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The administration of methotrexate in patients with Still's disease, "real-life" findings from AIDA Network Still Disease Registry

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ABSTRACT

Objectives: To describe clinical characteristics of patients with Still's disease treated with methotrexate (MTX) and to assess drug effectiveness evaluating change in disease activity, reduction of inflammatory markers, and glucocorticoid (GC)-sparing effect.
Methods: Patients with Still's disease treated with MTX were assessed among those included in AIDA Network Still Disease Registry.
Results: In this registry, 171 patients with Still's disease were treated with MTX (males 43.3%, age 37.1 ± 16.0 years). They were mainly characterised by joint features and fever without a prominent multiorgan involvement. MTX was administered with GCs in 68.4% of patients, with other conventional synthetic DMARDs in 6.4%, and with biologic DMARDs in 25.1%. A significant reduction of the modified systemic score was observed, and 38.6% patients were codified as being in clinical remission at the end of follow-up. The concomitant administration of a biologic DMARD resulted a predictor of the clinical remission. Furthermore, a reduction of inflammatory markers and ferritin levels was observed following the administration of MTX. Additionally, a marked reduction of the dosage of concomitant GCs was identified, while 36.7% discontinued such drugs. Male gender appeared as a predictor of GC discontinuation. MTX was discontinued in 12.3% of patients because of adverse effects, and in 12.3% for lack of efficacy.
Conclusions: Clinical characteristics of patients with Still's disease treated with MTX were described, mainly joint features and fever without a prominent multiorgan involvement. The clinical usefulness of MTX was reported in reducing the disease activity, decreasing the inflammatory markers, and as GC-sparing agent.

Key messages

Clinical characteristics of Still's disease patients treated with MTX were described in a large cohort.

MTX effectiveness was confirmed in reducing the disease activity and decreasing the inflammatory markers.

The GC-sparing effect of MTX was shown as additional relevant clinical benefit in these patients.

Background

Still's disease is a rare inflammatory disorder characterized by the typical triad of daily fever, arthritis, and evanescent salmon-coloured skin rash affecting both children and adults [1,2]. This condition has been codified as a multigenic autoinflammatory disorder, at the crossroad of autoinflammatory and autoimmune diseases [3,4]. Currently, Still's disease is named systemic juvenile idiopathic arthritis (sJIA) in children and adult-onset Still's disease (AOSD) in adults. In this context, multiple lines of evidence may support the similarity between AOSD and sJIA [5–9]. In addition to the above-mentioned cardinal features, these two diseases share many other clinical manifestations, such as hepatomegaly, splenomegaly, lymphadenopathy, and serositis. Furthermore, sJIA and AOSD also show similar laboratory abnormalities related to the inflammatory process, including increased erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and ferritin [8,9]. Analysing the disease courses of patients with Still's disease, different patterns are usually recognised: i. monocyclic, patients with a single episode of the disease; ii. polycyclic, patients characterised by phases of flares alternating with remissions during the follow-up; iii. chronic, patients with a persistent active disease, usually with polyarthritis [10,11]. Additionally, the clinical scenario of both sJIA and AOSD may be complicated by the occurrence of life-threatening complications, mainly macrophage activation syndrome (MAS), a secondary form of hemophagocytic lymphohistiocytosis [12–15]. According to these diverse clinical pictures, different therapeutic strategies are administered to patients with Still's disease [16,17]. In fact, glucocorticoids (GCs), conventional synthetic disease modifying anti rheumatic drugs (csDMARDs) and biologic DMARDs (bDMARDs) are variously used to treat these patients [18,19]. Usually, in case of failure of GCs or GC-dependence, csDMARDs may be considered in the management of Still's disease. Currently, methotrexate (MTX) remains one of the most common administered csDMARDs in these patients in daily clinical practice [16–19]. MTX mainly inhibits dihydrofolate reductase as it is an anti-folate cellular immunosuppressant [20]. Multiple mechanisms may contribute to the anti-inflammatory actions of MTX, inhibiting the proliferation as well as the activation of the immune cells, and reducing the production of pro-inflammatory cytokines, including interleukin (IL)−1β, IL-6, and tumor necrosis factor (TNF) [20,21]. Although its frequent administration in patients with Still's disease, a few studies specifically investigated the efficacy of MTX [22–24]. In these works, the administration of MTX contributed to disease control in association with a GC-sparing effect [22–24]. However, considering the relative low number of included patients and/or the short follow-up, further studies are needed to fully assess the clinical usefulness of MTX in this context. On these bases, we aimed at describing the clinical characteristics of patients with Still's disease, including SJIA and AOSD, treated with MTX, among those included in the AIDA Network Still Disease Registry. We also assessed the effectiveness of MTX evaluating the change of disease activity, the reduction of inflammatory markers, and the GC-sparing effect in an international multicentre large cohort of patients.

Methods

Study design, patients, and settings

Patients with Still's disease treated with MTX were selected among those included in the AIDA Network Still Disease Registry. This is an international, clinical, physician-driven, non-population and electronic-based registry for patients diagnosed with Still's disease, including a retrospective and a prospective data collection, as previously detailed [25]. Adult patients fulfilled Yamaguchi criteria and/or Fautrel criteria and/or Cush criteria [10,26,27]. Pediatric patients fulfilled International League of Associations for Rheumatology (ILAR) criteria for sJIA and/or Pediatric Rheumatology INternational Trials Organization (PRINTO) provisional criteria for sJIA [28,29]. Patients were selected among those attending Centres involved in AIDA network. This consists of centres from Europe, Middle East, far East, Africa, North and South America. All the units were characterised by experience in management of Still's disease as well as in observational studies. Clinical data of patients were recorded during the scheduled visits.

The Ethics Committee of the *Azienda Ospedaliero-Universitaria Senese*, Siena, Italy (Ref. N. 14,951; NCT05200715) approved the study, which was performed according to the Good Clinical Practice guidelines and the latest Declaration of Helsinki. Written informed consents for involved patients were collected. Clinical data are kept in accordance with the EU General Data Protection Regulations (GDPR), or other counterparts, on the processing of personal data and the protection of privacy (2016/679/EU) [30]. The STROBE checklist was followed in reporting the results of the present study.

Variables to be assessed

Clinical data were collected by reviewing the clinical charts of each patient attending the involved centres. Clinical features, systemic score, modified systemic score, life-threatening complications, laboratory markers, therapies, and patterns of the disease, were registered [25]. Furthermore, the following clinical features were recorded: fever, typical skin rash, arthralgia or arthritis, myalgia, lymphadenopathy, sore throat, splenomegaly, hepatomegaly or abnormal liver function tests, lymph node involvement, abdominal pain, sore throat, pleuritis, and pericarditis. In addition, at the time of diagnosis and during the subsequent follow-up, each patient was assessed for the presence of life-threatening complications. ESR, CRP, ferritin, and white blood cell count (WBC) were recorded. At the end of follow-up, patients were categorised into three different disease courses, monocyclic, polycyclic, chronic patterns. Systemic score and modified systemic score were derived as previously reported [31,32]. Clinical remission was meant as modified systemic score = 0, and/or by the discontinuation of MTX due to prolonged clinical benefit, and/or the achievement of the monocyclic pattern at the end of follow-up. The therapeutic strategies, GCs, csDMARDs, and bDMARDs were also collected.

