

Tocilizumab Treatment in Polyarteritis Nodosa

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KEY WORDS: biological therapy, interleukin (IL) 6, polyarteritis nodosa (PAN), tocilizumab, vasculitis

IMAJ 2019; 21: 560–562

Polyarteritis nodosa (PAN) is a systemic vasculitis characterized by the necrosis of medium and small arteries without involvement of arterioles, capillaries, and venules. PAN, like other vasculitides, affects multiple organ manifestations, although it most commonly affects skin, joints, peripheral nerves, intestines, and kidneys. The lungs are usually not affected by PAN [1].

As very few larger controlled studies have been conducted on PAN, treatment is mostly performed according to expert opinion recommendations. The treatment regimen is similar to what has been used in anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitides. Treatment includes corticosteroids with the addition of immunosuppressive agents if corticosteroids are not tolerated, cannot be tapered, or prognosis is poor. Treatment of viral-associated PAN is aimed at treating the underlying virus, with escalation of immunosuppression in severe cases. In patients with relatively mild disease and those with isolated cutaneous disease, initial monotherapy with oral corticosteroids has been suggested [1]. In patients with moderate to severe disease (e.g., any evidence of renal insufficiency; significant proteinuria; gastrointestinal, cardiac, or neurologic involvement) treatment with both corticosteroids and cyclophosphamide is recommended [1]. If patients do not respond adequately to corticosteroids

and cyclophosphamide treatment, alternative immunosuppressive agents (e.g., azathioprine, methotrexate, mycophenolate mofetil) could be administered [1].

We describe the case of a patient with PAN treated with the combination of methylprednisolone, methotrexate, and the interleukin (IL)-6 receptor inhibitor tocilizumab.

PATIENT DESCRIPTION

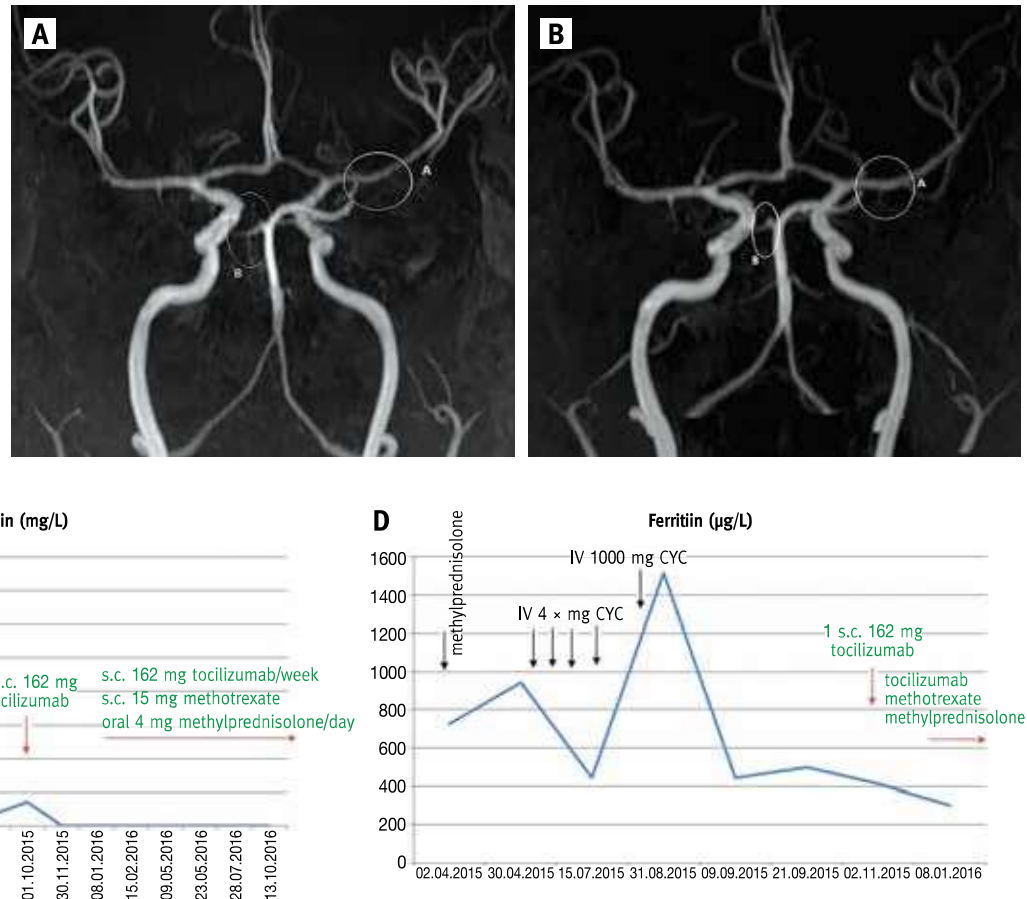
In 2015, at the age of 67, the male patient was admitted to the Department of Rheumatology, Faculty of Medicine, Institute of Medicine, University of Debrecen, Hungary. His first symptoms at the time of admission were fatigue, lack of appetite, 18 kg weight loss, dysphagia, myalgia, arthralgia, pain in upper and lower limbs, and polyneuropathy. A comprehensive tumor screening included abdominal ultrasound, computed tomography (CT) of the chest and abdomen, and colonoscopy with negative result. Upper endoscopy showed erosive gastritis in the antrum and barium swallowing X-ray showed decreased esophagus peristalsis. Most notable laboratory parameters of the patient were the following: D-dimer 28.23 FEU/L, white blood cell count 3.56 G/L, C-reactive protein (CRP) 20.3 mg/L, CH50 < 10 CH50/ml, C3 0.42 mg/L, and ferritin 725.5 µg/L. According to these complaints and findings, 16 mg/day methylprednisolone was initiated. As we decreased the dose, symptoms intensified and more weight loss occurred; therefore, the dose of methylprednisolone was increased to 32 mg/day. Two months after the disease onset, new symptoms including abdominal pain, nausea, vomiting, headache, and double vision developed. magnetic resonance (MR)-angiography of the

