

# Tocilizumab Efficacy in a Patient with Positive Anti-CCP Chronic Lyme Arthritis

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## Abstract

**Context:** Lyme arthritis, a manifestation of tick-borne Lyme disease, can prove to be refractory to classic treatment. **Case Report:** We present a case of a 48-year-old male, diagnosed with chronic Lyme arthritis, refractory to recurrent and prolonged courses of doxycycline, ceftriaxone, as well as hydroxychloroquine and methotrexate. The patient responded partially to tumor necrosis factor (TNF)-alpha blockade by etanercept and, finally, entered long-term remission after his treatment was switched to tocilizumab. **Conclusion:** Off label treatment by biologic disease modifying antirheumatic drugs can be considered in selected patients with severe antibiotic-resistant Lyme arthritis.C.

**Keywords:** Lyme arthritis, lyme disease, tocilizumab

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## Introduction

Lyme disease is an infection induced by *Borrelia burgdorferi* (*B. burgdorferi*), which is spread by a tick vector. The disease is endemic in the Northern Hemisphere's temperate regions, found often in the northeastern portion of the United States, with an incidence reported via the Centers for Disease Control and Prevention reaching levels up to 300,000 cases per year in the United States. Disease symptoms include a characteristic rash, fatigue, facial paralysis, headaches, and muscle aches. Arthritis is one of the possible sequelae of the disease and typically affects the knees. Ankles, elbows, wrists, and hip joints can also be involved in some of the patients. Joint pain and swelling may persist with possible joint erosions seen in severe cases. Treatment with doxycycline or ceftriaxone is usually curative; however, some disease features can persist for long periods of time

and be refractory to therapy. In the present case study, we describe a patient with intractable Lyme arthritis who, after failure of recurrent trials of antibiotic treatment and disease modifying antirheumatic medicines, went into prolonged remission while treated with tocilizumab monotherapy.

## Case Presentation

An otherwise healthy 48-year-old male was hospitalized in the rheumatology ward due to worsening joint pain. The patient's pain began four years prior after he was bitten by a tick while traveling in Germany. Shortly thereafter, the patient started experiencing relentless joint pain in his knees, shoulders and hands, accompanied by

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swelling and morning stiffness. The patient was treated with nonsteroidal anti-inflammatory drugs periodically that did not provide adequate relief of his symptoms. The patient did not recall skin rashes or other accompanying symptoms following the incident.

On admission, the patient had synovitis of the fifth distal interphalangeal (DIP) joints bilaterally and fourth right proximal interphalangeal joint (PIP) in the hands, both shoulders, and both knees, with massive bilateral knee effusions. A complete physical examination did not reveal any other significant findings. On technetium bone scan, all the above mentioned joints as well as both sacroiliac joints (SIJs) showed increased uptake. Roentgenograms demonstrated narrowing of joint spaces in both knees. The patient's laboratory results were remarkable for an elevated serum level of C-reactive protein, which was six times the upper limit of normal, positive IgM rheumatoid factor and elevated titers of anti-cyclic citrullinated protein antibodies (ACPA) of >150 units/mL (normal up to 20 units/mL). Complete blood count and general chemistries were normal. Both anti-*B. burgdorferi* Immunoglobulin M (IgM) and Immunoglobulin G (IgG) antibodies were positive in high titer. The pattern of articular disease in our patient, including involvement of DIP and SIJ, as well as huge knee effusions, was considered typical for Lyme disease and very unusual for rheumatoid arthritis (RA) even in the presence of positive ACPA. Therefore, the patient was diagnosed with chronic Lyme arthritis and treatment was begun with 200 mg of doxycycline daily, which was administered for 4 weeks. Although a gradual improvement in the patient's joint pain was noted and inflammation in hand joints and shoulders had resolved, huge effusions in both knees persisted and significantly reduced the patient's functioning. Various treatment plans were employed and included parenteral ceftriaxone for 1 month, retreatment was done with doxycycline for 6 weeks and hydroxychloroquine was given along with 15 mg per week of methotrexate. Intraarticular injections of glucocorticosteroids and osmic acid synovectomy were attempted as well and achieved only short-term and limited improvement. Failure of all of the aforementioned therapies led to a trial of etanercept in a weekly dose of 50 mg given along with methotrexate 15 mg/week. Almost complete resolution of the patient's knee effusions was attained within 2 months of treatment. However, after 6 months' treatment with this combination, the patient's arthritis flared again with exacerbated knee effusions. After another course of ceftriaxone proved ineffective, and an acute allergic reaction to infliximab, the patient was placed on tocilizumab, 8 mg/kg per month. After this switch of therapy, the patient's knee effusions resolved gradually over the course of 4 months and did not return. The patient has been receiving tocilizumab for the past

4 years. The patient still experiences residual knee pain at exertion, but no disease flares were noted during this period of time and his condition remains stable.

