Epidemiology and outcome of adult-onset Still's disease in the Northwestern Thrace region in Turkey

M.A. Balci[1], O.N. Pamuk[1], G.E. Pamuk[2], F.K. Uzundere[3], S. Donmez[1]

[1]Department of Rheumatology; [2]Department of Haematology, Trakya University Medical Faculty, Edirne, Turkey; [3]Department of Internal Medicine, Siirt State Hospital, Siirt, Turkey.

ABSTRACT

Objective

Adult-onset Still's disease (AOSD) is a rare disease that is classified among the multifactorial autoinflammatory disorders. It is characterised by fever, arthritis and, a typical salmon-coloured rash, and is accompanied by fever at nights. Currently, there is limited data on the prevalence of AOSD.

Methods

Patients diagnosed with AOSD at the Department of Rheumatology of Trakya University Medical Faculty, between 2003 to 2014 were reviewed retrospectively. Patients' clinical features, laboratory measurements, demographics, treatments, follow-up durations, disease courses, outcomes and complications were evaluated.

Results

Our study included 42 patients with AOSD of whom, 32 (76.2%) were females and 10 (23.8%) were males (female to male ratio: 3.2). Over the course of the study, the annual incidence of AOSD was 0.62/100,000; and the overall prevalence was 6.77/100,000. The most common findings were fever (97.6%), arthralgia (95.2%), arthritis (76.2%), rash (73.8%) and sore throat (40.5%).

Conclusion

In our hospital-based study on AOSD which is a disease with very limited epidemiological data, the frequency of AOSD was found to be significantly higher than in other series. Female gender was more common in our series; and polycyclic pattern was more common in patients with longer follow-ups.

Key words

adult-onset Still's disease, epidemiology

Mehmet Ali Balci, MD
Omer Nuri Pamuk, MD, PhD
Gulsum Emel Pamuk, MD, PhD
Fatma Keskin Uzundere, MD
Salim Donmez, MD, PhD

Please address correspondence to:
Dr Mehmet Ali Balci,
Department of Rheumatology,
Trakya University Medical Faculty,
22030 Edirne, Turkey.
E-mail: abalci13@gmail.com

Received on December 23, 2014; accepted in revised form on May 28, 2015.

Competing interests: none declared.

Introduction

Adult-onset Still's disease (AOSD) is a rare disease and it is classified as one of the multifactorial autoinflammatory disorders. It's characterised by fever, arthritis and, a typical salmon-coloured rash which is more pronounced and is accompanied fever at nights. It was first described by George Still in 1896 as an acute systemic-onset form of juvenile idiopathic arthritis in children. In 1971, Eric Bywaters described the disease in adults with similar clinical manifestations and named the disease as AOSD (1).

Previous studies stated that there were neither autoantibodies nor any HLA genetic associations in juvenile idiopathic arthritis (JIA) and that abnormalities of the innate immune system were most influential factor in systemic JIA (2). In addition, many studies reported that manifestations of systemic JIA were closely similar to those of autoinflammatory syndromes; *i.e.* aggravation of the innate immune response causing recurrent inflammation, activation of phagocytes, and increased secretion of interleukin-1 (3). Therefore, some authors suggested that this disorder should be included in the acquired autoinflammatory syndromes rather than in juvenile arthritides (4). It was also suggested that systemic-onset form of juvenile idiopathic arthritis (SOJA) and AOSD were, in fact, the same autoinflammatory disorder affecting, respectively, children and adults (4). For the reasons explained above, the incidence of *MEFV* gene mutations were investigated in Korean patients with AOSD. Interestingly, it was seen that the E148Q allele had a higher incidence in AOSD patients when compared to healthy controls (5).

Currently, there is limited data on the frequency of AOSD. Studies based on questionnaire data have reported an annual AOSD incidence of 0.22/100,000 in Japan (6), and 0.16/100,000 in France (7). A study using hospital-based database has found an annual AOSD incidence of 0.4/100,000 in northern Norway (8).

