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Adult Onset Still's Disease

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Abstract

The adult onset Still's disease is a rare affection characterised by occurrence of fever, arthralgia or arthritis and evanescent cutaneous eruption. Multiple other systemic lesions make the diagnosis more difficult. Several diagnostic criteria were formulated to confirm this disease. The physiopathology of the adult onset Still's disease is not well elucidated. However, several studies based on new facts in physiopathology, improved the therapy of refractory forms for which the biotherapy was an interesting alternative. The TNF alpha receptor antagonists are efficient on systemic and articular manifestations of this disease and allow a corticosteroid's saving. Tocilizumab (interleukin 6 receptor antagonist), and Anakinra (interleukin 1 receptor antagonist) are also new promising treatments for resistant forms.

Keywords

Adult Onset Still's Disease, Cytokine, TNF Alpha Receptor Antagonist, Interleukin 6 Receptor Antagonist, Interleukin 1 Receptor Antagonist

1. Introduction

Bywaters [1] described in 1971, in 14 young adults, a similar clinical feature to that of the systemic form of juvenile idiopathic arthritis described in pediatrics, individualized for the first time a century ago by a British pediatrician, George Frederick Still [1].

Adult onset Still's disease (AOSD) is orphan pathology that is typically characterized by the occurrence of fever, arthralgia or arthritis, evanescent rash associated with neutrophilic leukocytosis, a marked inflammatory syndrome and often a high serum level of ferritin.

Many systemic manifestations can complete the clinical feature, making the diagnosis more difficult.

Several clinical and biological studies of the disease have been conducted and presented in numerous publications, to provide diagnostic criteria for the disease.

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The pathogenesis of AOSD remains poorly established. However, recent work opens interesting paths on its physiopathology, improving the therapeutic management of this disease especially in its refractory forms.

Epidemiological data on the AOSD are very relative and imprecise.

Incidence and prevalence in different populations are not well definite. The AOSD is rare but ubiquitous. The majority of ethnic groups are affected by this disease. Most observations have been reported as isolated cases or small series.

2. Physiopathology

2.1. Genetic Study

Several studies have focused on genetic predisposition.

Thus, a retrospective study included 62 patients in whom the immune genetic study revealed a significant association of AOSD with HLA haplotypes B17, B18, B35 and DR2 [2]. However, the associations, including HLA-B14, DR7, BW35, Cw4 or DR4 and Dw6 were controversial in several other studies [3] [4].

The alleles HLA-DR7 and HLA BW35 were present with increased frequency in patients with AOSD [2]-[4].

In a Japanese cohort study, DRB1*1501 (DR2) and DRB1*1201 (DR5) were more common in chronic articular form compared to the systemic form, whereas DQB1*12 allele was common in both types [2]-[4].

2.2. Cytokines

A Japanese study evaluated gene polymorphism of the IL-18 showing the frequency of diplotype S01/S01, which was highly significant in AOSD [5].

Several cytokines are involved in AOSD [6]-[14].

IL-18, secreted by activated macrophages, Kuppfer cells, dendritic cells, and keratinocytes, is involved in hepatic cytolysis, joint damage, activation of T CD4 cells, production of IFN γ, macrophage activation and increased IgE [6].

The IL-6, secreted by monocytes-macrophages, T-cells (Th2), fibroblasts, endothelial cells, keratinocytes, causes fever, elevated CRP and ferritin, hemostasis disorders and hepatomegaly [6].

TNFα, secreted by macrophages, T cells (Th1) and NK, is involved in fever, cachexia, synovitis, joint destruction and coagulation disorders [6].

These cytokines are present at high levels correlating with disease activity [6].

2.3. Macrophages

Activated macrophages, producing IL-18 accelerates the proliferation of T CD4 cells that produce IFN γ, which enhances macrophage activation loop [15].

Cell hyperplasia of the reticuloendothelial system is frequently encountered in the study of tissue biopsies during AOSD [1] [6] [16].

AOSD may be complicated by a macrophage activation syndrome (MAS) which is a serious complication, sometimes fatal, and probably under-diagnosed during this diseases [6] [17]-[19].

A significant increase in IL-18 is seen in AOSD, as is the case of the MSA. MAS differs of AOSD by increased secretion of IL-1beta [6] [20].