brain revealed typical vasculitis-like lesions [Figure 1A]. In addition, CT-angiography of the abdomen showed infrarenal abdominal aortic aneurysm and patchy wall thickening of the common iliac arteries on both sides. Thus, the patient met the 1990 American College of Rheumatology diagnostic criteria for PAN [1]: weight loss ≥ 4 kg, myalgia/leg tenderness, polyneuropathy, and arteriographic abnormalities. Treatment with both corticosteroids (IV methylprednisolone 125 mg/day, followed by PO 16 mg/day) and cyclophosphamide (IV cyclophosphamide 1000 mg/month five times followed by 125 mg PO daily) was administered. Control cerebral MR-angiography showed that the immunosuppressive treatment was effective, at least regarding the vascular lesions [Figure 1B].

Six months after disease onset PAN was still active, and new symptoms occurred including tinnitus, high fever, and dizziness. Due to repeated relapses and sustained high demand for corticosteroids, we decided to initiate tocilizumab as an off-label indication. We administered 162 mg tocilizumab infusions weekly. Almost every clinical symptoms disappeared after the first tocilizumab infusion. Treatment after 2 months was completed by the administration of SC methotrexate (15 mg/week) and PO methylprednisolone (4 mg/day). Today the patient is in good clinical condition, he had even gained weight, and no fatigue is present. He has no abdominal pain and no dysphagia. In 2017 he only had some dizziness as a neurological residual symptom. In addition to excellent clinical response to tocilizumab, CRP, ESR, and ferritin levels also returned to the normal range. Changes of these parameters during the course are demonstrated in Figures 1C and 1D.

Figure 1. Cerebral magnetic resonance angiography images of the patient with polyarteritis nodosa (PAN).

[A] Thickening on the proximal segment of the middle cerebral artery left side and posterior cerebral artery hypoplasia right side; **[B]** Caliber fluctuation of the basilar artery branches is decreased, no wall thickening on the proximal segment of the middle cerebral artery left side, only mild hypoplasia of the posterior cerebral artery right side; **[C]** Changes in C-reactive protein during follow-up of the patient. **[D]** Changes in serum ferritin during follow-up of the patient



CYC = cyclophosphamide, IV = intravenous

COMMENT

Larger, controlled clinical trials are needed to determine the real efficacy and place of biologic therapy in the treatment of PAN. Considering the effectiveness of rituximab in patients with ANCA-associated vasculitis [1,2], in patients with refractory PAN without hepatitis B virus infection, rituximab has been considered as an option by some investigators [1,2], although its use has not been formally evaluated in this disease. Successful treatment using TNF- α inhibitors, such as infliximab or etanercept, has been previously reported in children with systemic PAN unresponsive to conventional therapy [1,2].