AOSD has three clinical forms: monocyclic, polycyclic and chronic. Recently, biological treatments have begun to be used for polycyclic and chronic forms refractory to standard therapies (9). The most widely used biologic agents in refractory patients are TNF-alpha blockers and IL-6 receptor blockers (10). It is known that IL-1β plays a critical role in the pathogenesis of most autoinflammatory disorders; therefore, anti-IL-1 monotherapy with either anakinra, canakinumab, or rilonacept results in regression of disease activity (11-14).

Nowadays, knowledge about the epidemiology of the diseases has become more important than ever because of the era of novel agents. While case series of AOSD have been reported from our country (15, 16), there have been no epidemiological studies so far. In our study, we determined the epidemiology, general clinical features and outcomes of AOSD based on hospital-based data in Thrace region, which is in northwestern Turkey. We also reviewed other epidemiological studies about AOSD; and compared our results to results of previously published studies.

Materials and methods

Patients diagnosed with AOSD at the Department of Rheumatology of Trakya University Medical Faculty, Edirne, Turkey, between 2003 and 2014, were reviewed retrospectively. The names and hospital protocol numbers of all AOSD patients were retrieved from our hospital's computer database by using the ICD code for AOSD. The patients' hospital files (both inpatient and outpatient) were obtained from the archives; and all medical data were reviewed in detail. Patients older than 16 years of age were included in the study. For diagnosis of AOSD, the diagnostic criteria suggested by Yamaguchi et al. (17) was used; patients who did not fulfill the criteria were excluded. The major criteria reported by Yamaguchi *et al.* are fever, arthralgia, typical rash and leukocytosis. Minor criteria include sore throat, lymphadenopathy, splenomegaly, hepatic dysfunction, rheumatoid factor (RF) negativity and anti-nuclear antibody negativity. In order to confirm the diagnosis of AOSD, a patient had to meet five of these criteria, two of which should be major criteria.

Clinical and laboratory data were retrieved from hospital records. Patients'

clinical features, laboratory measurements, demographics, received treatments, follow-up durations, disease course, outcomes and complications were evaluated. For patients who were lost to follow-up, phone calls were made to learn their current status. Information was received from the patients if they could be contacted, otherwise their relatives were asked to provide the information.

Estimation of prevalence and incidence

As a tertiary care centre for rheumatologic diseases, our hospital serves approximately 620,447 adults (306,036 females and 314,411 males) from both rural and urban areas. The population count was based on the reports of the Turkish Statistical Institute. Paediatric patients (<16 years) were not included. Edirne city is located in Thrace region, in northwestern partof Turkey; and it makes borders with Greece and Bulgaria. Our hospital is the only tertiary care reference centre for rheumatic diseases for both Edirne and Kırklareli, another city to the north of Edirne. The clinical features of AOSD patients diagnosed in our centre within the last decade were recorded down. The incidence rates were calculated for each 100,000 people aged ≥16 years.

Any AOSD patient living in our region in June 2014 was considered as a prevalent case. Prevalence of AOSD by June 2014 was estimated as the number of prevalent cases of AOSD divided by the whole population in our region.

Literature review

The literature was scanned for incidence, prevalence and case review studies on AOSD performed between 1995 and 2014. Four epidemiological studies on AOSD were found. In addition to these, 2 multicentre series compiling the general clinical features of AOSD patients from our country and 3 international AOSD series were analysed in detail.

Statistical analysis

The 95% confidence intervals (CI) were calculated based on a Poisson distribution and the standard error of a Poisson distribution was based on the square root of the numerator. Chi-square test was used to compare categoric variables between groups; and Fisher's exact test was used as needed. For the comparison of continuous variables between two groups, unpaired *t*-test was used.

Results

Annual incidence of AOSD

Our study included 42 patients with AOSD. Of them, 32 (76.2%) were females and 10 (23.8%) were males (female to male ratio: 3.2). Over the course of the study, the annual incidence of AOSD was 0.62/100,000 and the overall prevalence was 6.77/100,000.

Prevalence of AOSD

As of June 2014, the overall prevalence of AOSD among people above the age of 16 years in our region was 6.77/100,000 (95%CI: 4.72–8.82). Prevalence in women was higher (10.8/100,000, 95%CI: 7.1–13.9) compared to men (3.2/100,000, 95%CI: 1.2–5.2). The prevalence of AOSD did not differ significantly from year to year. There were 13 cases in the first 4 years, 13 cases during the 4th to 8th years, and 16 further cases were identified during the 8th to 11th years.

