)	
Full response (remission)	N (%)	13 (65)		
Partial response	N (%)	3 (15)		
No response	N (%)	4 (20)		
Treatment before COL			Treatment after COL	
GCs:	N	11		
GCs monotherapy	N	1	Non-responder	
GCs+MTX	N	4	Discontinuation – 2 patients, achieved 5 mg of prednisolone- 1 patient, non-responder – 1 patient	
GCs+NSAIDs	N	6	Discontinuation – 4 patients, achieved 5 mg of prednisolone- 1 patient, non-responder – 1 patient	
NSAIDs	N	10	5	
Achieved 5 mg of prednisolone	N	2		
GCs withdrawal because of COL	N	6		
MTX withdrawal because of COL	N	2		

COL: colchicine; NSAIDs: non-steroidal anti-inflammatory drugs; MTX: methotrexate; GCs: glucocorticoids; CTCAE: common terminology criteria for adverse events.

GCs monotherapy. Eight patients were treated with different NSAIDs, and ten patients were treated with a combination therapy, including NSAIDs and medium dose of GCs (n=6) and MTX and medium dose of GCs (n=4).

Colchicine in combination with NSAIDs were administered in similar doses as in the guidelines for IRP (20). In most cases, NSAIDs were given in full dose (Ibuprofen 600–800 mg every 8 hours). All patients took COL 0.5 mg twice a day, with the exception of 2 patients for whom the dose was reduced to prevent side effects (diarrhoea in one and cytotoxicity in the other).

A therapeutic response was observed within 2 weeks (3 days - 4 weeks). 65% of patients achieved remission during

the first month. COL was administered for a period of at least 6 months. The dose of NSAIDs was reduced each month until it was discontinued. Patients under GCs could reduce the dose: six patients were discontinued and two patients were able to taper dose up to 5 mg of prednisolone. The mean duration of COL therapy after achieving remission was 15 months (6–30). The mean follow-up period was 29 months (6–71). 6 patients (out of 12 who achieved remission) discontinued the therapy. 3 of them had a recurrence within the following 4 months (1–8 months), which required the re-introduction of this combination. In all these cases, the remission was achieved again.

A partial response was achieved in

Table III. Summary of the literature review: colchicine use in AOSD cases (sorted according to publication date).

Case	Number of patient	Age (years), sex	Previous treatment	Symptoms	Daily dose of COL	Effect	Other
Oh <i>et al.</i> (22)	1	25-year-old, female	prednisolone sulfasalazine hydroxychloroquine methotrexate	fever maculopapular rash polyarthritis leukocytosis elevated level of CRP hyperferritinaemia	1.2 mg per os	Steroid-sparing effect	Combination of treatment with prednisolone, cyclophosphamide and colchicine
Plaçaïs <i>et al.</i> (23)	1	38-year-old, female	Glucocorticoids in a combination with colchicine: intravenous immunoglobulins	During pregnancy: fever arthralgias sore throat abdominal pain pericarditis hepatomegaly elevated level of CRP elevated liver function test hyperferritinaemia glycosylated ferritin <5%	NR	Partial effect	Replaced to anakinra and GCs
Ou-Yang <i>et al.</i> (24)	1	30-year-old, female	aceclofenac prednisolone cyclosporine	fever rash polyarthritis lymphadenopathy hepatosplenomegaly leukocytosis elevated liver function test elevated level of CRP hyperferritinaemia	2 mg per os	Partial effect	Replaced to tocilizumab
Asano <i>et al.</i> (25)	1	24-year-old, female	prednisolone MTX (replaced to tacrolimus) tocilizumab (switched to infliximab and cyclosporin A)	fever rash arthritis sore throat leukocytosis elevated level of CRP elevated liver function test hyperferritinaemia	1,5 mg per os	Steroid-sparing effect	The effect was achieved by a combination of GCs and colchicine, not by a biologic

CRP: reactive protein; GCs: glucocorticoids; COL: colchicine; NR: not reported.

an additional 20% of patients. In the group with a partial response, NSAIDs were replaced by GCs, and COL was continued: three patients were prescribed 10 mg, and one patient 20 mg of prednisolone. In these patients, COL showed a good steroid-sparing effect and made it possible to completely taper off of prednisolone in the next 6 months. COL therapy was continued without cancellation.

Only 20% of patients did not respond to these combinations and were prescribed another therapy.

There were no serious side effects (SE); among class-specific SE, diarrhoea was documented in 3 cases (15%), a transient increase in liver function tests from initially elevated values in one case (5%), a decrease in neutrophil levels in 2 cases (10%). All clinical data and prevalence of symptoms before and after treatment are presented in Table II.