Data sources, bias, and study size

Relevant clinical data were collected at study beginning, reassessed at the first available observation, and at the end of follow-up, during the scheduled visits for each involved patient characterised by an extensive clinical history. The Research Electronic Data Capture (REDCap) tool was used to collect and store data for AIDA network. Considering the observational design, this study could be subjected to a number of possible biases. The main methodological problems were minimised by a careful definition of each variable to be assessed. Furthermore, patients with significant missing data, which were considered to be meaningful for the analyses, were removed. Since the "real-life" purposes of the present study, no sample size estimation was provided.

Statistical methods

Statistics firstly provided a descriptive assessment of registered clinical features of assessed patients. Collected continuous variables were presented as mean and standard deviation (SD) or median and interquartile range (IQR) according to their distribution. Dosage of GCs, modified systemic score, inflammatory laboratory markers were firstly compared before and after the administration of MTX by Kruskal–Wallis test. Concerning the reduction of GCs and of modified systemic score following the administration of MTX, linear mixed models were set up as random intercept and random slope model, assuming an unstructured covariance matrix. Age, gender, presence of arthritis, systemic score, and concomitant bDMARD were also added in this model, as performed for the regression analyses. In addition, Cox regression analyses were exploited to evaluate the role of MTX in predicting the achievement of

clinical remission and the discontinuation of GCs. These models were adjusted for age, gender, presence of arthritis, systemic score, which was used as marker of disease severity at the first observation [33,34], and the concomitant administration of bDMARDs. Two-sided P values < 0.05 were considered as being statistically significant. The Statistics Package for Social Sciences (SPSS for Windows, version 20.0, SPSS Inc., Chicago, IL, USA) was used for all analyses.

Results

Descriptive data of patients treated with MTX

As a whole, 171 out of 374 (45.7%) patients with Still's disease were treated with MTX, among those included in AIDA Network Still Disease Registry. Clinical characteristics of patients who were not treated with MTX were reported in Supplementary Table 1. Patients treated with MTX were mostly female (56.75), with a mean age of 37.1 ± 16.0 years, and a median disease duration of 12.0 (IQR 35.0) months at the time of MTX administration. Twenty patients had a pediatric disease whereas 16 were aged over 60 years at the onset of the disease. In Table 1, clinical features of these patients were reported at the first observation. The most common disease manifestation at the first evaluation was joint involvement (67.2%) characterised by arthralgia and/or arthritis. Less frequently, these patients were characterised by fever (50.9%), skin rash (31.0%), and myalgia (18.7%). A small percentage of patients showed a multiorgan involvement due to the disease. The median systemic score resulted to be 3.0 (IQR 3.0) and the median modified systemic score 3.0 (IQR 4.0). No patient was characterised by MAS at the first observation and during the subsequent follow-up. Monocyclic disease course was recognised in 29.2% of patients, polycyclic in 26.9%, and chronic in 25.7%. In the remaining patients, a disease pattern was not established due to a short follow-up.

Table 1
Descriptive characteristics patients treated with MTX in AIDA Network Still Disease Registry at the first observation.

Clinical characteristics	171 patients treated with MTX
Demographic features	
Age, years, mean ± sd	37.1 ± 16.0
Male gender, n (%)	74 (43.3)
Disease characteristics	
Disease duration, months, median (IQR)	12.0 (35.0)
Joint involvement, n (%)	115 (67.2)
Arthralgia, n (%)	98 (57.3)
Arthritis, n (%)	64 (37.4)
Fever, n (%)	87 (50.9)
Skin Rash, n (%)	53 (31.0)
Sore throat, n (%)	35 (20.5)
Myalgia, n (%)	32 (18.7)
Lymph node involvement, n (%)	24 (14.0)
Liver involvement, n (%)	12 (7.0)
Spleen involvement, n (%)	11 (6.4)
Pericarditis, n (%)	7 (4.1)
Lung disease, n (%)	7 (4.1)
Pleuritis, n (%)	6 (3.5)
Abdominal pain, n (%)	4 (2.3)
Systemic score, median (IQR)	3.0 (3.0)
Modified systemic score, median (IQR)	3.0 (4.0)
Laboratory markers	
CRP, mg/dL, median (IQR)	5.3 (15.7)
ESR, mm/h, median (IQR)	48.0 (51.0)
Ferritin, ng/mL, median (IQR)	781.2 (1718.4)
WBC, cells/mm^3, median (IQR)	10,500.0 (9225.0)
Therapies	
MTX dosages, mg/weekly	14.7 ± 3.7
Duration of MTX therapy, month (IQR)	14.0 (30.0)
Side effects leading to MTX discontinuation	21 (12.3)
GCs, n (%)	117 (68.4)
Other csDMARDs, n (%)	11 (6.4)
bDMARDs, n (%)	43 (25.1)

Abbreviations: SD: standard deviation; IQR: interquartile range; CRP: C reactive protein; ESR: erythrocyte sedimentation rate; IQR: interquartile range; MTX: methotrexate; GCs: glucocorticoids; csDMARDs: conventional synthetic disease modifying anti rheumatic drugs; bDMARDs: biologic disease modifying anti rheumatic drugs.

MTX was administered in all evaluated patients, the mean dosage resulted to be 14.7 ± 3.7 mg/weekly and the median duration of therapy 14.0 (IQR 30.0) months. Oral MTX was administered in 7.6% of patients whereas subcutaneous route of administration was used in others. MTX was administered with GCs in 68.4% of patients, with other csDMARDs in 6.4%, and with bDMARDs in 25.1%. Concerning other csDMARDs, 7 patients were treated with hydroxychloroquine whereas 4 with leflunomide in combination with MTX. IL-1 inhibitors were administered in 25 patients (15 anakinra, 10 canakinumab), IL-6 inhibitor in 10 patients (10 tocilizumab), TNF inhibitors in 7 patients (3 infliximab, 2 etanercept, 1 adalimumab, 1 certolizumab pegol), and IL-12/23 inhibitor in 1 patient (1 ustekinumab). Out of these patients treated with bDMARDs, 24 were treated with the combination therapy MTX and bDMARD, whereas the others were previously treated with MTX and subsequently with the combination therapy MTX and bDMARD. No difference was retrieved assessing the administration of MTX according to the disease patterns. Finally, side effects leading to the discontinuation of MTX were recorded in 12.3% of patients. Specifically, liver abnormalities were reported in 6 patients, nausea in 5, dyspepsia in 4, diarrhea in 3, vomiting in 2, fatigue in 2, anemia in 1, and kidney failure in 1.

Effectiveness of mtx on disease activity and inflammatory markers

In this cohort, the effectiveness of MTX was evaluated by the assessment of the modified systemic score in patients with Still's disease. As reported in Fig. 1, a significant reduction of the modified systemic score was observed during the follow-up [Baseline: 3 (IQR 4), Second Assessment: 0 (IQR 1), Last Assessment: 0 (IQR 1), $p < 0.001$]. The effect of MTX on the decrease of modified systemic score was also performed by using a linear mixed model. A significant effect of MTX was also shown on the overall reduction of the modified systemic score (β: −0.30, $p = 0.011$, 95%CI −0.71 to −0.53) adjusting the model for age, gender, presence of arthritis, systemic score, and concomitant bDMARD. At the end of the study, 38.6% of patients were codified as being in clinical remission since characterised by modified systemic score = 0, and/or by the discontinuation of MTX due to prolonged clinical benefit, and/or the achievement of the monocyclic pattern. Descriptively stratifying these results according to the combination treatment with MTX and bDMARD, 69.8% of such patients achieved the clinical remission (19 treated with IL-1 inhibitor, 7 with IL-6 inhibitor, and 4 with TNF inhibitor). Multivariate regression analysis was exploited to evaluate the possible predictive role of selected clinical variables (i.e., age, gender, presence of arthritis, systemic score, and concomitant bDMARD) on the likelihood that patients could be in the clinical remission at the end of follow up. The concomitant administration of bDMARD resulted to be a significant predictor of the achievement of clinical remission in patients treated with MTX [HR: 4.80, 95%CI: 1.91–12.06, $p = 0.001$], as reported in Table 2.