Clinical features of AOSD and laboratory results

The most common findings were fever (97.6%), arthralgia (95.2%), arthritis (76.2%), rash (73.8%) and sore throat (40.5%). Leukocytosis, neutrophilia and elevated ferritin levels were, respectively, 92.8%, 80.9% and 97.6%. RF was negative in 97.6%, and ANA was negative in 90.5% of patients. ANA positivity was of low-titers and patients positive for ANA had no clinical evidence of SLE. Of the 42 AOSD patients, 27 (64.3%) had a monocyclic pattern, 10 (23.8%) had a polycyclic pattern, and the remaining 5 (11.9%) had a chronic pattern. Hand x-rays of 15 patients with polycyclic/chronic AOSD were available. Erosive lesions were detected in 4 of these patients. Clinical features and laboratory findings at the time of diagnosis are seen in Table I.

Treatment

As the first-line treatment modality, patients were given nonsteroidal anti-inflammatory drugs (NSAIDs) (92.9%), steroids (90.4%), hydroxychloroquine (76.1%) or methotrexate (28.6%). The second line treatment for patients with a relapsing patttern were NSAIDs (88.1%), steroids (95.2%), hydroxychloroquine (80.9%) or methotrexate (50%).

Five patients who were non-responsive to current therapies, and whose condition recurred frequently or had a chronic course were administered biologic agents. One received etanercept (7.1%), 2 received infliximab (14.3%) and 2 received tocilizumab (14.3%). Patients who received biological agents were followed up for a median of 96 months (range 2–132 months). Recurrence was not observed in any of the patients treated with biological agents and their symptoms improved.

Follow-up results

The median duration of follow-up in our 42 AOSD patients was 75 months (range 2–168 months). Fifteen patients had relapses. The median time to relapse was 24 months (range 9–72 months). Twenty-seven patients were relapse-free. The median duration of follow-up for relapse-free patients was 44 months (range 2–168 months); and the median duration of follow-up for relapsing patients was 96 months (range 2–156 months). The groups were similar with respect to their durations of follow-up.

Pleural involvement was significantly more frequent in the group with polycyclic and/or chronic form than in the monocyclic group (26.7% *vs*. 3.7%, p=0.047). Lymphadenopathy tended to be more common in these two groups; however, it was not statistically significant (40.7% *vs*. 13.3%, p=0.09). The mean ESR, CRP and ferritin levels were similar in patients with monocyclic pattern and in other patients (p-values >0.05). The two groups did not differ statistically significantly with respect to other clinical and laboratory parameters (Table II).

Three patients developed haemophagocytosis over the follow-up period. Treatment initiation with salazopyrine in one and with methotrexate in the

Table I. Clinical features and laboratory findings at the time of diagnosis in AOSD patients.

Clinical features	n. (%)
Female/Male	32/10 (76.2/23.8)
Median age at diagnosis (years)	44.5 (18-74)
Fever, n (%)	41 (97.6)
Arthralgia, n (%)	40 (95.2)
Arthritis, n (%)	32 (76.2)
Rash, n (%)	31 (73.8)
Lymphadenopathy, n (%)	13 (31)
Sore throat, n (%)	17 (40.5)
Splenomegaly, n (%)	6 (14.3)
Hepatomegaly, n (%)	8 (19)
Pericarditis, n (%)	2 (4.8)
Pleural involvement, n (%)	5 (11.9)
Neutrophilia (>%80 neutrophils)	34 (80.9)
Leukocyte count (/mm^3)*	14118 (5200-32400)
Haemoglobin (g/dL)	10.9 (7.1-15.5)
Ferritin (ng/mL)	1629 (55-7410)
Erythrocyte sedimentation rate (ESR) (mm/hr)	101.1 (40-140)
C-reactive protein (CRP) (mg/dl)	18.6 (3-54)

*Continuous variables were expressed as means and ranges were put into parentheses.

