

# Adult-onset Still's disease: autoinflammation beyond fever

P.L.A. van Daele

In the current issue of the journal, Wang et al. present a patient with adult-onset Still's disease suffering from macrophage activation syndrome (MAS) with pulmonary involvement.

Adult-onset Still's disease is a rare acquired autoinflammatory disorder with similar presentation to the present-day systemic juvenile idiopathic arthritis (sJIA). Some regard it a continuum of a single disease entity.<sup>1</sup> The frequently-used term 'periodic fever syndrome' is not justified as fever and is not always part of the presentation. Incidence is approximately 0.16 per 100,000 individuals with an equal distribution between men and women.<sup>2</sup> The clinical course can be divided in a mono-phasic, intermittent and chronic disease pattern and severity is variable. Skin and joint disease, lymphadenopathy and spleen and liver involvement are common. MAS is regarded the most serious presentation with high mortality despite treatment.<sup>3</sup> Markedly elevated ferritin levels are often a clue to diagnosis.<sup>4</sup>

Treatment is aimed at inhibiting pro-inflammatory signs and symptoms, and thereby preventing organ damage and life-threatening complications. Yet, optimal treatment for this disease remains to be elucidated as large clinical trials are lacking. For mild disease with mainly joint involvement, nonsteroidal anti-inflammatory drugs (NSAIDs) are prescribed. Corticosteroids are given to patients with more aggressive disease. In severe refractory disease, it has been common use to start treatment with disease-modifying antirheumatic drugs (DMARDs).<sup>5</sup>

Wang et al. successfully treated the patient with cyclophosphamide after corticosteroids alone failed to control disease activity. She fully recovered. In their discussion, they suggest that blocking pro-inflammatory cytokines would have been an attractive treatment option for this patient; pro-inflammatory cytokines such as IL-1, IL-6 and IL-18 play a prominent role in the pathogenesis of sJIA and adult-onset Still's disease, and high-dose corticosteroids and cyclophosphamide have considerable side effects, especially in young patients.<sup>6</sup>

Biologics blocking IL-1 and IL-6 are available and studies have demonstrated very effective control of disease activity with acceptable side effects.<sup>7,8</sup> Also recently, a study has

been published showing the effect of blocking IL-18.<sup>9</sup> Perhaps in the near future, there may also be a role for blocking interferon gamma.<sup>10</sup>

There is discussion whether cytokine blocking should be administered earlier in the disease process to avoid side effects of other drugs such as high-dose corticosteroids. Unfortunately, medication costs still hamper this. In addition, quality of life during and after treatment should equally be weighed while deciding what treatment is best for patients.

## REFERENCES

1. Nirmala N., Brachat A, Feist E, et al. 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.* 2015;13:50.
2. 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;54:587-90.
3. Ruscitti P, Rago C, Breda L, et al. Macrophage activation syndrome in Still's disease: analysis of clinical characteristics and survival in paediatric and adult patients. *Clin Rheumatol.* 2017;36:2839-45.
4. Bagnari V, Colina M, Ciancio G, Govoni M, Trotta F. Adult-onset Still's disease. *Rheumatol Int.* 2010;30:855-62.
5. Govoni M, Bortoluzzi A, Rossi D, Modena V. How I treat patients with adult onset Still's disease in clinical practice. *Autoimmun Rev.* 2017;16:1016-23.
6. de Jager W, Vastert SJ, Beekman JM, et al. Defective phosphorylation of interleukin-18 receptor beta causes impaired natural killer cell function in systemic-onset juvenile idiopathic arthritis. *Arthritis Rheum.* 2009;60:2782-93.
7. Junge G, Mason J, Feist E. Adult onset Still's disease-The evidence that anti-interleukin-1 treatment is effective and well-tolerated (a comprehensive literature review). *Semin Arthritis Rheum.* 2017;47:295-302.
8. Kaneko Y, Kameda H, Ikeda K, et al. Tocilizumab in patients with adult-onset still's disease refractory to glucocorticoid treatment: a randomised, double-blind, placebo-controlled phase III trial. *Ann Rheum Dis.* 2018;77:1720-9.
9. Gabay C, Fautrel B, Rech J, et al. Open-label, multicentre, dose-escalating phase II clinical trial on the safety and efficacy of tadekinig alfa (IL-18BP) in adult-onset Still's disease. *Ann Rheum Dis.* 2018;77:840-7.
10. Han JH, Suh CH, Jung JY, et al. Elevated circulating levels of the interferon- $\gamma$ -induced chemokines are associated with disease activity and cutaneous manifestations in adult-onset Still's disease. *Sci Rep.* 2017;7:46652.