In addition, a significant reduction of values of ESR [Baseline: 48.0 (IQR 51.0) mm/h, Second Assessment: 13.0 (IQR 19.0) mm/hr, Last Assessment: 8.0 (IQR 14.0) mm/hr, $p < 0.001$] and of CRP [Baseline: 5.0 (IQR 15.7) mg/dL, Second Assessment: 0.9 (IQR 3.0) mg/dL, Last Assessment: 0.4 (IQR 2.6) mg/dL, $p < 0.001$] was recorded, respectively, as shown in Fig. 1. Furthermore, the values of serum ferritin significantly reduced in patients treated with MTX [Baseline: 781.2 (IQR 1718.4) ng/mL, Second Assessment: 140.0 (IQR 372.0) ng/mL, Last Assessment: 127 (IQR 194.3) ng/mL, $p < 0.001$]. Similarly, WBC significantly decreased in these patients during the follow-up [Baseline: 10,500.0 (IQR 9225.0) cells/mm^3, Second Assessment: 8000 (IQR 5590) cells/mm^3, Last Assessment: 7250 (IQR 3120) cells/mm^3, $p < 0.001$], as shown in Fig. 2.

At the end of the study, 12.3% of patients were registered of having discontinued the MTX due to inefficacy.

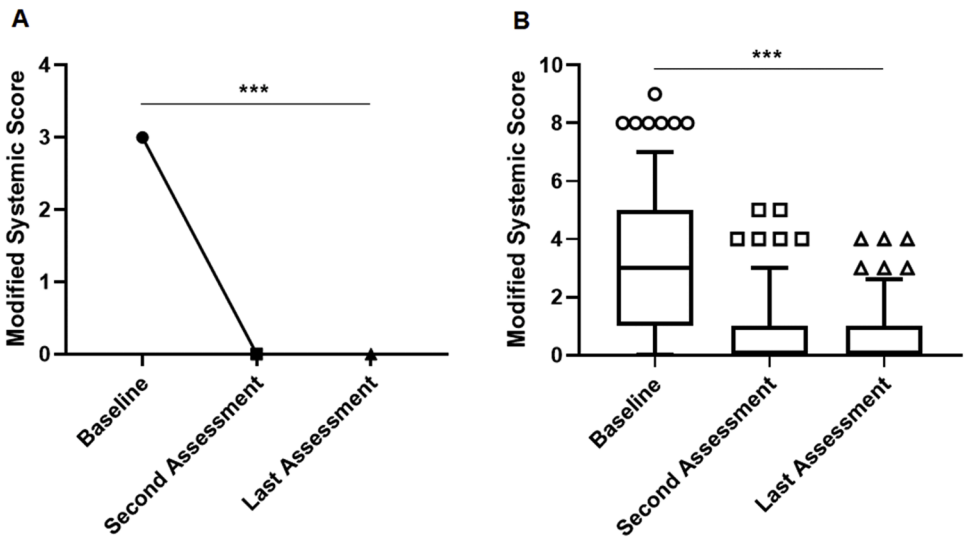

Fig. 1. In this figure, the effectiveness of MTX is described by the assessment of modified systemic score [Baseline: 3 (IQR 4), Second Assessment: 0 (IQR 1), Last Assessment: 0 (IQR 1)].
A) median values of modified systemic score, B) median values of modified systemic score and 10–90 percentiles;
***: $p < 0.001$.

Table 2
Multivariate Cox regression analyses exploiting the possible predictive role of selected clinical variables on the likelihood of clinical remission and GC discontinuation in patients treated by MTX.

Clinical Variables	HR	95% CI	P value
Clinical remission			
Multivariate analysis			
Age	1.01	0.98–1.02	0.838
Gender	1.50	0.82–2.74	0.190
Systemic score	1.01	0.89–1.14	0.858
Arthritis	0.71	0.39–1.29	0.256
bDMARDs	4.80	1.91–12.06	**0.001**
GC discontinuation			
Multivariate analysis			
Age	1.01	0.98–1.02	0.946
Gender	2.08	1.03–4.28	**0.046**
Systemic score	1.06	0.92–1.22	0.450
Arthritis	1.10	0.54–2.26	0.797
bDMARDs	1.14	0.14–9.40	0.904

Abbreviations: MTX: methotrexate; HR: hazard ratio; 95%CI: 95% confidence interval; bDMARDs: biologic disease modifying anti rheumatic drugs. $P < 0.05$ is considered statistically significant.

GC-sparing effect of MTX

In this cohort, the GC-sparing effect of MTX was also investigated. A marked and sustained reduction of the dosage of concomitant GCs was observed in these patients treated with MTX [Baseline: 25.0 (IQR 30.0) mg/day, Second Assessment: 9 (IQR 10) mg/day, Last Assessment: 0 (IQR 5) mg/day, $p < 0.001$], as reported in Fig. 3. The effect of MTX on the reduction of GCs was also assessed by using a linear mixed model. A significant effect of MTX was shown on the overall reduction of GCs (β: −19.1, $p < 0.001$, 95%CI −25.9 to −12.2) adjusting the model for age, gender, presence of arthritis, systemic score, and concomitant bDMARD. Furthermore, at the end of follow-up, 36.7% of patients discontinued the GCs. Descriptively analysing these results according to the combination treatment with MTX and bDMARD, 58.1% of such patients stopped the GCs (16 treated with IL-1 inhibitor, 6 with IL-6 inhibitor, and 3 with TNF inhibitor). Multivariate regression analysis was built to evaluate the possible predictive role of selected clinical variables (i.e., age, gender, presence of arthritis, systemic score, and concomitant bDMARD) on the likelihood that patients could discontinue the concomitant GCs. Male gender appeared to be a significant predictor of the discontinuation of the concomitant GCs in patients treated with MTX [HR: 2.08, 95%CI: 1.01–4.28, $p = 0.046$], as summarised in Table 2.

Discussion

The clinical characteristics of patients with Still's disease treated with MTX were described among those included in the AIDA Network Still Disease Registry, a large multicentre international cohort. Furthermore, the clinical usefulness of MTX was reported in reducing the disease activity, decreasing the inflammatory markers, and as GC-sparing agent in these patients.

In this cohort, MTX was mainly administered with GCs, but also in combination with other csDMARDs or bDMARDs. In fact, this drug is commonly administered after the failure of first-line GCs, before the administration of bDMARDs in patients with Still's disease [18,19]. Concerning the clinical features of patients treated with MTX, these were mainly characterised by joint involvement (arthralgia and/or arthritis), fever, and skin rash. A small percentage of these patients displayed a multi-organ involvement and no MAS was recognised. Thus, MTX may appear as a suitable therapeutic option in combination with either GCs, csDMARDs, or bDMARDs in patients with Still's disease with no prominent multi-organ involvement. Furthermore, this finding may provide further insights in tailoring the therapeutic strategy based on the patient clinical picture [35].