## Discussion

Lyme borreliosis is a major tick-borne bacterial infection, which causes joint involvement seen in 15-60% of patients.<sup>[1,2]</sup> Knee involvement is a typical presentation and knee synovitis with huge joint effusions may be present. However, virtually all joints including sacroiliac and DIP joints may be affected, presenting usually as asymmetric oligoarthritis.

The diagnosis of Lyme arthritis is clinical and requires support by the presence of specific IgM antibodies in the serum. These anti-*B. burgdorferi* antibodies may persist for years, despite successful treatment. Initial antibiotic therapy should employ 4-6 weeks of amoxicillin 1,500-2,000 mg daily in divided doses, cefuroxime 500 mg twice daily or doxycycline 100 mg twice daily, or a minimum of 21 days of azithromycin 250-500 mg daily. For patients with significant impairments and/or a minimal or absent therapeutic response, a combination of oral antibiotics, injectable penicillin G benzathine, or intravenous ceftriaxone is preferred.<sup>[3]</sup> In patients with chronic disease activity, retreatment should be considered. There remains a small subset of patients who do not respond to therapy and chronic arthritis may be one of the manifestations of refractory Lyme disease. The majority of these patients will experience gradual improvement of symptoms within months to years while others may develop joint erosions and permanent damage.<sup>[1,4]</sup>

The mechanism of chronic Lyme arthritis has not been deduced definitively. Three hypotheses have been proposed as an explanation; these include chronic infection, T-cell epitope mimicry, and bystander activation.<sup>[4]</sup> The relationship of antibiotic-refractory Lyme arthritis to HLA-DR4 as well as reported ACPA positivity in some patients with Lyme disease may further support the speculation that *B. burgdorferi* may cause chronic arthritis through the activation of ACPA in a genetically susceptible individual.<sup>[5,6]</sup> However, the presence of ACPA in large cohorts of patients with refractory Lyme arthritis has never been reported, and the possibility of coexistence of Lyme disease and RA in these patients cannot be definitely excluded. It has been suggested that a particular enzyme, lysosomal  $\beta$ -glucuronidase, is a common link present in both RA and Lyme disease.<sup>[7]</sup> The hypomorphic form of the enzyme is suggested as linked to increased severity of arthritis.

Of relevance, a study was performed to compare the MRI findings of Lyme arthritis in six patients to those

of eight patients with RA.<sup>[8]</sup> Both diseases were found to share many of the same MRI features including synovial proliferation, bone marrow edema, and bare area erosions. Some MRI findings were judged to be relatively specific for Lyme arthritis, including patellar sparing or presence of popliteal fossa lymph nodes and were present in five of the six patients with Lyme arthritis in the aforementioned study.

In patients with chronic synovitis despite eradication of *B. burgdorferi*, therapeutic recommendations are similar to those for patients with RA and include treatment with synthetic disease-modifying antirheumatic drugs. Short-term treatment with infliximab has been suggested, as well, based on the presence of high levels of tumor necrosis factor (TNF)-alpha in the synovial tissue of patients with chronic Lyme arthritis.<sup>[9]</sup>

Etanercept has not yet been reported as a therapy used for treatment of refractory Lyme arthritis. Based on registry data and reduced risk of tuberculosis compared to antibody anti-TNF agents, it may possess a more favorable safety profile in regards to infectious complications as compared to the other anti-TNF-alpha treatments. In the setting of a possible ongoing infectious process caused by *B. burgdorferi*, etanercept was chosen as a first line biological therapy in our patient. While major improvement followed etanercept therapy, the patient experienced a flare several months later.

In considering alternative treatment options, tocilizumab, an anti-interleukin (IL)-6 receptor antagonist, was considered. Administration of tocilizumab in a dosage recommended for the treatment of RA led to a full and long-standing remission in our patient with refractory Lyme arthritis. While there is no available data on the part IL-6 plays in the pathogenesis of Lyme disease, our reported experience suggests that IL-6 can play a role, at least in the mechanisms of development of Lyme arthritis.

## Conclusion

In summary, we report, herein, a first case of severe antibiotic-resistant Lyme arthritis where complete remission was achieved with the anti-IL-6 therapy, tocilizumab.

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## Conflicts of interest

There are no conflicts of interest.

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