CASE REPORT

C reactive protein may not be reliable as a marker of severe bacterial infection in patients receiving tocilizumab

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SUMMARY

This is a case of a 65-year-old man with seropositive erosive rheumatoid arthritis (RA), well controlled on methotrexate, sulfasalazine, low-dose prednisolone and monthly infusions of tocilizumab. He presented with a 3-week history of pain and swelling in his left knee, gradually increasing in severity with an inability to bear weight . He was systemically well with normal vital signs. Examination confirmed an effusion and aspiration was turbid in appearance. C reactive protein (CRP) was normal. He was treated empirically with antibiotics. Synovial fluid and blood cultures confirmed *Staphylococcus aureus* infection. He completed a 6 weeks course of antibiotics with complete resolution of symptoms. Throughout the treatment his CRP remained normal which is likely to have been the result of prior treatment with tocilizumab.

BACKGROUND

This case illustrates that systemic symptoms and an elevated C reactive protein (CRP) may not be present in patients treated with tocilizumab even in the context of severe life-threatening sepsis. A high index of suspicion should be retained in all patients presenting with new symptoms or signs. It is well recognised that in patients receiving disease modifying antirheumatic drugs (DMARDs) the symptoms and signs of infection may be diminished. However, with these drugs CRP still usually increases in the context of acute infection and can therefore be used as a marker of response to treatment. In patients receiving tocilizumab, CRP may remain suppressed even in the context of severe infection and may therefore be less useful for diagnostic or monitoring purposes.

CASE PRESENTATION

We present a case of a 65-year-old man with seropositive erosive RA, well controlled on methotrexate, sulfasalazine, low-dose prednisolone and monthly infusions of tocilizumab. He presented with a 3-week history of gradually worsening pain and swelling in his left knee. There was no history of trauma and he denied any fever, rigours or recent infection.

On examination he was systemically well, no fever with a moderate effusion of the left knee. There was no synovitis in other joints.

INVESTIGATIONS

Investigations revealed a total white cell count of 11.8×10^9/L (normal $4–11\times10^9$/L) with normal neutrophil count, CRP 4 mg/dL (normal <10 mg/dL); renal and liver function tests were also normal. Synovial fluid aspirated from the knee was turbid in appearance. Microscopy demonstrated polymorphs, but no visible organisms on Gram stain. Blood and synovial fluid cultures subsequently confirmed infection with *Staphylococcus aureus*.

DIFFERENTIAL DIAGNOSIS

The differential diagnoses considered in this case prior to synovial and blood culture results were:

- Septic arthritis
- Crystal arthropathy
- Monoarticular flare of RA

TREATMENT

Despite the absence of fever and the normal CRP, the turbid appearance of the synovial fluid and prior immunosuppression led to empirical treatment with intravenous flucloxacillin 2 gm and oral fusidic acid 500 mg. Culture of synovial fluid and blood subsequently confirmed *S aureus* septic arthritis and septicaemia. The organism was sensitive to flucloxacillin and fusidic acid. Tocilizumab was disconitnued. Arthroscopic washout of the knee was performed and a total of 2 weeks of intravenous and 4 weeks of oral antibiotics were administered with complete resolution of his symptoms and signs. The CRP remained normal throughout.

OUTCOME AND FOLLOW-UP

The patient made a full recovery following arthroscopic lavage and 6 weeks of antibiotic treatment. The British Society of Rheumatology guidelines' recommend avoiding tocilizumab therapy for a year after an acute, severe infection such as septic arthritis. However, in this case the patient suffered a flare of RA and due to persistent disease activity, tocilizumab was restarted after 4 months. The patient was fully informed of reinfection risks. Six months later there has been no recurrence of infection and the patient remains well.

DISCUSSION

Tocilizumab is licensed for the treatment of RA. It can be used as a first-line biological agent after inadequate response to or intolerance of DMARDs, or after inadequate response or intolerance to other biologics such as TNF-α inhibitors and rituximab.[1] It is a humanised monoclonal antibody targeting circulating Interleukin-6 (IL-6) receptors. It blocks the proinflammatory effects of IL-6, affecting the function of neutrophils, T cells, B cells, monocytes and osteoclasts.[2]

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Learning points

- Tocilizumab is a biological drug licensed for the treatment of rheumatoid arthritis. It inhibits the action of the proinflamatory cytokine interleukin-6 and thus impairs the acute-phase response.
- Tocilizumab may completely suppress C reactive protein (CRP) production even in the context of severe sepsis. Caution is therefore advised in using a normal CRP to exclude sepsis in patients treated with tocilizumab.
- Monoarthritic flares of rheumatoid arthritis are unusual and septic arthritis should always be considered if these patients present with a single inflammed joint.
- Biologics should be stopped in patients with acute severe infections according to the British Society of Rheumatology guidelines.

IL-6 is a key driver of the acute-phase response and has an important role in the production of CRP in the liver. CRP is used in clinical practice as a marker of inflammation and infection. Although it is well recognised that patients on immunosuppressants may not exhibit the usual symptoms and signs of sepsis such as fever, there is still usually an elevation of CRP levels in such cases.[3 4] Three case reports[5–7] have reported the absence or masking of symptoms of severe infections in patients treated with tocilizumab. The suppression of CRP in patients treated with tocilizumab could lead to delay in diagnosis of serious infection in patients on this treatment. Physicians must be aware of the potential for infection when patients treated with tocilizumab present with new symptoms. The rate of infection in patients with RA treated with tocilizumab in clinical practice is higher than in the clinical trial populations. Risk may be increased in patients with longer disease duration, previous exposure to multiple DMARDs and those receiving concomitant leflunomide, prednisolone or proton-pump inhibitor treatment.[8]

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Competing interests None.

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