In addition, the effectiveness of MTX was evaluated in this cohort of patients. A significant reduction of the modified systemic score was observed together with a decrease of laboratory markers of disease activity during the follow-up. Therefore, MTX could be considered as an efficacious therapeutic option in the management of Still's disease with either GCs, csDMARDs, or bDMARDs. A relevant percentage of patients were also codified to be in clinical remission at the end of follow-up. Interestingly, the concomitant administration of bDMARDs resulted as a significant predictor of the achievement of the clinical remission. This finding may parallel with available literature which reported the long-term effectiveness of combination therapy between MTX and bDMARD, mostly IL-1 and IL-6 inhibitors, in treating patients with Still's disease [36–38]. Furthermore, no bDMARD monotherapy demonstrated a consistent clinical superiority when compared with such combination therapy [39–41]. Thus, the clinical usefulness of the combination therapy between MTX and bDMARD may be suggested in Still's disease. A possible early administration of this therapeutic strategy may be also advocated in increasing the achievement of the clinical remission [42], although further studies are needed to entirely elucidate this issue.

In this study, a marked and sustained GC sparing effect of MTX was also shown. A clinically relevant reduction of almost 20 mg/day of GCs was estimated by our analysis during the follow-up. This is a significant clinical benefit of MTX since the GC dependence is a relevant issue in the

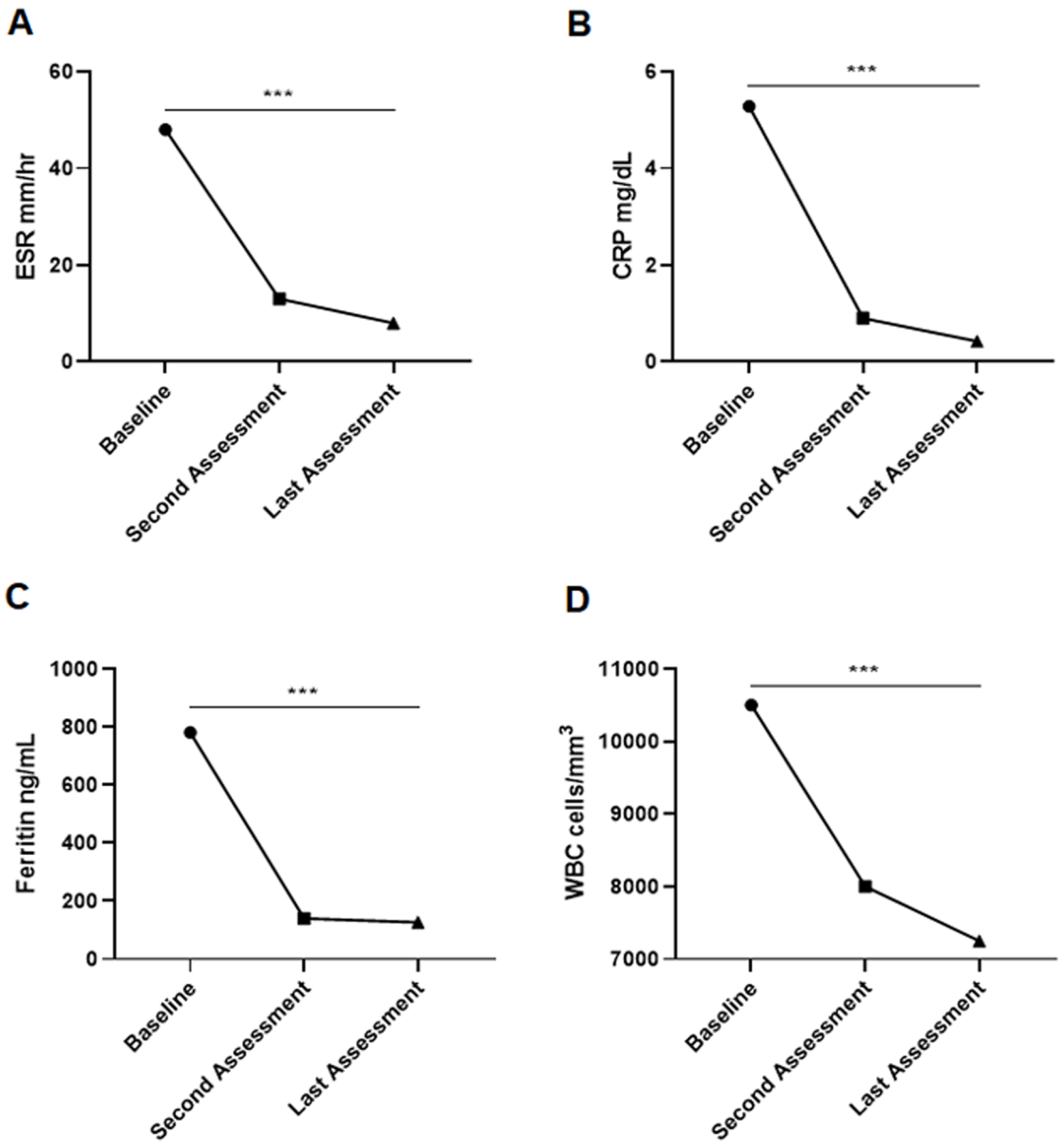

Fig. 2. In this figure, the effectiveness of MTX is reported by the assessment of inflammatory markers of disease activity:
A) the reduction of median erythrocyte sedimentation rate (ESR) is shown [Baseline: 48.0 (IQR 51.0) mm/h, Second Assessment: 13.0 (IQR 19.0) mm/hr, Last Assessment: 8.0 (IQR 14.0) mm/hr];
B) the reduction of median C reactive protein (CRP) is shown [Baseline: 5.0 (IQR 15.7) mg/dL, Second Assessment: 0.9 (IQR 3.0) mg/dL, Last Assessment: 0.4 (IQR 2.6) mg/dL];
C) the reduction of median ferritin is shown [Baseline: 781.2 (IQR 1718.4) ng/mL, Second Assessment: 140.0 (IQR 372.0) ng/mL, Last Assessment: 127 (IQR 194.3) ng/mL];
D) the reduction of median white blood cells (WBC) is shown [Baseline: 10,500.0 (IQR 9225.0) cells/mm^3, Second Assessment: 8000 (IQR 5590) cells/mm^3, Last Assessment: 7250 (IQR 3120) cells/mm^3];
***: $p < 0.001$.

management of patients with Still's disease, suggesting the necessity of an early administration of GC-sparing agents to minimize the risks of cumulative dosages [43,44]. In fact, in rheumatic diseases, patients treated with GCs in a long-term are exposed to several side effects including increased cardiovascular risk, osteoporotic fractures, infections, and diabetes [45,46]. Thus, the administration of MTX could reduce these issues due to long exposure to GCs, consequently improving the patient outcomes. Interestingly, a large percentage of patients in our cohort, about 40%, discontinued the GCs. Concerning the predictors of this clinical finding, male gender was an independent factor associated with the withdrawal of GCs. Although there is some evidence showing the prognostic negative role of the female gender [47–49], the need of further studies is suggested to fully elucidate this finding according to possible gender-related differences in Still's disease. Finally, the reduction of GCs should be considered as a main goal in the management of Still's disease. In fact, the possible discontinuation of GCs, maintaining the clinical response, may be considered as a further improvement in the treatment of these patients.