Table II. Comparative clinical and laboratory results of monocyclic and polycyclic and chronic patients at the time of diagnosis.

	Monocyclic patients (n=27)	Polycyclic & chronic patients (n=15)	*p*-value
Female/male	21/6	11/4	NS*
Median age at diagnosis (years)	45 (22-74)	43 (18-71)	NS*
Fever, n (%)	26 (96.3)	15 (100)	NS*
Arthralgia, n (%)	26 (96.3)	14 (93.3)	NS*
Arthritis, n (%)	22 (81.5)	10 (66.7)	NS*
Rash, n (%)	20 (74.1)	11 (73.3)	NS*
Lymphadenopathy, n (%)	11 (40.7)	2 (13.3)	0.089
Sore throat, n (%)	13 (48.1)	4 (26.7)	NS*
Splenomegaly, n (%)	4 (14.8)	2 (13.3)	NS*
Hepatomegaly, n (%)	7 (25.9)	1 (6.7)	NS*
Pericarditis, n (%)	1 (3.7)	1 (6.7)	NS*
Pleural involvement, n (%)	1 (3.7)	4 (26.7)	0.047
Neutrophilia (>%80 leucocytes)	22 (81.4)	12 (80)	NS
Leukocyte count (/mm^3)**	13885 (5200-28600)	14538 (6670-32400)	NS*
Haemoglobin (g/dL)	10.9 (7.1-15.5)	10.9 (7.7-14.1)	NS*
Ferritin (ng/mL)	1475 (67-7279)	1906 (55-7410)	NS*
Erythrocyte sedimentation rate (ESR) (mm/hr)	103.3 (40-140)	96.9 (41-130)	NS*
C-reactive protein (CRP) (mg/dl)	15.2 (3-34)	24.8 (3-54)	NS^v

*NS: Not significant.
**Continuous variables were expressed as means and ranges were put into parentheses.

other were noted as triggering factors; however, no risk factor could be identified for the third patient. High-dose steroids were given to the three patients with haemophagocytosis; two patients also received cyclosporine. Following the above-mentioned treatment modalities, clinical and laboratory parameters improved dramatically. One patient died due to a myocardial infarction.

Literature review

Four epidemiological studies and five case series were identified when we made literature search about AOSD-related studies. Relevant data from these studies are provided in Table III.

Discussion

In our study, the annual incidence of AOSD was 0.62/100,000 and the prevalence was 6.77/100,000 in Thrace region of Turkey. The incidence in our study seemed to be higher than reported series from France (0.16/100,000) (7), Japan (0.22/100,000) (6), and northern Norway (0.4/100,000) (8). A recent Japanese study (18) reported that the prevalence of AOSD was almost half of that in our study (3.9/100,000). Methodological differences may contribute to differences in incidences of AOSD across studies. Studies from Japan and France reflect survey results in the general population. The study reported from northern Norway and our study cover hospital-based epidemiological data; and the former study is the one with the closest results to ours.

In our study, the incidence and prevalence AOSD were higher in females compared to males (for females and males, respectively: annual incidence, 0.95 and 0.25; prevalence, 10.8 and 3.2). In the series reported from Japan, the prevalence of AOSD in female and male populations were, respectively, 1.47 and 0.73 in 100,000: which means an approximately two-fold prevalence in females (6). In our series, female to male ratio was 3.2, whereas in two other series reported from our country, the ratio was 1.1 (15) and 1.4 (16). In other series listed in table 3 (6-8,18-21), the ratio varied between 0.3 to 2.73. In our study, there were significantly more female patients compared to other studies.

The most common form of AOSD in our study was monocyclic form (64.3%), followed by polycyclic (23.8%) and chronic forms (11.9%). In different studies, monocyclic pattern was reported to occur in between 21.1% and 46% of patients (7, 8, 15, 16, 18-21). Thus, the proportion of patients with monocyclic pattern in our study was higher than those reported in other series. This may be explained with the relatively shorter follow-up duration in our study. This is substantiated by the longer follow-up duration in our relapsing patients.