Little information is available on the possible use of tocilizumab in PAN. Tocilizumab is a humanized monoclonal antibody against

the IL-6 receptor. According to Nakahama et al. [3], serum IL-6 level correlates with disease activity in PAN. Thus, it might be useful in diagnosing and monitoring PAN. There is a rationale to target this cytokine in this disease. So far there have been only two reports in the literature about PAN treated successfully with tocilizumab. Tocilizumab was successfully administered to one patient with PAN-related secondary amyloidosis and a pediatric PAN patient [4,5]. IL-6 plays a central role not only in PAN, but also in amyloid A (AA) amyloid production [4]. In 2013, Hočevár and colleagues [4] reported the case of a patient with PAN complicated by AA amyloidosis treated with tocilizumab [4]. The first report of successful treatment of PAN using a combination of cyclophosphamide and tocilizumab was presented in 2016 by Watanabe et al. [5]. A 3-year-old

boy with vertebral artery vasculitis who met diagnostic criteria for PAN was treated by this combination [5].

During disease progress we could not keep the patient in remission during the first 6 months. Relapses occurred again and again with new symptoms such as abdominal discomfort or central neurological complaints. Traditional treatment (corticosteroids, cyclophosphamide) was ineffective, but tocilizumab therapy resulted in significant improvement. We have no information how long tocilizumab treatment should be continued in PAN.

To the best of our knowledge this is the first description of successful treatment of an adult PAN patient using a combination of tocilizumab, methotrexate, and methylprednisolone. We emphasize that right after the administration of the IL-6 receptor inhibitor

both clinical and laboratory signs of disease activity decreased. Further investigations are needed to define the role of this biologic agent regarding the treatment of PAN.

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Capsule

Broadening targeted therapy in cystic fibrosis

There are more than 1700 mutations in the CFTR (cystic fibrosis transmembrane conductance regulator) gene that cause cystic fibrosis. Some mutations occur frequently, whereas others affect very few or individual patients. Modulators have been developed to target specific CFTR mutations classified according to their functional impact on the encoded protein. In a perspective, **Manfredi** and colleagues discussed the emerging view that many CFTR

mutations have pleiotropic effects and so more patients could benefit from modulator therapy but do not receive it. Moreover, individuals with ultrarare CFTR mutations are often do not receive these targeted drugs. The authors outlined the approaches needed to broaden the personalization of these modulators to treat more patients.

Science 2019; 365: 220

Eitan Israel

Capsule

Synthetic bacterial cancer therapy

Some bacteria preferentially grow in tumors, because exclusion of immune cells and reduced oxygen favor their proliferation. This phenomenon offers the opportunity to exploit nonpathogenic engineered bacteria to deliver drugs directly into the tumor. **Chowdhury** et al. developed a synthetic *Escherichia coli* strain programmed to target the innate immune regulator CD47. A single-domain antibody fragment (nanobody) therapeutic loaded into the bacteria

blocks CD47 and promotes antitumor responses. In mice, this treatment led to regression of both primary tumors and metastases. Bacterial delivery of the CD47 nanobody to tumors, combined with bacterial lysis, stimulates antitumor immune responses and immune memory, indicating that this could be a viable therapeutic approach.

Nat Med 2019; 25: 1057

Eitan Israeli

Capsule

Transcutaneous ultrasound energy harvesting using capacitive triboelectric technology

Implanted medical devices, such as pacemakers and neurological stimulators, require a source of power, usually in the form of a battery. If a battery is implanted with the device, replacing it would require additional surgery. However, external power packs are prone to lead to infections where their wires enter the body. **Hinchet** and co-authors used ultrasound to deliver mechanical energy through skin and liquids and demonstrate a thin implantable vibrating triboelectric generator able to effectively harvest it. The ultrasound can induce micrometer-scale displacement of a polymer thin

membrane to generate electrical energy through contact electrification. The authors recharged a lithium-ion battery at a rate of 166 microcoulombs per second in water. The voltage and current generated ex vivo by ultrasound energy transfer reached 2.4 volts and 156 microamps under porcine tissue. These findings show that a capacitive triboelectric-electret is the first technology able to compete with piezoelectricity to harvest ultrasound in vivo and to power medical implants.

Science 2019; 365: 491

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