2.4. T Lymphocytes

The increased levels of IFN γ and sIL-2R in AOSD is sign of T lymphocyte activation [6] [18]. Only one study has specifically examined T cell populations in the blood of 12 patients affected of AOSD [6] [18] where an increase in T$\gamma\delta$ + lymphocytes whose preferred repertoire Vγ9/Vδ2 has been reported in AOSD flares [21].

Cytotoxic lymphocyte deficits including deficits in NK, cytotoxic T lymphocyte and perforin were reported in systemic juvenile idiopathic arthritis and MAS offering new etiologic explanation of macrophage activation in AOSD [6] [22].

These deficits, either by the decline in absolute numbers or by decreasing the expression of perforin, could explain a lack of infectious antigens clearance, responsible then of the excessive activation of macrophages [6].

The physiopathology of AOSD, remains a mystery. A better understanding of the physiopathological mechanisms will lead to the development of more targeted therapeutic protocols for this disease.

3. Biology

In AOSD, the values of ferritin are often much higher than would be the only inflammatory syndrome; the levels are greater than 10,000 ng/mL even reaching 100,000 ng/mL [23].

The elevation in serum ferritin can acoompany hemophagocytosis or severe hepatic cytolysis which are differential diagnoses of AOSD [19] [23].

This ferritin could be related to the activation of certain pro-inflammatory cytokines such as interleukin 1 (IL-1) and IL-6, which stimulate transcription of ferritin [23] [24].

The specificity of the elevated ferritin in AOSD is only 85% [23] [24].

In AOSD, the elevation in serum ferritin is associated with a reduction of the glycosylated ferritin fraction below than 20%, the standard level is 60% to 80% [19] [24]-[26].

The glycosylated ferritin fraction appears to have a more interesting diagnostic value, since a significant reduction of the glycosylated fraction persists during AOSD flare despite normalization of serum ferritin [27].

As the elevation of serum ferritin, the decline of this fraction glycosylated is not pathognomonic of AOSD as it may be also in MAS [23] [28].

Elevation of serum ferritin to at least 5 times of normal values, coupled with a decrease in glycosylated fraction less than 20%, has a specificity of 92.9%, but unfortunately a sensitivity of only 43.2% [23] [26].

4. Classification Criteria of AOSD

There is no typical feature evoking the diagnosis of AOSD. Clinical recommendations used on clinical practices are based on classification criteria. The triad fever-arthralgia-rash orients to this diagnosis, but the clinician should eliminate all infectious, systemic and cancerous etiologies before confirming the AOSD diagnosis.

4.1. Classification Criteria of Yamaguchi *et al.* for AOSD [24]

The criteria for classification of Yamaguchi *et al.* [24] published in 1992 and credited with a sensitivity of 92% - 96% and a specificity of 92% are the most used. But, it is necessary to exclude infectious, neoplastic and systemic diseases which may manifest like AOSD.

Major criteria:
1) Fever $\geq 39°$C for at least 1 week
2) Arthralgia lasting for at least 2 weeks
3) Typical Rash (a)
4) Leukocytosis (at least 10,000/mm^3) with at least 80% of neutrophils

Minor criteria:
1) Pain throat
2) Lymph Nodes (b) and/or splenomegaly (c)
3) Disturbances of liver tests (d)
4) Lack of antinuclear antibodies and rheumatoid factor (e)

Exclusion criteria:
I. Infections (especially sepsis and infectious mononucleosis)
II. Neoplasia (especially lymphoma)
III. Systemic diseases (especially polyarteritis nodosa and rheumatoid arthritis with extra-articular manifestations)

At least 5 criteria are needed, among them at least two major criteria (f), in the absence of any exclusion criterion:

a) macular or maculopapular rash

b) Lymph nodes of recent onset and significant volume.

c) Splenomegaly confirmed by palpation or ultrasound.

d) Elevated transaminases and/or lactico-dehydrogenase related illness, excluding drug toxicity or other cause.

e) Negativity on common tests to detect IgM rheumatoid factor and antinuclear antibody by immunofluorescence.

f) All criteria can't be taken into account in the absence of another explanation.

4.2. Classification Criteria of Fautrel *et al.* [29]

Recently Fautrel *et al.* [29] proposed new criteria involving first the reduction of the glycosylated fraction of ferritin. Comparing the criteria of Yamaguchi, the new criteria appear to provide a minimal gain in terms of sensitivity but higher specificity, reaching 98.5%. The absence of exclusion criteria allows a simpler application, if laboratory performing the dosage of glycosylated ferritin is available.

Fautrel classification criteria *et al.* for AOSD [29].