Furthermore, a low percentage of side effects in inducing MTX discontinuation was recorded. This finding may reinforce the idea of the clinical usefulness of this drug in the management of patients with Still's disease. In fact, MTX is currently considered the first therapeutic choice

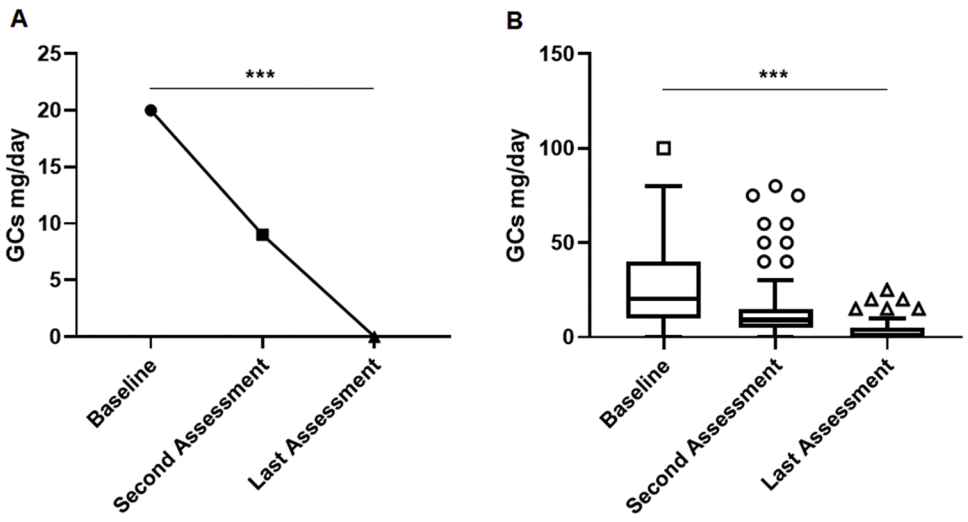

Fig. 3. In this figure, the glucocorticoids (GCs)-sparing effect of MTX is shown [Baseline: 25.0 (IQR 30.0) mg/day, Second Assessment: 9 (IQR 10) mg/day, Last Assessment: 0 (IQR 5) mg/day].
A) median values of GCs, B) median values of GCs and 10–90 percentiles;
***: $p < 0.001$.

and the "anchor" drug in many rheumatic diseases because of its favourable risk/benefit ratio and good safety profile [20,21,50]. The combination treatment between MTX and bDMARD may indeed represent a major therapeutic strategy in the management of patients with Still's disease who are refractory to first line medications [50]. However, the need for a careful monitoring of Still's disease patients with liver involvement requires to be pointed out in case of MTX administration.

Taking together all these considerations, Still's disease may be considered as a complex and heterogeneous disease. In fact, despite the similarities at the beginning, a highly heterogeneous clinical picture may characterize these patients according to different manifestations, presence of life-threatening complications, and outcomes in long term [35,42]. In this context, by a robust method for stratification, four clusters were derived and validated, with similar main clinical manifestations, including fever, joint involvement, and skin rash, highlighting a disease continuum. However, some relevant clinical differences were also retrieved, specific for each cluster, accounting for the patient heterogeneity [51]. The latter could be associated with differences in therapeutic strategies based on different clinical manifestations and outcomes over time [35,42,51].

Despite providing useful insights about the administration of MTX in Still's disease, this study is affected by some limitations. In fact, although providing a large number of observations, center-specific bias, organizational issues, and errors in data reporting may affect the validity of the results. According to our study design, we could not fully evaluate the possible differential effects of MTX combined with GCs, csDMARDs, or bDMARDs. However, this study mainly aimed to describe the clinical characteristics of patients treated with Still's disease, providing the basis for further confirmatory studies specifically designed to evaluate these issues.

In conclusion, the clinical features of patients with Still's disease treated with MTX were described among patients enrolled in the AIDA Network Still Disease Registry dedicated to such disease. In particular, joint involvement and fever were more frequently observed, while major multi-organ affection was absent. Furthermore, the effectiveness of this drug was confirmed in reducing the disease activity and decreasing the inflammatory markers. The GC-sparing effect of MTX was also shown in this large multicentre international cohort of patients with Still's disease as additional relevant clinical benefit. Finally, due to our study design, the differential effects of MTX combined with GCs, csDMARDs, or bDMARDs could not be fully evaluated, thus suggesting the need of further studies to entirely evaluate these issues.

Ethics approval and consent to participate

The Ethics Committee of the *Azienda Ospedaliero-Universitaria Senese*, Siena, Italy (Ref. N. 14,951; NCT05200715) approved the study, which was performed according to the Good Clinical Practice guidelines and the latest Declaration of Helsinki. Written informed consents for involved patients were collected. Clinical data are kept in accordance with the EU General Data Protection Regulations (GDPR), or other counterparts, on the processing of personal data and the protection of privacy (2016/679/EU).

Consent for publication

Not applicable, all the patients' data are de-identified.

Data availability

All data relevant to the study are included in the article.

Authors' contributions

All authors made substantial contributions to the conception or design of the work, the acquisition and interpretation of data. All authors contributed to the critical review and revision of the manuscript and approved the final version. All the authors agreed to be accountable for all aspects of the work.

Declaration of Competing Interest

The authors declare that they have no conflicts of interest for this work.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.semarthrit.2023.152244.

References

[1] Lee JJY, Schneider R. Systemic juvenile idiopathic arthritis. Pediatr Clin North Am 2018;65(4):691–709. https://doi.org/10.1016/j.pcl.2018.04.005. PMID: 30031494.

[2] Giacomelli R, Ruscitti P, Shoenfeld Y. A comprehensive review on adult onset Still's disease. J Autoimmun 2018;93:24–36. https://doi.org/10.1016/j.jaut.2018.07.018. Epub 2018 Aug 1. PMID: 30077425.

[3] Jamilloux Y, Gerfaud-Valentin M, Martinon F, Belot A, Henry T, Sève P. Pathogenesis of adult-onset Still's disease: new insights from the juvenile counterpart. Immunol Res 2015;61(1–2):53–62. https://doi.org/10.1007/s12026-014-8561-9. PMID: 25388963.

[4] Feist E, Mitrovic S, Fautrel B. Mechanisms, biomarkers and targets for adult-onset Still's disease. Nat Rev Rheumatol 2018;14(10):603–18. https://doi.org/10.1038/s41584-018-0081-x. PMID: 30218025; PMCID: PMC7097309.

[5] Inoue N, Shimizu M, Tsunoda S, Kawano M, Matsumura M, Yachie A. Cytokine profile in adult-onset Still's disease: comparison with systemic juvenile idiopathic arthritis. Clin Immunol 2016;169:8–13. https://doi.org/10.1016/j.clim.2016.05.010. Epub 2016 Jun 3. PMID: 27263804.

[6] Nirmala N, Brachat A, Feist E, Blank N, Specker C, Witt M, Zernicke J, Martini A, Junge G. Gene-expression analysis of adult-onset Still's disease and systemic juvenile idiopathic arthritis is consistent with a continuum of a single disease entity. Pediatr Rheumatol Online J 2015;13:50. https://doi.org/10.1186/s12969-015-0047-3. PMID: 26589963; PMCID: PMC4654831.

[7] Nigrovic PA, Raychaudhuri S, Thompson SD. Review: genetics and the classification of arthritis in adults and children. Arthritis Rheumatol 2018;70(1):7–17. https://doi.org/10.1002/art.40350. Epub 2017 Dec 1. PMID: 29024575; PMCID: PMC5805142.