Discussion

Colchicine is successfully used in a number of monogenic and non-monogenic AID. One of the reasons for this success is its effect on inflammatory interleukins IL-1 and IL-18 (28). During the COVID-19 pandemic, more and more attention is paid to COL and the clinical range of its application is expanding. However, the data of using COL in patients with AOSD is still limited. A literature search with the keywords “colchicine, adult Still’s disease, AOSD” yielded only four case reports (Table III) (22-25).

The use of COL for pericarditis treatment has become a standard option, especially after the publication of current Recommendations of the European Society of Cardiology (20). COL administration is usually restricted to the presence of pericarditis, and its ef-

ficacy is assessed based on precise response of pericardial involvement.

In this article, we publish the first report of the efficacy on COL treatment together with NSAIDs in patients with AOSD with the predominant manifestation of serositis. After analysing the case history of patients who received COL as an additional drug due to pericarditis, we noted that the effect was achieved not only for pericarditis, but also for other manifestations, such as arthritis/arthralgia, rashes, leukocytosis, inflammatory markers. More than half of the patients achieved complete remission of the disease, 15% of patients had a partial response and about 20% did not respond to this therapy.

Due to its favourable safety profile, colchicine could become a relevant alternative for first-line therapy of systemic form of AOSD with serositis especially in comparison with methotrex-

ate, where the effect on systemic manifestations of the disease is limited. The low cost and wide availability of COL makes this option even more attractive. Thus, randomised studies are required to confirm the efficacy and safety of COL in AOSD.

Our study is limited by its design as a retrospective, non-randomised, clinical observation. Moreover, only cases of the systemic form of AOSD have been included, where serositis is the leading symptom. We cannot assess the effect of colchicine in patients without serositis. However, our data show that COL can also improve other symptoms of AOSD and the reintroduction was effective as well.

It is noteworthy to state that the frequency of pericarditis resolution recorded during colchicine therapy in patients in the CORP study was comparable to our data. In light of new data on the clinical phenotype of acute pericarditis with strong systemic manifestations, such as neutrophilic leukocytosis, significant pleuropulmonary involvement, high concentrations of acute phase reactant and liver tests (12), the effect on therapy can also be an additional argument to speculate about the common origin of systemic AOSD and IRP.

Conclusion

Administration of colchicine can result in high proportion of remission and decrease of disease activity in AOSD complicated by serositis. The data open a new field for colchicine treatment in AOSD, and it may generally represent the foundation for future randomised clinical trials of this treatment for AOSD.