Major criteria:
High fever $\geq$ 39°C
Arthralgia
evanescent rash
pharyngitis
Neutrophil count $\geq$ 80%
Glycosylated ferritin $\leq$ 20%

Minor criteria:
Maculopapular rash
Leukocytosis $\geq$ 10,000/mm^3

At least 4 major criteria or three major criteria plus 2 minor criteria are necessary to retain the diagnosis of AOSD. These criteria don't include exclusion criteria.

5. Treatment

The heterogeneity of the AOSD and its unpredictable course explain the difficulties encountered in the development of treatment guidelines.

In addition, the rarity of this disease makes it impossible to achieve controlled therapeutic trials.

Therapeutic indications remain largely empirical, based on the analysis of the reported observations and analogies with the treatment of major inflammatory rheumatism [23].

5.1. Non Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs are administered as first-line in moderate severity forms, but they are not efficient in 20% of cases. This treatment should be continued for at least 2 weeks before concluding about its effectiveness [30].

Careful monitoring of liver function is necessary to avoid worsening liver damage due to the disease under this treatment [23].

5.2. Corticosteroids Therapy

When NSAIDs are ineffective or that the clinical situation is more severe, steroid therapy is indicated [23].

It is necessary, initially or during the evolution, in approximately 77% of patients with a good response in 76 to 95% [4] [31].

The effectiveness of corticosteroids on fever and other systemic manifestations as well as joint damage is usually spectacular but does not prevent the progression of destructive joint damage [4] [23].

5.3. Maintenance Treatment

In the refractory AOSD or steroid-dependent forms, it is necessary to establish a basic treatment.

Many studies have reported the effective role of methotrexate on both systemic and articular AOSD and its role in glucocorticoid saving [4] [23].

All therapeutic use in rheumatoid arthritis have been tried in the AOSD, but it is difficult to conclude about their effectiveness since they are prescribed only in a limited number of patients including D-penicillamine, antimalarial synthesis, thalidomide, sulfasalazine and leflunomide [4] [23].

Prescribing other immunosuppressants is exceptional and is only indicated for refractory disease or in case of life threatening. Cyclophosphamide and azathioprine have been the most prescribed molecules [4] [23]. Mycophenolate mofetil was rarely prescribed [32] [33].

Cyclosporin is useful in presence of hemophagocytosis [4] [23].

Plasma exchange have been exceptionally used [23].

The treatment of joint manifestations may require local infiltration of corticosteroids or synoviorthesis. Prosthetic surgery can have an input in chronic joint forms [23].

5.4. Intravenous Immunoglobulines (IVIG)

In several studies, IVIG were administered monthly at a dose of 2 g/kg administered in 2 to 5 days. They were effective with a low toxicity, obtaining remission, sometimes prolonged after stopping all treatment [34]-[37].

A study published in 2012, about 44 patients with AOSD, used IVIG in 23 cases of steroid-resistance with good clinical and biological evolution and significant corticosteroid savings [36].

5.5. Anti-TNF α (Infliximab, Etanercept)

Several publications have shown the efficacy of anti-TNFα in refractory forms of AOSD.

A study [38] interested 6 patients with refractory AOSD, which were treated with infliximab of 3 - 5 mg/kg at 0, 2, and 6 weeks thereafter at intervals of 6 to 8 weeks depending on the activity of the disease. The clinical and biological evolution was good with normalization of CRP and serum ferritin.

Another study [39] concerned 12 patients with refractory AOSD treated with etanercept had shown a clinical and biological resolution.

A third series [40] involving 8 patients with refractory AOSD who were treated with infliximab with the dose of 3 - 5 mg/kg at 0, 2 and 6 weeks; then the rate of administration of this treatment varied according the evolution of the disease. Mean follow-up was between 1 and 5 years. 7 patients had a good clinical and biological response. 5 patients remained in remission after discontinuation of treatment. The patient who did not respond were switched by etanercept with good response.

Another series [41] concerned 20 patients affected of refractory AOSD with an average age of 40.7 years and a mean disease duration of 8.5 years. There were 5 systemic forms and 15 articular forms, all refractory to corticosteroids and methotrexate. Infliximab was used in 15 patients. 10 patients received etanercept. 5 patients received both treatments in time. 18 patients were on corticosteroids therapy and 17 were under immunosuppressive treatment concomitantly with anti-TNFα. Mean follow-up was 13 months. Complete remission occurred in 5 cases (1 etanercept and infliximab 4). A partial response was observed in 16 patients (7 etanercept and infliximab 9). The treatment was ineffective in 4 cases (2 etanercept 2infliximab).