[8] Pay S, Türkçapar N, Kalyoncu M, Simşek I, Beyan E, Ertenli I, Oztürk MA, Düzgün N, Erdem H, Ozbalkan Z, Kiraz S, Kinikli G, Besbas N, Dinç A, Ateş A, Olmez U, Calgüneri M, Aydintuğ OT, Bakkaloğlu A, Turan M, Turgay M, Karaaslan Y, Topaloğlu R, Duman M, Ozen S. 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(5):639–44. https://doi.org/10.1007/s10067-005-0138-5. Epub 2005 Dec 20. PMID: 16365690.

[9] Ruscitti P, Natoli V, Consolaro A, Caorsi R, Rosina S, Giancane G, Naddei R, Di Cola I, Di Muzio C, Berardicurti O, Iacono D, Pantano I, Rozza G, Rossi S, De Stefano L, Balduzzi S, Vitale A, Caso F, Costa L, Prete M, Navarini L, Iagnocco A, Atzeni F, Guggino G, Perosa F, Cantarini L, Frediani B, Montecucco C, Ciccia F, Cipriani P, Gattorno M, Giacomelli R, Ravelli A. Disparities in the prevalence of clinical features between systemic juvenile idiopathic arthritis and adult-onset Still's disease. Rheumatology (Oxford) 2022;61(10):4124–9. https://doi.org/10.1093/rheumatology/keac027. PMID: 35078234; PMCID: PMC9536787.

[10] Cush JJ, Medsger Jr TA, Christy WC, Herbert DC, Cooperstein LA. Adult-onset Still's disease. Clinical course and outcome. Arthritis Rheum 1987;30(2):186–94. https://doi.org/10.1002/art.1780300209. PMID: 3827959.

[11] Nigrovic PA. Review: is there a window of opportunity for treatment of systemic juvenile idiopathic arthritis? Arthritis Rheumatol 2014;66(6):1405–13. https://doi.org/10.1002/art.38615. PMID: 24623686.

[12] Javaux C, El-Jammal T, Neau PA, Fournier N, Gerfaud-Valentin M, Perard L, Fouillet-Desjonqueres M, Le Scanff J, Vignot E, Durupt S, Hot A, Belot A, Durieu I, Henry T, Sève P, Jamilloux Y. Detection and prediction of macrophage activation syndrome in Still's disease. J Clin Med 2021;11(1):206. https://doi.org/10.3390/jcm11010206. PMID: 35011947; PMCID: PMC8745834.

[13] Ruscitti P, Iacono D, Ciccia F, Emmi G, Cipriani P, Grembiale RD, Perosa F, Emmi L, Triolo G, Giacomelli R, Valentini G. Macrophage activation syndrome in patients affected by adult-onset Still Disease: analysis of survival rates and predictive factors in the Gruppo Italiano di Ricerca in Reumatologia Clinica e Sperimentale Cohort. J Rheumatol 2018;45(6):864–72. https://doi.org/10.3899/jrheum.170955. Epub 2018 Apr 15. PMID: 29657144.

[14] Saper VE, Chen G, Deutsch GH, Guillerman RP, Birgmeier J, Jagadeesh K, Canna S, Schulert G, Deterding R, Xu J, Leung AN, Bouzoubaa L, Abulaban K, Baszis K, Behrens EM, Birmingham J, Casey A, Cidon M, Cron RQ, De A, De Benedetti F, Ferguson I, Fishman MP, Goodman SI, Graham TB, Grom AA, Haines K, Hazen M, Henderson LA, Ho A, Ibarra M, Inman CJ, Jerath R, Khawaja K, Kingsbury DJ, Klein-Gitelman M, Lai K, Lapidus S, Lin C, Lin J, Liptzin DR, Milojevic D, Mombourquette J, Onel K, Ozen S, Perez M, Phillippi K, Prahalad S, Radhakrishna S, Reinhardt A, Riskalla M, Rosenwasser N, Roth J, Schneider R, Schonenberg-Meinema D, Shenoi S, Smith JA, Sönmez HE, Stoll ML, Towe C, Vargas SO, Vehe RK, Young LR, Yang J, Desai T, Balise R, Lu Y, Tian L, Bejerano G, Davis MM, Khatri P, ED; Mellins. Childhood Arthritis and Rheumatology Research Alliance Registry Investigators. Emergent high fatality lung disease in systemic juvenile arthritis. Ann Rheum Dis 2019;78(12):1722–31. https://doi.org/10.1136/annrheumdis-2019-216040. Epub 2019 Sep 27Erratum in: Ann Rheum Dis. 2022 Feb;81(2):e35PMID: 31562126; PMCID: PMC7065839.

[15] Ruscitti P, Bruno F, Berardicurti O, Acanfora C, Pavlych V, Palumbo P, Conforti A, Carubbi F, Di Cola I, Di Benedetto P, Cipriani P, Grassi D, Masciocchi C, Iagnocco A, Barile A, Giacomelli R. Lung involvement in macrophage activation syndrome and severe COVID-19: results from a cross-sectional study to assess clinical, laboratory and artificial intelligence-radiological differences. Ann Rheum Dis 2020;79(9):1152–5. https://doi.org/10.1136/annrheumdis-2020-218048. Epub 2020 Jul 21. PMID: 32719039; PMCID: PMC7456556.

[16] Onel KB, Horton DB, Lovell DJ, Shenoi S, Cuello CA, Angeles-Han ST, Becker ML, Cron RQ, Feldman BM, Ferguson PJ, Gewanter H, Guzman J, Kimura Y, Lee T, Murphy K, Nigrovic PA, Ombrello MJ, Rabinovich CE, Tesher M, Twilt M, Klein-Gitelman M, Barbar-Smiley F, Cooper AM, Edelheit B, Gillispie-Taylor M, Hays K, Mannion ML, Peterson R, Flanagan E, Saad N, Sullivan N, Szymanski AM, Trachtman R, Turgunbaev M, Veiga K, Turner AS, Reston JT. 2021 American College of Rheumatology Guideline for the treatment of juvenile idiopathic arthritis: therapeutic approaches for oligoarthritis, temporomandibular joint arthritis, and systemic juvenile idiopathic arthritis. Arthritis Rheumatol 2022;74(4):553–69. https://doi.org/10.1002/art.42037. Epub 2022 Mar 1. PMID: 35233993.

[17] Efthimiou P, Kontzias A, Hur P, Rodha K, Ramakrishna GS, Nakasato P. Adult-onset Still's disease in focus: clinical manifestations, diagnosis, treatment, and unmet needs in the era of targeted therapies. Semin Arthritis Rheum 2021;51(4):858–74. https://doi.org/10.1016/j.semarthrit.2021.06.004. Epub 2021 Jun 13. PMID: 34175791.

[18] Di Cola I, Cipriani P, Ruscitti P. Perspectives on the use of non-biological pharmacotherapy for adult-onset Still's disease. Expert Opin Pharmacother 2022;23(14):1577–87. https://doi.org/10.1080/14656566.2022.2126764. Epub 2022 Sep 22. PMID: 36124816.

[19] Ambler WG, Nanda K, Onel KB, Shenoi S. Refractory systemic onset juvenile idiopathic arthritis: current challenges and future perspectives. Ann Med 2022;54(1):1839–50. https://doi.org/10.1080/07853890.2022.2095431. PMID: 35786149; PMCID: PMC9258439.