There are no randomised controlled studies on the treatment of AOSD; and treatment is largely empirical and steroid-based. In our series, steroids were usually preferred for first-line treatment, although we also used hydroxychloroquine and methotrexate in the presence of severe arthritis and when high-dose steroids were required. We used biological treatments in patients with refractory and frequently

Table III. Comparison of data in various epidemiologic studies about AOSD.

	Our study	Evensen *et al.* (8)	Magadur-Joly *et al.* (7)	Wakai *et al.* (6)	Pay *et al.* (15)	Kalyoncu *et al.* (16)	Gerfaud-Valentin *et al.* (19)	Colina *et al.* (20)	Asanuma *et al.* (18)	Kim *et al.* (21)
Incidence (per 100,000 person-years)	0.62	0.4	0.16	0.22	NA*	NA*	NA*	NA*	NA*	NA*
Prevalence (per 100,000)	6.77	6.8	NA*	2	NA*	NA*	NA*	NA*	3.9	NA*
Female/male	3.2	0.3	1.06	2.1	1.1	1.4	1.11	1.3	2.57	2.73
Monocyclic pattern	64.3%	46%	44%	NA*	21.1%	46%	30%	26%	39.7%	40.2%
Polycyclic pattern	23.8%	NA*	32%	NA*	16.8%	33%	44%	30%	34.2%	40.2%
Chronic	11.9%	NA*	24%	NA*	41.1%	21%	26%	44%	10.3%	17.1%
Haemophagocytosis	7.1%	NA*	NA*	NA*	4.8%	6.7%	14%	3%	15%	10.7%
Pleural involvement	11.9%	NA*	16%	NA*	22.1%	7.9%	18%	NA*	3.7%	30.5%
Mortality	2.3%	8%	NA**	NA*	NA*	0%	5.2%	NA*	0%	2.4%

*NA: Not available.

recurring disease and found them to be effective. One noteworthy finding was that we identified no relapses over a median duration of 61 months in the limited number of patients who were given biological treatments. Our preferred modalities of biologic agents were anti-TNF and anti-IL-6 therapies because of their availability in Turkey.

As IL-1β is largely held responsible for the underlying pathology in AOSD, IL-1β antagonists drew attention in the treatment of the disease (22). Especially anakinra monotherapy was observed to be quite effective in patients who failed standard agents, like corticosteroids and methotrexate (22-24).

Another benefit of blocking the IL-1 pathway with anakinra and/or canakinumab is their higher safety when compared to TNF-α or IL-6 blockers (25). In addition, anakinra and canakinumab did not seem to increase the risk of tuberculosis reactivation (26). Contrarily, recent data suggested that there would be benefit in using anti-IL-1 agents in geographical areas where tubercolosis could be a public concern (25-27). IL-1 appears to be involved in the delayed hypersensitivity to *Mycobacterium tuberculosis*; however, it does not have the major role in the control of this infection (28). Therefore, it might be presumed that there is little or no risk of developing tuberculosis in patients treated with IL-1 antagonists (28). A phase III study recently performed with rilonacept in 1315 patients with gout showed that there were tuberculosis nor other opportunistic infections (29). Unfortunately, we did not have the chance to use anti-IL-1 therapy in our study, because, anti-IL-1 agents are not currently available in our country. It can only be used under specific conditions, like refractory FMF.

In our AOSD group, the presence of pleural involvement was the only predictive finding for relapses. In a similar study, Gerfaud-Valentin *et al.* (19) compared relapsing and non-relapsing subjects and reported a similar rate of pleural involvement. In our study, the frequency of pleural involvement was 11.9% while this frequency varied between 3.7% and 30.5% in other series (7, 15, 16, 18, 19, 21). In the study by Gerfaud-Valentin *et al.* (19), the predictive presenting findings in monocyclic pattern, chronic pattern and complicated pattern were, respectively, fever (>39.5°C), arthritis, and thrombocytopenia.