The anti-TNF can be effective in some patients with refractory AOSD, but the response is most often partial.

5.6. Interleukin 6 Receptors Antagonist (Tocilizumab)

The Tocilizumab is a promising new treatment for refractory forms of AOSD.

It was prescribed since 2002 sporadically by analogy to other inflammatory rheumatism with clinical and biological success in several cases published in the literature [42].

A study published in 2011 [43] reported the first series of patients with refractory AOSD treated with tocilizumab.

There were 14 patients who were administered from May to August 5 to 8 mg/kg every 2 or 4 weeks (8 mg/kg/month, n = 9). 11 patients continued the study until the 6th month.

A study discontinuation was due to severe skin necrosis, another decision was due to the occurrence of chest pain during the infusion of tocilizumab, a third was due to a systemic treatment escape.

A good EULAR response was observed in 64% of patients (9/14) in 3 months and EULAR remission was reported in 57% of patients (8/14) in 6 months. Systemic syndrome was managed in 86% of patients (6/7).

Glucocorticoid dose was reduced by 56%. There were no other adverse effects [43].

Another study published in 2012, involved 16 patients with refractory AOSD who were treated with either etanercept or infliximab and switched by tocilizumab. The evolution was marked by treatment effectiveness on articular and systemic manifestations and a reduction in the dose of corticosteroids administered to these patients [44].

A third study showed a decrease of several inflammatory markers including CRP and serum ferritin after administration of Tocilizumab in refractory cases of AOSD. IL18 persisted high, hence the interest for studies to search for antagonists of IL 18 that could be promising in refractory forms of AOSD [45].

5.7. Interleukin 1 Receptors Antagonists (Anakinra)

Many publications were interested to Anakinra prescription in the AOSD [46]-[49].

A study [46] had involved four patients with refractory AOSD, 2 of which were treated with methotrexate and corticosteroids, the other 2 had the same treatment and were switched by etanercept. A treatment with anakinra at the dose of 100 mg/day was introduced to them. The evolution was marked by clinical improvement with disappearance of fever, normalization of white blood cells, CRP and serum ferritin.

A second study [47] conducted in 2008 concerned 35 patients of which 20 had juvenile idiopathic arthritis and 15 had a refractory form of AOSD, who received 100 mg/day (in adults) of Anakinra. 11/15 patients with AOSD had an improvement of at least 50% of all markers of the disease with a mean follow up of 17.5 months (11 - 27 months). The steroid treatment was stopped in two cases and the dose was reduced by 45% - 95% in 12 patients. Treatment was discontinued in 2 patients following severe skin complications, in 2 others because of infectious complications.

A third study [48] published in 2011 involved 25 patients (13 men and 12 women) with an average age of 32 years followed for a refractory AOSD with an average duration of disease course of 7 months. 16 patients received Anakinra at a dose of 100 mg/day in combination with other treatments, 9 patients received Anakinra alone. Mean follow-up was 15 months (1.5 to 71 months). 84% of patients showed improvement in an average time of 0.2 months. A relapse was reported in one patient. Disappearance of clinical and biological signs with a delay of 3 months was reported in 80% of patients. A partial clinical and laboratory improvement was found in respectively 12% and 16% of patients. The ACR score had reached the value of 20 corresponding to 20% of improvement, in 82% of patients after one month and 100% of patients after one year.

The dose of corticosteroids was significantly lowered.

The Anakinra was arrested at a poorly compliant patient and in one case of relapse.

3 patients had severe skin reactions. 7 patients had infectious complications.

This good maintained response encourages the use of Anakinra in case of refractory AOSD.

5.8. Anti-CD20 (Rituximab)

The anti-CD20 had been tried successfully in some cases of refractory AOSD [50]-[54].

6. Conclusion

The physiopathology of AOSD, a century after its description, remains mysterious. The recent acquisition of knowledge of the cytokine profile allows an improvement in the therapeutic approach including biological therapy which appears to be very promising in this disease.

References

[1] Bywaters, E.G.L. (1971) Still's Disease in the Adult. *Annals of the Rheumatic Diseases*, **30**, 121-133. http://dx.doi.org/10.1136/ard.30.2.121

[2] Pouchot, J., Sampalis, J.S., Beaudet, F., Carette, S., Décary, F., Salusinsky-Sternbach, M., *et al.* (1991) Adult Still's Disease: Manifestations, Disease Course, and Outcome in 62 Patients. *Medicine*, **70**, 118-136.