[20] Cipriani P, Ruscitti P, Carubbi F, Liakouli V, Giacomelli R. Methotrexate: an old new drug in autoimmune disease. Expert Rev Clin Immunol 2014;10(11):1519–30. https://doi.org/10.1586/1744666X.2014.962996. Epub 2014 Sep 22. PMID: 25245537.

[21] Cronstein BN, Aune TM. Methotrexate and its mechanisms of action in inflammatory arthritis. Nat Rev Rheumatol 2020;16(3):145–54. https://doi.org/10.1038/s41584-020-0373-9. Epub 2020 Feb 17. PMID: 32066940.

[22] Fautrel B, Borget C, Rozenberg S, Meyer O, Le Loët X, Masson C, Koeger AC, Kahn MF, Bourgeois P. Corticosteroid sparing effect of low dose methotrexate treatment in adult Still's disease. J Rheumatol 1999;26(2):373–8. PMID: 9972972.

[23] Franchini S, Dagna L, Salvo F, Aiello P, Baldissera E, Sabbadini MG. Efficacy of traditional and biologic agents in different clinical phenotypes of adult-onset Still's disease. Arthritis Rheum 2010;62(8):2530–5. https://doi.org/10.1002/art.27532. PMID: 20506370.

[24] Kalyoncu U, Solmaz D, Emmungil H, Yazici A, Kasifoglu T, Kimyon G, Balkarli A, Bes C, Ozmen M, Alibaz-Oner F, Erten S, Cagatay Y, Cetin GY, Yilmaz S, Yildiz F, Pamuk ON, Kucuksahin O, Kilic L, Yazisiz V, Karadag O, Koca SS, Hayran M, Akar S, Aksu K, Akkoc N, Keser G, Gonullu E, Kisacik B, Onat AM, Soy M, Inanc N, Direskeneli H, Sayarlioglu M, Erken E, Turgay M, Cefle A, Ertenli I, Pay S. 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. https://doi.org/10.1016/j.jaut.2016.02.010. Epub 2016 Mar 9. PMID: 26970681.

[25] Vitale A, Della Casa F, Lopalco G, Pereira RM, Ruscitti P, Giacomelli R, Ragab G, La Torre F, Bartoloni E, Del Giudice E, Lomater C, Emmi G, Govoni M, Maggio MC, Maier A, Makowska J, Ogunjimi B, Sfikakis PP, Sfriso P, Gaggiano C, Iannone F, Dagostin MA, Di-Cola I, Navarini L, Ahmed Mahmoud AA, Cardinale F, Riccucci I, Paroli MP, Marucco EM, Mattioli I, Sota J, Abbruzzese A, Antonelli IPB, Cipriani P, Tufan A, Fabiani C, Ramadan MM, Cattalini M, Kardas RC, Sebastiani GD, Giardini HAM, Hernández-Rodríguez J, Mastrorilli V, Więsik-Szewczyk E, Frassi M, Caggiano V, Telesca S, Giordano HF, Guadalupi E, Giani T, Renieri A, Colella S, Cataldi G, Gentile M, Fabbiani A, Al-Maghlouth IA, Frediani B, Balistreri A, Rigante D, Cantarini L. Development and implementation of the AIDA international registry for patients with Still's disease. Front Med (Lausanne) 2022;9:878797. https://doi.org/10.3389/fmed.2022.878797. PMID: 35463015; PMCID: PMC9021753.

[26] Yamaguchi M, Ohta A, Tsunematsu T, Kasukawa R, Mizushima Y, Kashiwagi H, Kashiwazaki S, Tanimoto K, Matsumoto Y, Ota T, et al. Preliminary criteria for classification of adult Still's disease. J Rheumatol 1992;19(3):424–30. PMID: 1578458.

[27] Fautrel B, Zing E, Golmard JL, Le Moel G, Bissery A, Rioux C, Rozenberg S, Piette JC, Bourgeois P. Proposal for a new set of classification criteria for adult-onset still disease. Medicine (Baltimore) 2002;81(3):194–200. https://doi.org/10.1097/00005792-200205000-00003. PMID: 11997716.

[28] Martini A, Ravelli A, Avcin T, Beresford MW, Burgos-Vargas R, Cuttica R, Ilowite NT, Khubchandani R, Laxer RM, Lovell DJ, Petty RE, Wallace CA, Wulffraat NM, Pistorio A, Ruperto N, Pediatric Rheumatology International Trials Organization (PRINTO). Toward new classification criteria for juvenile idiopathic arthritis: first steps, Pediatric Rheumatology International Trials Organization International Consensus. J Rheumatol 2019;46(2):190–7. https://doi.org/10.3899/jrheum.180168. Epub 2018 Oct 1. PMID: 30275259.

[29] Petty RE, Southwood TR, Manners P, Baum J, Glass DN, Goldenberg J, He X, Maldonado-Cocco J, Orozco-Alcala J, Prieur AM, Suarez-Almazor ME, Woo P. International League of Associations for Rheumatology. International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. J Rheumatol 2004;31(2):390–2. PMID: 14760812.

[30] UR-Lex - 32016R0679 - EN - EUR-Lex. Available online at: https://eur-lex.europa.eu/legal-content/IT/TXT/?uri=celex%3A32016R0679 (accessed May 21, 2023).

[31] Pouchot J, Sampalis JS, Beaudet F, Carette S, Décary F, Salusinsky-Sternbach M, Hill RO, Gutkowski A, Harth M, Myhal D, et al. Adult Still's disease: manifestations, disease course, and outcome in 62 patients. Medicine (Baltimore) 1991;70(2):118–36. PMID: 2005777.

[32] Rau M, Schiller M, Krienke S, Heyder P, Lorenz H, Blank N. Clinical manifestations but not cytokine profiles differentiate adult-onset Still's disease and sepsis. J Rheumatol 2010;37(11):2369–76. https://doi.org/10.3899/jrheum.100247. Epub 2010 Sep 1. PMID: 20810496.

[33] Ruscitti P, Cipriani P, Masedu F, Iacono D, Ciccia F, Liakouli V, Guggino G, Carubbi F, Berardicurti O, Di Benedetto P, Valenti M, Triolo G, Valentini G, Giacomelli R. 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(1):194. https://doi.org/10.1186/s12916-016-0738-8. PMID: 27903264; PMCID: PMC5131497.

[34] 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 (GIRRCS) cohort of patients. Arthritis Res Ther 2020;22:151.

[35] Berardicurti O, Conforti A, Iacono D, Pantano I, Caso F, Emmi G, Grembiale RD, Cantatore FP, Atzeni F, Perosa F, Scarpa R, Guggino G, Ciccia F, Giacomelli R, Cipriani P, Ruscitti P. Dissecting the clinical heterogeneity of adult-onset Still's disease: results from a multi-dimensional characterization and stratification. Rheumatology (Oxford) 2021;60(10):4844–9. https://doi.org/10.1093/rheumatology/keaa904. PMID: 33404641.

[36] Vitale A, Caggiano V, Maggio MC, Lopalco G, Emmi G, Sota J, La Torre F, Ruscitti P, Bartoloni E, Conti G, Fabiani C, Mattioli I, Gaggiano C, Cardinale F, Dagna L, Campochiaro C, Giacomelli R, Balistreri A, Laskari K, Tufan A, Ragab G, Almaghlouth IA, Więsik-Szewczyk E, Pereira RM, Frediani B, Iannone F, Sfikakis PP, Cantarini L. Canakinumab as first-line biological therapy in Still's disease and differences between the systemic and the chronic-articular courses: real-life experience from the international AIDA registry. Front Med (Lausanne) 2022;9:1071732. https://doi.org/10.3389/fmed.2022.1071732. PMID: 36619631; PMCID: PMC9813488.