Haemophagocytosis, or macrophage activation syndrome, is an important complication of AOSD; and it might be triggered by drugs in some cases. In our AOSD series, the frequency of haemophagocytosis was 7.1% compared to 4.8 to 15% in other series (15-21). The triggerring factor in 2 cases were thought to be treatment initiation with sulphasalazine and methotrexate, while the cause was unclear in the remaining case. Haemophagocytosis can be a cause of mortality in AOSD. However, improvements were achieved in two of our patients with high-dose steroids and/or cyclosporine. During the course of the study, only one patient died and the cause of death was not AOSD-related. Mortality data is usually insufficient in AOSD series. As seen in table 3, mortality rates vary between 0% and 8% (15, 16, 19, 21). Long-term cohort studies are needed to evaluate the exact effect of Still's disease on mortality. Available data support that Still's disease is not a fatal condition.

The retrospective design of our study and the fact that it was based on hospital database were limitations of our study. The very rare occurrence of the disease makes it difficult to design a prospective study. However, our study carries importance because it is the first epidemiological study from Turkey and one of the few studies across the world, despite many case series reported from Turkey and other countries. Another limitation was that we did not evaluate glycosylated ferritin level in our study group. Several recent articles reported that glycosylated fraction of ferritin was lower than 20% of the total ferritin in AOSD, while in healthy subjects it was reported to vary between 50–80% (19). By combining the data of total and glycosylated ferritin, it is possible to increase the diagnostic specificity for AOSD.

In conclusion, in our hospital-based study on AOSD – for which very limited epidemiological data is available – we observed a significantly higher frequency of AOSD compared to other series. Female gender was more common in our series. As the duration of follow-up was shorter compared to other series, monocyclic pattern was observed more frequently. Data in this study is the first epidemiological data on AOSD reported from Turkey.