[3] Van de Putte, L.B. and Wouters, J.M. (1991) Adult-Onset Still's Disease. *Clinical Rheumatology*, **5**, 263-275. http://dx.doi.org/10.1016/s0950-3579(05)80283-3

[4] Bagnari, V., Colina, M., Ciancio, G., Govoni, M. and Trotta, F. (2010) Adult-Onset Still's Disease. *Rheumatology International*, **30**, 855-862. http://dx.doi.org/10.1007/s00296-009-1291-y

[5] Sugiura, T., Maeno, N., Kawaguchi, Y., Takei, S., Imanaka, H., Kawano, Y., *et al.* (2006) A Promoter Haplotype of the Interleukin-18 Gene Is Associated with Juvenile Idiopathic Arthritis in the Japanese Population. *Arthritis Research & Therapy*, **8**, R60. http://dx.doi.org/10.1186/ar1930

[6] Arlet, J.B., Boutin, L.E., Thi Huong, D., Pouchot, J. and Piette, J.C. (2005) Physiopathologie de la maladie de Still de l'adulte. *La Revue de Médecine Interne*, **26**, 549-556. http://dx.doi.org/10.1016/j.revmed.2004.11.021

[7] Fujii, T., Nojima, T., Yasuaka, H., Satoh, S., Nakamura, K., Kuwana, M., *et al.* (2001) Cytokine and Immunogenetic Profiles in Japanese Patients with Adult Still's Disease. Association with Chronic Articular Disease. *Journal of Rheumatology*, **40**, 1398-1404. http://dx.doi.org/10.1093/rheumatology/40.12.1398

[8] Gerfaud-Valentin, M., Jamilloux, Y., Iwaz, J. and Sève, P. (2014) Adult-Onset Still's Disease. *Autoimmunity Reviews*,

13, 708-722. http://dx.doi.org/10.1016/j.autrev.2014.01.058

[9]   Hoshino, T., Ohta, A., Yang, D., Kawamoto, M., Kikuchi, M., Inoue, Y., *et al*. (1998) Elevated Serum Interleukin 6, Interferon-Gamma, and Tumor Necrosis Factor-Alpha Levels in Patients with Adult Still's Disease. *Journal of Rheumatology*, **35**, 396-398.

[10]   Scheinberg, M.A., Chapira, E., Fernandes, M.L. and Hubscher, O. (1996) Interleukine 6: A Possible Marker of Disease Activity in Adult Onset Still's Disease. *Clinical and Experimental Rheumatology*, **14**, 653-655.

[11]   Maria, A.T., Le Quellec, A., Jorgensen, C., Touitou, I., Rivière, S. and Guilpain, P. (2014) Adult Onset Still's Disease (AOSD) in the Era of Biologic Therapies: Dichotomous View for Cytokine and Clinical Expressions. *Autoimmunity Reviews*, **13**, 1149-1159. http://dx.doi.org/10.1016/j.autrev.2014.08.032

[12]   Kawachima, M., Yamamura, M., Taniai, M., Yamamura, M., Taniai, M.,Yamauchi, H., *et al*. (2001) Levels of Interleukin-18 and Its Binding Inhibitors in the Blood Circulation of Patients with Adult-Still's Disease. *Arthritis & Rheumatism*, **44**, 550-560. http://dx.doi.org/10.1002/1529-0131(200103)44:3<550::AID-ANR103>3.0.CO;2-5

[13]   Kawagushi, Y., Terajima, H., Harigai, M., Hara, M. and Kamatani, N. (2001) Interleukin-18 as a Novel Diagnostic Marker and Indicator of Disease Severity in Adult-Onset Still's Disease. *Arthritis & Rheumatism*, **44**, 1716-1717. http://dx.doi.org/10.1002/1529-0131(200107)44:7<1716::AID-ART298>3.0.CO;2-I

[14]   Matsui, K., Tsuchida, T., Hiroishi, K., Tominaga, K., Hayashi, N., Hada, T., *et al*. (1999) High Serum Level of Macrophage-Colony Stimulating Factor (M-CSF) in Adult Still's Disease. *Rheumatology*, **38**, 477-478. http://dx.doi.org/10.1093/rheumatology/38.5.477

[15]   Choi, J.H., Suh, C.L., Lee, Y.M., Suh, Y.J., Lee, S.K., Kim, S.S., *et al.* (2003) Serum Cytokine Profiles in Patients with Adult Onset Still's Disease. *The Journal of Rheumatology*, **30**, 2422-2427.