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References

1. FEIST E, MITROVIC S, FAUTREL B: Mechanisms, biomarkers and targets for adult-onset Still's disease. *Nat Rev Rheumatol* 2018; 14: 603-18.
2. CUSH JJ, MEDSGER TA JR, CHRISTY WC, HERBERT DC, COOPERSTEIN LA: Adult-onset Still's disease. Clinical course and outcome. *Arthritis Rheum* 1987; 30: 186-94.
3. YAMAGUCHI M, OHTA A, TSUNEMATSU T *et al.*: Preliminary criteria for classification of adult Still's disease. *J Rheumatol* 1992; 19: 424-30.
4. FAUTREL B, ZING E, GOLMARD JL *et al.*: Proposal for a new set of classification criteria for adult-onset still disease. *Medicine (Baltimore)*. 2002; 81: 194-200.
5. MITROVIC S, FAUTREL B: Clinical phenotypes of adult-onset sStill's disease: new insights from pathophysiology and literature findings. *J Clin Med* 2021; 10: 2633.
6. BYWATERS EG: Still's disease in the adult. *Ann Rheum Dis* 1971; 30: 121-33.
7. 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.
8. RUSCITTI P, BERARDICURTI O, IACONO D *et al.*: Parenchymal lung disease in adult-onset Still's disease: an emergent marker of disease severity-characterisation and predictive factors from Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale (GIRRC) cohort of patients. *Arthritis Res Ther* 2020; 22: 151.
9. MYACHIKOVA VY, MASLYANSKY AL, GAY-DUKOVA IZ, NOVIKOVA AN, KARPOVA DV, SHLYAKHTO EV: Difficulties in diagnosis and treatment of adult-onset Still's disease concurrent with pericardial effusion as a leading clinical manifestation. *Mod Rheumatol* 2016; 10: 31-6. (In Russ.).
10. BODARD Q, LANGLOIS V, GUILPAIN P *et al.*: Cardiac involvement in adult-onset Still's disease: manifestations, treatments and outcomes in a retrospective study of 28 patients. *J Autoimmun* 2021; 116: 102541.
11. KAWAGUCHI H, TSUBOI H, YAGISHITA M *et al.*: Severe adult-onset Still disease with constrictive pericarditis and pleuritis that was successfully treated with tocilizumab in addition to corticosteroids and cyclosporin A. *Intern Med* 2018; 57: 1033-8.
12. BIZZI E, PICCHI C, MASTRANGELO G, IMAZIO M, BRUCATO A: Recent advances in pericarditis. *Eur J Intern Med* 2021 Sep 20: S0953-6205(21)00302-2.
13. GIACOMELLI R, SOTA J, RUSCITTI P *et al.*: The treatment of adult-onset Still's disease with anakinra, a recombinant human IL-1 receptor antagonist: a systematic review of literature. *Clin Exp Rheumatol* 2021; 39: 187-95.
14. KIR S, ÖZGEN M, ZONTUL S: Adult-onset still's disease and treatment results with tocilizumab. *Int J Clin Pract* 2021; 75: e13936.
15. CIPRIANI P, RUSCITTI P, CARUBBI F *et al.*: Tocilizumab for the treatment of adult-onset Still's disease: results from a case series. *Clin Rheumatol* 2014; 33: 49-55.
16. KEDOR C, LISTING J, ZERNICKE J *et al.*: Canakinumab for Treatment of Adult-Onset Still's Disease to Achieve Reduction of Arthritic Manifestation (CONSIDER): phase II, randomised, double-blind, placebo-controlled, multicentre, investigator-initiated trial. *Ann Rheum Dis* 2020; 79: 1090-7.
17. KANEKO Y, KAMEDA H, IKEDA K *et al.*: Tocilizumab in patients with adult-onset still's disease refractory to glucocorticoid treatment: a randomised, double-blind, placebo-controlled phase III trial. *Ann Rheum Dis* 2018; 77: 1720-9.
18. IMAZIO M, BRUCATO A, CEMIN R *et al.*: Colchicine for recurrent pericarditis (CORP): a randomized trial. *Ann Intern Med* 2011; 155: 409-14.
19. IMAZIO M, BELLI R, BRUCATO A *et al.*: Efficacy and safety of colchicine for treatment of multiple recurrences of pericarditis (CORP-2): a multicentre, double-blind, placebo-controlled, randomised trial. *Lancet* 2014; 383: 2232-7.
20. ADLER Y, CHARRON P, IMAZIO M *et al.*: 2015 ESC Guidelines for the diagnosis and management of pericardial diseases: The Task Force for the Diagnosis and Management of Pericardial Diseases of the European Society of Cardiology (ESC) Endorsed by: The European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J* 2015; 36: 2921-64.
21. CHHABRA L, DUA K, SPODICK D: CORP-2 trial and the role of colchicine in non-idio-pathic pericarditis. *Nat Rev Cardiol* 2014; 11: 442.
22. OH YB, BAE SC, JUNG JH *et al.*: Secondary renal amyloidosis in adult-onset Still's disease: case report and review of the literature. *Korean J Intern Med* 2000; 15: 131-4.
23. PLAÇAIS L, MEKINIAN A, BORNES M *et al.*: Adult-onset Still's disease occurring during pregnancy: Case-report and literature review. *Semin Arthritis Rheum* 2018; 47: 575-7.
24. OU-YANG LJ, TANG KT: A case of adult-onset Still's disease with mutations of the MEFV gene who is partially responsive to colchicine. *Medicine (Baltimore)* 2018; 97: e0333.
25. ASANO T, FURUYA MY, SATO S, KOBAYASHI H, WATANABE H, SUZUKI E, MIGITA K: Adding colchicine to immunosuppressive treatments; a potential option for biologics-refractory adult-onset Still's disease. *BMC Res Notes* 2018; 11: 320.
26. RUSCITTI P, CIPRIANI P, MASEDU F *et al.*: Adult-onset Still's disease: evaluation of prognostic tools and validation of the systemic score by analysis of 100 cases from three centers. *BMC Med* 2016; 14: 194.
27. EFTHIMIOU P, KADAVATH S, MEHTA B: Life-threatening complications of adult-onset Still's disease. *Clin Rheumatol* 2014; 33: 305-14.
28. LEUNG YY, YAO HUI LL, KRAUS VB: Colchicine – Update on mechanisms of action and therapeutic uses. *Semin Arthritis Rheum* 2015; 45: 341-50.