References

1. STILL GF: On a form of chronic joint disease in children. *Med Chir Trans* 1897; 80: 47.
2. MELLINS ED, MACAUBAS C, GROM AA: Pathogenesis of systemic juvenile idiopathic arthritis: some answers, more questions. *Nat Rev Rheumatol* 2011; 7: 416-26.
3. ROSSI-SEMERANO L, KONÉ-PAUT I: Is Still's disease an autoinflammatory syndrome? *Int J Inflam* 2012; 2012: 480373.
4. RIGANTE D, CANTARINI L: The systemic-onset variant of juvenile idiopathic arthritis needs to be recorded as an autoinflammatory syndrome: comment on the review by Nigrovic. *Arthritis Rheumatol* 2014; 66: 2645.
5. KIM JJ, KIM JK, SHIM SC *et al*.: MEFV gene mutations and their clinical significance in Korean patients with adult-onset Still's disease. *Clin Exp Rheumatol* 2013; 31 (Suppl. 77): 60-3.
6. WAKAI K, OHTA A, TAMAKOSHI A *et al*.: Estimated prevalence and incidence of adult Still's disease: findings by a nationwide epidemiological survey in Japan. *J Epidemiol* 1997; 7: 221–5.
7. MAGADUR-JOLY G, BILLAUD E, BARRIER JH *et al*.: Epidemiology of adult Still's disease: estimate of the incidence by a retrospective study in west France. *Ann Rheum Dis* 1995; 54: 587.
8. EVENSEN KJ, NOSSENT HC: Epidemiology and outcome of adult-onset Still's disease in Northern Norway. *Scand J Rheumatol* 2006; 35: 48-51.
9. 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.
10. POUCHOT J, ARLET J-B: Biological treatment in adult-onset Still's disease. *Best Pract Res Clin Rheumatol* 2012; 26: 477-87.
11. RIGANTE D, ANSUINI V, CALDARELLI M, BERTONI B, LA TORRACA I, STABILE A: Hydrocephalus in CINCA syndrome treated with anakinra. *Childs Nerv Syst* 2006; 22: 334-7.
12. VITALE A, RIGANTE D, LUCHERINI OM *et al*.: Biological treatments: new weapons in the management of monogenic autoinflammatory disorders. *Mediators Inflamm* 2013; 2013: 939847.
13. TER HAAR N, LACHMANN H, OZEN S *et al*.: Paediatric Rheumatology International Trials Organisation (PRINTO) and the Eurofever/Eurotraps Projects. Treatment of autoinflammatory diseases: results from the Eurofever Registry and a literature review. *Ann Rheum Dis* 2013; 72: 678-85.
14. CANTARINI L, LUCHERINI OM, FREDIANI B *et al*.: Bridging the gap between the clinician and the patient with cryopyrin-associated periodic syndromes. *Int J Immunopathol Pharmacol* 2011; 24: 827-36.
15. PAY S, TURKCAPAR N, KALYONCU M *et al*.: Ankara Rheumatology Study Group. A multicenter study of patients with adult-onset Still's disease compared with systemic juvenile idiopathic arthritis. *Clin Rheumatol* 2006; 25: 639-44.
16. KALYONCU U, YAZISIZ V, EMMUNGIL H *et al*.: "Delay of diagnosis in Still's disease is associated with a chronic/relapsing pattern: national, multicenter study of 356 patients. *Ann Rheum Dis* 2013; 72 (Suppl. 3): 330.
17. YAMAGUCHI M, OHTA A, TSUNEMATSU T *et al*.: Preliminary criteria for classification of adult Still's disease. *J Rheumatol* 1992; 19: 424-30.
18. ASANUMA YF, MIMURA T, TSUBOI H *et al*.: Nationwide epidemiological survey of 169 patients with adult Still's disease in Japan. *Mod Rheumatol* 2014; 10: 1-8.
19. GERFAUD-VALENTIN M, MAUCORT-BOULCH D, HOT A *et al*.: Adult-onset still disease: manifestations, treatment, outcome, and prognostic factors in 57 patients. *Medicine* (Baltimore) 2014; 93: 91-9.
20. COLINA M, ZUCCHINI W, CIANCIO G, ORZINCOLO C, TROTTA F, GOVONI M: The evolution of adult-onset Still disease: an observational and comparative study in a cohort of 76 Italian patients. *Semin Arthritis Rheum* 2011; 41: 279-85.
21. KIM YJ, KOO BS, KIM YG, LEE CK, YOO B: Clinical features and prognosis in 82 patients with adult-onset Still's disease. *Clin Exp Rheumatol* 2014; 32: 28-33.
22. LOPALCO G, CANTARINI L, VITALE A *et al*.: Interleukin-1 as a common denominator from autoinflammatory to autoimmune disorders: premises, perils, and perspectives. *Mediators Inflamm* 2015; 2015: 194864.
23. GIAMPIETRO C, RIDENE M, LEQUERRE T *et al*.: CRI (Club Rhumatismes et Inflammation). Anakinra in adult-onset Still's disease: long-term treatment in patients resistant to conventional therapy. *Arthritis Care Res* (Hoboken) 2013; 65: 822-6.
24. ILIOU C, PAPAGORAS C, TSIFETAKI N, VOULGARI PV, DROSOS AA: Adult-onset Still's disease: clinical, serological and therapeutic considerations. *Clin Exp Rheumatol* 2013; 31: 47-52.
25. SELMI C, CERIBELLI A, NAGUWA SM, CANTARINI L, SHOENFELD Y: Safety issues and concerns of new immunomodulators in rheumatology. *Expert Opin Drug Saf* 2015; 14: 389-99.
26. CANTARINI L, LOPALCO G, CASO F *et al*.: Effectiveness and tuberculosis-related safety profile of interleukin-1 blocking agents in the management of Behçet's disease. *Autoimmun Rev* 2015; 14: 1-9.
27. CAKIR E, ERDEM E, OZLU N, SEBER E, GENCER S, KILICASLAN Z: Demographic and microbial characteristics and drug resistance of childhood tuberculosis in Istanbul: analysis of 1,541 cases. *J Infect Dev Ctries* 2014; 8: 304-9.
28. ZUÑIGA J, TORRES-GARCÍA D, SANTOS-MENDOZA T, RODRIGUEZ-REYNA TS, GRANADOS J, YUNIS EJ: Cellular and humoral mechanisms involved in the control of tuberculosis. *Clin Dev Immunol* 2012; 2012: 193923.
29. SUNDY JS, SCHUMACHER HR, KIVITZ A *et al*.: Rilonacept for gout flare prevention in patients receiving uric acid-lowering therapy: results of RESURGE, a phase III, international safety study. *J Rheumatol* 2014; 41: 1703-11.