[16]   Andres, E., Kurtz, J.E., Perrin, A.E., Pfumio, F., Ruellan, A., Goichot, B., *et al*. (2003) Retrospective Monocentric Study of 17 Patients with Adult Still's Disease, with Special Focus on Liver Abnormalities. *Hepato-Gastroenterology*, **50**, 1992-1995.

[17]   Min, J.K., Cho, C.S., Kim, H.Y. and Oh, E.J. (2003) Bone Marrow Findings in Patients with Adult Still's Disease. *Scandinavian Journal of Rheumatology*, **32**, 119-121. http://dx.doi.org/10.1080/03009740310000148

[18]   Zollner, R.C., Kerm, P., Steininger, H., Kalden, J.R. and Manger, B. (1997) Hyperferritinemia in Still Syndrome in the Adult and Reactive Hemophagocytic Syndrome. *Medizinische Klinik*, **92**, 494-498. http://dx.doi.org/10.1007/BF03044919

[19]   Coffernils, M., Soupart, A., Pradier, O., Feremans, W., Neve, P. and Decaux, G. (1992) Hyperferritinemia in Adult Onset Still's Disease and the Hemophagocytic Syndrome. *The Journal of Rheumatology*, **19**, 1425-1427.

[20]   Saiki, O., Uda, H., Nishimoto, N., Miwa, T., Mima, T., Ogawara, T., *et al*. (2004) Adult Still's Disease Reflects a Th2 Rather than a Th1 Cytokine Profile. *Clinical Immunology*, **112**, 120-125. http://dx.doi.org/10.1016/j.clim.2004.03.023

[21]   Hoshino, T., Ohta, A., Nakao, M., Ota, T., Inokuchi, T., Matsueda, S., *et al*. (1996) TCR *γδ*+ T Cells in Peripheral Blood of Patients with Adult Still's Disease. *The Journal of Rheumatology*, **23**, 124-129.

[22]   Wulffraat, N.M., Rijkers, G.T., Elst, E., Brooimans, R. and Kuis, W. (2003) Reduced Perforin Expression in Systemic Juvenile Idiopathic Arthritis Is Restored by Autologous Stem-Cell Transplantation. *Rheumatology*, **42**, 375-379. http://dx.doi.org/10.1093/rheumatology/keg074

[23]   Pouchot, J. and Vinceneux, P. (2004) La maladie de Still de l'adulte: Diagnostic, évolution et pronostic, pathogénie et traitement de la maladie de Still de l'adulte. *La Presse Médicale*, **33**, 1019-1025. http://dx.doi.org/10.1016/S0755-4982(04)98831-8

[24]   Yamaguchi, M., Ohta, A., Tsunematsu, T., Kasukawa, R., Mizushima, Y., Kashiwagi, H., *et al*. (1992) Preliminary Criteria for Classification of Adult Still's Disease. *The Journal of Rheumatology*, **19**, 424-430.

[25]   Van Reeth, C., Le Moël, G., Lasne, Y., Revenant, M.C., Agneray, J., Kahn, M.F., *et al*. (1994) Serum Ferritin and Isoferritins Are Tools for Diagnosis of Active Adult Still's Disease. *The Journal of Rheumatology*, **21**, 890-895.

[26]   Fautrel, B., Le Moel, G., Saint-Marcoux, B., Taupin, P., Vignes, S., Rozenberg, S., *et al*. (2001) Diagnostic Value of Ferritin and Glycosylated Ferritin in Adult Onset Still's Disease. *The Journal of Rheumatology*, **28**, 322-329.

[27]   Vignes, S., Le Moel, G., Fautrel, B., Wechsler, B., Godeau, P. and Piette, J.C. (2000) Percentage of Glycosylated Serum Ferritin Remains Low throughout the Course of Adult Onset Still's Disease. *Annals of the Rheumatic Diseases*, **59**, 347-350. http://dx.doi.org/10.1136/ard.59.5.347

[28]   Lambotte, O., Cacoub, P., Costedoat, N., Le Moel, G., Amoura, Z. and Piette, J.C. (2003) High Ferritin and Low Glycosylated Ferritin May Also Be a Marker of Excessive Macrophage Activation. *The Journal of Rheumatology*, **30**, 1027-1028.

