

# A puzzling haptoglobin level in a patient who is treated with tocilizumab

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*To the editor,*

Mrs. D is a 65-year-old lady who was diagnosed with giant cell arteritis in 2016. Since then, she has been treated with corticosteroids. As it was not possible to taper corticosteroids without inducing a relapse, methotrexate and leflunomide were consecutively added without much effect. Eventually, tocilizumab was started, leading to a rapid normalization of C-reactive protein (CRP) and erythrocyte sedimentation rate. However, a mild anaemia (Hb 6,9 mmol/l) was noted with a slightly increased lactate dehydrogenase (LDH) level (304 U/l, normal value < 247). An analysis to reveal the cause of the anaemia was initiated. Bilirubin as well as vitamin B12, folic acid, and ferritin levels were within normal limits. However, the haptoglobin level was repeatedly undetectable, leading to a suspicion of haemolytic anaemia. However, when her haemoglobin level spontaneously increased to the pre-existent value, the presence of haemolysis was questioned. We then focused on the cause of the decreased haptoglobin level.

This patient was treated with tocilizumab at the time of measurement of haptoglobin. Tocilizumab is a monoclonal antibody directed against the membrane-bound and soluble interleukin-6 (IL-6) receptor.<sup>1</sup> It is used to treat a variety of auto-immune and auto-inflammatory diseases including giant cell arteritis.<sup>1</sup> IL-6 is produced by many different cells of the immune system and has numerous effector functions. An important function of IL-6 is to induce the production of acute-phase proteins such as CRP, serum amyloid A, and fibrinogen by hepatocytes.<sup>2</sup> Therefore, it is not surprising that CRP levels are low in patients who are treated with tocilizumab.<sup>3</sup> Haptoglobin is also an acute-phase reactant which is produced by hepatocytes in response to IL-6.<sup>4</sup> Indeed, in a cohort of 132 patients with rheumatoid arthritis, haptoglobin levels decreased in parallel to CRP after the start of tocilizumab.<sup>5</sup> Consequently, the serum haptoglobin level is not a reliable marker for haemolysis in patients who are treated

with tocilizumab. Of course, other causes of decreased haptoglobin levels always need to be considered when evaluating a patient, such as hepatic dysfunction, elevated oestrogen levels, haemodilution, multiple transfusions, or technical flaws.<sup>6</sup>

For Mrs. D, the initial diagnosis of haemolytic anaemia was abandoned based on a spontaneous increase in haemoglobin level and low bilirubin levels. The undetectable levels of CRP and procalcitonin confirmed our hypothesis that the haptoglobin level was decreased secondary to tocilizumab. Moreover, we found decreased haptoglobin levels in three other patients treated with tocilizumab, ranging from undetectably low levels to 0.11 g/l.

In conclusion, the serum haptoglobin level is not a reliable marker in patients who are treated with tocilizumab.

## CONFLICTS OF INTEREST

The authors have no relevant conflicts of interest to report.

## REFERENCES

1. Mollan SP, Horsburgh J, Dasgupta B. Profile of tocilizumab and its potential in the treatment of giant cell arteritis. *Eye Brain*. 2018;10:1-11.
2. Naka T, Nishimoto N, Kishimoto T. The paradigm of IL-6: from basic science to medicine. *Arthritis Res*. 2002; 4:S233-42.
3. Bari SF, Khan A, Lawson T. C reactive protein may not be reliable as a marker of severe bacterial infection in patients receiving tocilizumab. *BMJ Case Rep*. 2013;2013.
4. Raynes JG, Eagling S, McAdam KP. Acute-phase protein synthesis in human hepatoma cells: differential regulation of serum amyloid A (SAA) and haptoglobin by interleukin-1 and interleukin-6. *Clin Exp Immunol*. 1991;83:488-91.
5. Isaacs JD, Harari O, Kobold U, Lee JS, Bernasconi C. Effect of tocilizumab on haematological markers implicates interleukin-6 signalling in the anaemia of rheumatoid arthritis. *Arthritis Res Ther*. 2013;15:R204.
6. Shih AW, McFarlane A, Verhovsek M. Haptoglobin testing in hemolysis: measurement and interpretation. *Am J Hematol*. 2014;89:443-7.