[37] Sota J, Vitale A, Lopalco G, Pereira RMR, Giordano HF, Antonelli IPB, Makowska J, Brzezińska O, Lewandowska-Polak A, Ruscitti P, Cipriani P, Cola ID, Govoni M, Ruffili F, Sfikakis PP, Laskari K, Ragab G, Hussein MA, Gentileschi S, Gaggiano C, La-Torre F, Maier A, Emmi G, Marino A, Ciccia F, Sfriso P, Maggio MC, Bartoloni E, Lomater C, Hegazy MT, Tektonidou M, Dagostin MA, Opinc A, Sebastiani GD, Giacomelli R, Giudice ED, Olivieri AN, Tufan A, Kardas RK, Nuzzolese R, Cardinale F, Więsik-Szewczyk E, Veronica P, Tarsia M, Iannone F, Della-Casa F, Fabiani C, Frediani B, Balistreri A, Rigante D, Cantarini L. Efficacy and safety of tocilizumab in adult-onset Still's disease: real-life experience from the international AIDA registry. Semin Arthritis Rheum 2022:152089. https://doi.org/10.1016/j.semarthrit.2022.152089. Epub 2022 Aug 30. PMID: 36063578.

[38] Giacomelli R, Sota J, Ruscitti P, Campochiaro C, Colafrancesco S, Dagna L, Iacono D, Iannone F, Lopalco G, Sfriso P, Cantarini L. 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(1):187–95. https://doi.org/10.55563/clinexprheumatol/fsq5vq. Epub 2020 May 12. PMID: 32452353.

[39] Vitale A, Berlengiero V, Sota J, Ciarcia L, Ricco N, Barneschi S, Mourabi M, Lopalco G, Marzo C, Bellisai F, Iannone F, Frediani B, Cantarini L. Real-life data on the efficacy of Canakinumab in patients with adult-onset Still's disease. Mediators Inflamm 2020;2020:8054961. https://doi.org/10.1155/2020/8054961. PMID: 33122969; PMCID: PMC7584965.

[40] Vitale A, Cavalli G, Ruscitti P, Sota J, Colafrancesco S, Priori R, Valesini G, Argolini LM, Baldissera E, Bartoloni E, Cammelli D, Canestrari G, Cavallaro E, Massaro MG, Cipriani P, De Marchi G, De Vita S, Emmi G, Frassi M, Gerli R, Gremese E, Iannone F, Fornaro M, Paladini A, Lopalco G, Manna R, Mathieu A, Montecucco C, Mosca M, Piazza I, Piga M, Pontikaki I, Romano M, Rossi S, Rossini M, Silvestri E, Stagnaro C, Talarico R, Frediani B, Tincani A, Viapiana O, Vitiello G, Galozzi P, Sfriso P, Gaggiano C, Grosso S, Rigante D, Dagna L, Giacomelli R, Cantarini L. Comparison of early vs. delayed anakinra treatment in patients with adult onset still's disease and effect on clinical and laboratory outcomes. Front Med (Lausanne). 2020;7:42. https://doi.org/10.3389/fmed.2020.00042. PMID: 32154255; PMCID: PMC7047849.

[41] Vitale A, Cavalli G, Colafrancesco S, Priori R, Valesini G, Argolini LM, Baldissera E, Bartoloni E, Cammelli D, Canestrari G, Sota J, Cavallaro E, Massaro MG, Ruscitti P, Cipriani P, De Marchi G, De Vita S, Emmi G, Ferraccioli G, Frassi M, Gerli R, Gremese E, Iannone F, Lapadula G, Lopalco G, Manna R, Mathieu A, Montecucco C, Mosca M, Piazza I, Piga M, Pontikaki I, Romano M, Rossi S, Rossini M, Silvestri E, Stagnaro C, Talarico R, Tincani A, Viapiana O, Vitiello G, Galozzi P, Sfriso P, Gaggiano C, Rigante D, Dagna L, Giacomelli R, Cantarini L. Long-term retention rate of anakinra in adult onset Still's disease and predictive factors for treatment response. Front Pharmacol 2019;10:296. https://doi.org/10.3389/fphar.2019.00296. PMID: 31001115; PMCID: PMC6454864.

[42] Ruscitti P, Berardicurti O, Giacomelli R, Cipriani P. The clinical heterogeneity of adult onset Still's disease may underlie different pathogenic mechanisms. Implications for a personalised therapeutic management of these patients. Semin Immunol 2021;58:101632. https://doi.org/10.1016/j.smim.2022.101632. Epub 2022 Jul 1. PMID: 35787972.

[43] Tang KT, Hsieh CW, Chen HH, Chen YM, Chang SH, Huang PH, Lan JL, Chen DY. The effectiveness of tocilizumab in treating refractory adult-onset Still's disease with dichotomous phenotypes: IL-18 is a potential predictor of therapeutic response. Clin Rheumatol 2022;41(2):557–66. https://doi.org/10.1007/s10067-021-05921-2. Epub 2021 Sep 17. PMID: 34535869.

[44] Ruscitti P, Ursini F, Sota J, De Giorgio R, Cantarini L, Giacomelli R. The reduction of concomitant glucocorticoids dosage following treatment with IL-1 receptor antagonist in adult onset Still's disease. A systematic review and meta-analysis of observational studies. Ther Adv Musculoskelet Dis 2020;12:1759720X20933133. https://doi.org/10.1177/1759720X20933133. PMID: 32595777; PMCID: PMC7301658.

[45] Kondo T, Amano K. Era of steroid sparing in the management of immune-mediated inflammatory diseases. Immunol Med 2018;41(1):6–11. https://doi.org/10.1080/09114300.2018.1451593. Epub 2018 Apr 9. PMID: 30938261.

[46] Berardicurti O, Ruscitti P, Pavlych V, Conforti A, Giacomelli R, Cipriani P. Glucocorticoids in rheumatoid arthritis: the silent companion in the therapeutic strategy. Expert Rev Clin Pharmacol 2020;13(6):593–604. https://doi.org/10.1080/17512433.2020.1772055. Epub 2020 Jun 8. PMID: 32434398.

[47] 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(1):28–33. Epub 2013 Sep 18. PMID: 24050706.

[48] 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(11):1089–97. https://doi.org/10.1080/1744666X.2017.1375853. Epub 2017 Sep 21. PMID: 28870100.

[49] García-González CM, Baker J. Treatment of early rheumatoid arthritis: methotrexate and beyond. Curr Opin Pharmacol 2022;64:102227. https://doi.org/10.1016/j.coph.2022.102227. Epub 2022 Apr 19. PMID: 35453032.

[50] Castañeda S, Blanco R, González-Gay MA. Adult-onset Still's disease: advances in the treatment. Best Pract Res Clin Rheumatol 2016;30(2):222–38. https://doi.org/10.1016/j.berh.2016.08.003. Epub 2016 Oct 5. PMID: 27886796.

[51] Ruscitti P., Masedu F., Vitale A., Di Cola I., Valenti M., Giacomelli R., Cantarini L., on behalf of GIRRCS-AOSD study group and on behalf of AIDA Network Still Disease Registry. Different patient clusters may be recognized in Still's disease based on a clinical and laboratory multidimensional characterization. Abstract 066. ISSAID Congress 2023. https://www.issaid.org/issaid2023/abstracts.html.