[29]   Fautrel, B., Zing, E., Golmard, J.L., Le Moel, G., Bissery, A., Rioux, C., *et al.* (2002) Proposal for a New Set of Classification Criteria for Adult-Onset Still Disease. *Medicine*, **81**, 194-200.

http://dx.doi.org/10.1097/00005792-200205000-00003

[30] Kojima, M., Nakamura, S., Miyawaki, S., Yashiro, K., Oyama, T. and Itoh, H. (2002) Lymph Node Lesion in Adult-Onset Still's Disease Resembling Peripheral T-Cell Lymphoma: A Report of Three Cases. *International Journal of Surgical Pathology*, **10**, 197-202. http://dx.doi.org/10.1177/106689690201000305

[31] Efthimiou, P., Paik, P.K. and Bielory, L (2006) Diagnosis and Management of Adult Onset Still's Disease. *Annals of the Rheumatic Diseases*, **65**, 564-572. http://dx.doi.org/10.1136/ard.2005.042143

[32] Bennett, A.N., Peterson, P., Sangle, S., Hangartner, R., Abbs, I.C., Hughes, G.R., *et al*. (2004) Adult Onset Still's Disease and Collapsing Glomerulopathy: Successful Treatment with Intravenous Immunoglobulins and Mycophenolate Mofetil. *Rheumatology*, **43**, 795-799. http://dx.doi.org/10.1093/rheumatology/keh172

[33] Emad, Y., Ragab, Y. and El-Shaarawy, N. (2012) Lichen Planus in Association with Adult-Onset still's Disease Successfully Treated with Mycophenolate Mofetil. *The Journal of Rheumatology*, **39**, 1305-1306. http://dx.doi.org/10.3899/jrheum.120032

[34] Permal, S., Wechsler, B., Cabane, J., Perrot, S., Blum, L. and Imbert, J.C. (1995) Traitement de la maladie de Still de l'adulte par immunoglobulines intraveineuses. *La Revue de Médecine Interne*, **16**, 250-254. http://dx.doi.org/10.1016/0248-8663(96)80703-X

[35] Vignes, S., Wechsler, B., Amoura, Z., Papo, T., Francès, C., Huong, D.L., *et al.* (1998) Intravenous Immunoglobulin in Adult Still's Disease Refractory to Non-Steroidal Anti-Inflammatory Drugs. *Clinical and Experimental Rheumatology*, **16**, 295-298.

[36] Kim, H.A., Sung, J.M. and Suh, C.H. (2012) Therapeutic Responses and Prognosis in Adult-Onset Still's Disease. *Rheumatology International*, **32**, 1291-1298. http://dx.doi.org/10.1007/s00296-011-1801-6

[37] Neto, N.S., Waldrich, L., de Carvalho, J.F. and Pereira, R.M. (2009) Adult-Onset Still's Disease with Pulmonary and Cardiac Involvement and Response to Intravenous Immunoglobulin. *Acta Reumatológica Portuguesa*, **34**, 628-632.

[38] Kraetsch, H.G., Antoni, C., Kalden, J.R. and Manger, B. (2001) Successful Treatment of a Small Cohort of Patients with Adult Onset of Still's Disease with Infliximab: First Experiences. *Annals of the Rheumatic Diseases*, **60**, iii55-iii57.

[39] Husni, M.E., Maier, A.L., Mease, P.J., Overman, S.S., Fraser, P., Gravallese, E.M., *et al*. (2002) Etanercept in the Treatment of Adult Patients with Still's Disease. *Arthritis & Rheumatism*, **46**, 1171-1176. http://dx.doi.org/10.1002/art.10231

[40] Dechant, C., Schauenberg, P., Antoni, C.E., Kraetsch, H.G., Kalden, J.R. and Manger, B. (2004) Longterm Outcome of TNF Blockade in Adult-Onset Still's Disease. *Deutsche Medizinische Wochenschrift*, **129**, 1308-1312. http://dx.doi.org/10.1055/s-2004-826865

[41] Fautrel, B., Sibilia, J., Mariette, X. and Combe, B., the Club Rhumatismes et Inflammation (2005) Tumour Necrosis Factor Alpha Blocking Agents in Refractory Adult Still's Disease: An Observational Study of 20 Cases. *Annals of the Rheumatic Diseases*, **64**, 262-266. http://dx.doi.org/10.1136/ard.2004.024026

[42] Iwamoto, M., Nara, H., Hirata, D., Minota, S., Nishimoto, N. and Yoshizaki, K. (2002) Humanized Monoclonal Anti-Interleukin-6 Receptor Antibody for Treatment of Intractable Adultonset Still's Disease. *Arthritis & Rheumatism*, **46**, 3388-3389. http://dx.doi.org/10.1002/art.10620

[43] Puéchal, X., DeBandt, M., Berthelot, J.M., Breban, M., Dubost, J.J., Fain, O., *et al.* (2011) Tocilizumab in Refractory Adult Still's Disease. *Arthritis Care & Research*, **63**, 155-159. http://dx.doi.org/10.1002/acr.20319

[44] Suematsu, R., Ohta, A., Matsuura, E., Takahashi, H., Fujii, T., Horiuchi, T., *et al*. (2012) Therapeutic Response of Patients with Adult Still's Disease to Biologic Agents: Multicenter Results in Japan. *Modern Rheumatology*, **22**, 712-719. http://dx.doi.org/10.3109/s10165-011-0569-6

[45] Yoshida, Y., Sakamoto, M., Yokota, K., Sato, K. and Mimura, T. (2011) Tocilizumab Improved both Clinical and Laboratory Manifestations Except for Interleukin-18 in a Case of Multiple Drug-Resistant Adult-Onset Still's Disease. *Internal Medicine*, **50**, 1757-1760. http://dx.doi.org/10.2169/internalmedicine.50.4771

[46] Fitzgerald, A.A., Leclercq, S.A., Yan, A., Homik, J.E. and Dinarello, C.A. (2005) Rapid Responses to Anakinra in Patients with Refractory Adult-Onset Still's Disease. *Arthritis & Rheumatism*, **52**, 1794-1803. http://dx.doi.org/10.1002/art.21061

[47] Lequerré, T., Quartier, P., Rosellini, D., Alaoui, F., De Bandt, M., Mejjad, O., *et al*. (2008) Interleukin-1 Receptor Antagonist (Anakinra) Treatment in Patients with Systemic-Onset Juvenile Idiopathic Arthritis or Adult Onset Still Disease: Preliminary Experience in France. *Annals of the Rheumatic Diseases*, **67**, 302-308. http://dx.doi.org/10.1136/ard.2007.076034

[48] Laskari, K., Tzioufas, A.G. and Moutsopoulos, H.M. (2011) Efficacy and Long-Term Follow-Up of IL-1R Inhibitor Anakinra in Adults with Still's Disease: A Case-Series Study. *Arthritis Research & Therapy*, **13**, R91. http://dx.doi.org/10.1186/ar3366

[49] Hong, D.S., Yang, Z.H., Han, S.Y., Liang, X.G., Ma, K.F. and Zhang, X.G. (2014) Interleukin 1 Inhibition with Anakinra in Adult-Onset Still Disease: A Meta-Analysis of Its Efficacy and Safety. *Drug Design*, *Development and Therapy*, **8**, 2345-2357.

[50] Ahmadi-Simab, K., Lamprecht, P., Jankowiak, C. and Gross, W.L. (2006) Successful Treatment of Refractory Adult Onset Still's Disease with Rituximab. *Annals of the Rheumatic Diseases*, **65**, 1117-1118. http://dx.doi.org/10.1136/ard.2005.047621

[51] Bartoloni, E., Alunno, A., Luccioli, F., Santoboni, G. and Gerli, R. (2009) Successful Treatment of Refractory Adult-Onset Still's Disease with Anti-CD20 Monoclonal Antibody. *Clinical and Experimental Rheumatology*, **27**, 888-889.

[52] Kadavath, S. and Efthimiou, P. (2015) Adult-Onset Still's Disease—Pathogenesis, Clinical Manifestations, and New Treatment Options. *Annals of Medicine*, **47**, 6-14. http://dx.doi.org/10.3109/07853890.2014.971052

[53] Jamilloux, Y., Gerfaud-Valentin, M., Henry, T. and Sève, P. (2014) Treatment of Adult-Onset Still's Disease: A Review. *Journal of Therapeutics and Clinical Risk Management*, **11**, 33-43.

[54] Narula, N., Narula, T. and Abril, A. (2015) Seizing the Clinical Presentation in Adult Onset Still's Disease. An Extensive Literature Review. *Autoimmunity Reviews*, **14**, 472-477. http://dx.doi.org/10.1016/j.autrev.2015.01.007