

Interleukin-6 blockade improves autonomic dysfunction in rheumatoid arthritis

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ABSTRACT

Autonomic nervous system (ANS) involvement in rheumatoid arthritis (RA) is well recognised and contributes to arrhythmia and sudden death. However, there is no published study documenting the therapeutic efficacy on autonomic neuropathy (AN) in RA. This is the first reported observation of improvement in AN with interleukin-6 (IL-6) blockade with tocilizumab in RA. We report a case of 61-year old female with seropositive RA with severe disease activity, investigated for autonomic neuropathy. Several non invasive tests were used for accurate evaluation of AN function based on assessment of peripheral sympathetic autonomic function and cardiovascular reflex tests. Cardiovascular autonomic function tests at baseline showed marked abnormalities of parasympathetic cardiovascular reflexes. Tocilizumab 8mg/kg intravenous infusion at weeks 0, 4 and 8 was added to her treatment regimen. After the first dose of tocilizumab there was a rapid improvement with normalization of parasympathetic autonomic activity. IL-6 blockade with tocilizumab seems to have the potential to improve the vagus nerve mediated parasympathetic neuropathy and hence has the potential to restore cholinergic anti-inflammatory pathway.

Keywords: Rheumatoid arthritis; Tocilizumab; Autonomic dysfunction; Cardiovascular autonomic neuropathy.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease which affects about 1% of the general population¹. This primarily occurs in the synovium and joint tissues, with typical clinical features being swollen painful joints and stiffness. Important extra-articular features include lung and cardiovascular disease. Other organ involvement and manifestations are anemia, fatigue, skin nodules, ocular disease, splenomegaly, vasculitis, pleuropericarditis, peripheral and autonomic neuropathy (AN)². Peripheral neuropathy is particularly well recognised occurring in about 25% of patients. Autonomic nervous system (ANS) involvement in RA has been reported in several studies with varying degree of involvement between 24-100%^{3,4,5,6,7}. Recently sudomotor function estimation, which represents peripheral sympathetic autonomic function, employing novel Sudoscan has been carried out in RA, ankylosing spondylitis (AS) and psoriatic arthritis (PsA) patients^{7,8}. It is not clear why patients with RA develop autonomic dysfunction. It could result from vasculitis, amyloidosis or therapeutic side effect, circulating auto-antibodies directed against nervous structures, represented by superior cervical ganglia and vagus nerve⁴. In a recent study it was found that elevated intrathecal proinflammatory cytokine interleukin-1 β , reduces the vagus activity and interferes with the cholinergic neurotransmission in RA patients⁹. Increasing evidence has demonstrated that interleukin-6 (IL-6) is a crucial proinflammatory cytokine in the central nervous system (CNS) and pathogenesis of RA. IL-6 is important in the regulation of hepatocytes, hematopoietic progenitor cells, the skeleton, endocrine system, the placenta and the nervous and the cardiovascular systems¹⁰. IL-6 has a notorious role in neurogenesis. Moreover IL-6 was highly found in cerebrospinal fluid (CSF) of patients with systemic lupus erythematosus (SLE) with CNS involvement¹⁰.

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Tocilizumab is a humanized anti-IL-6 receptor monoclonal antibody that specifically inhibits the actions of IL-6 and it has been reported to be effective in controlling the inflammation. It has also been shown to improve endothelial dysfunction in RA^{11,12}. However, the efficacy of IL-6 inhibitor as a therapeutic agent on autonomic neuropathy in connective tissue diseases has not yet been reported. To the best of our knowledge this is first reported observation of improvement in AN with IL-6 inhibitor, tocilizumab, in RA.

CASE REPORT

We here in report a case of 61-year-old, normotensive, non diabetic and euthyroid female, with 25 years of seropositive severe RA being treated with combination of methotrexate 15 mg/week, sulphasalazine 3g/day and leflunomide 20 mg/day. The patient was investigated for AN. A battery of non invasive tests was used for accurate assessment of AN function which was based on assessment of cardiovascular reflex tests diagnosed according to Ewing¹³ and peripheral sympathetic autonomic function (Sudoscans-Impeto Medical Device, EZS 01750010193, Paris-France)¹⁴. These tests reflect both sympathetic and parasympathetic activities. Five cardiovascular reflex tests have been widely used in the assessment of cardiovascular autonomic neuropathy (CAN). They are the heart rate responses to the Valsalva manoeuvre, standing up and deep breathing, and the blood pressure responses to standing up and sustained handgrip¹³. Symptoms of ANS dysfunction were assessed by administering the

survey of autonomic symptoms¹⁵. The patient did not consume alcohol and had no other comorbidities. No other cause for neuropathy was found on biochemical screening. In particular, vitamin B12, thyroid, renal and liver functions were normal.

A detailed neurological examination was performed in the patient and was normal. Cardiovascular autonomic function tests conducted before initiation of treatment showed marked abnormalities of parasympathetic cardiovascular reflexes (Table I). There was no sympathetic and sudomotor dysfunction. The patient did not have any symptom of AN. Tocilizumab 8mg/kg intravenous infusion at weeks 0, 4 and 8 was added to her treatment regimen in view of active RA with erythrocyte sedimentation rate (ESR) of 79 mm/1st hr, C-reactive protein (CRP) of 6.8 mg/dl and Disease Activity Score in 28 joints (DAS28) score 6.13 despite treatment with combination disease modifying anti-rheumatic drugs (Table I). Autonomic function tests were repeated before every dose of tocilizumab till 12 weeks. After the first dose of tocilizumab, there was a rapid improvement in heart rate response to deep breathing and standing reflecting parasympathetic autonomic activity and these attained normal values after the second dose which was maintained until the end of observation period of 12 weeks. There was no significant change in other autonomic functions with tocilizumab therapy. ESR and CRP also normalized after the first infusion of tocilizumab and were maintained till the end of observation period of 12 weeks. DAS 28 score improved from 6.13 to 2.21 over the 12 weeks therapy with tocilizumab (Table I).

DISCUSSION

TABLE I. RESULTS OF AUTONOMIC PROFILE AND CLINICAL TESTS OF REPORTED CASE

	0 week	4 week	8 week	12 week	Normal value
HR response to deep breath (PS)	08*	10	18	17	≥15
HR response to standing (PS)	0.93*	1.0	1.06	1.06	≥1.04
HR response to Valsalva (PS)	1.26	1.24	1.24	1.23	≥1.21
BP response to standing (S)	04	02	04	04	SBP≤10
BP response to handgrip (S)	18	16	18	18	DBP≥16
Sudoscans (S)	72	64	71.5	73.5	>60 μs
ESR mm/1st hr	79	10	03	04	0-10
CRP mg/dl	6.8	0.8	0.6	0.9	<6
DAS-28	6.13	4.0	1.89	2.21	<2.5

Key: PS parasympathetic damage; S sympathetic damage; HR heart rate; SBP systolic blood pressure; DBP diastolic blood pressure; ESR erythrocyte sedimentation rate, CRP C-reactive protein, DAS-28; diseases activity score in 28 joints . * Indicates autonomic dysfunction.

We have shown that this patient with active RA, has definite involvement of cardiovascular autonomic reflexes according to Ewing, predominantly involving the parasympathetic autonomic function. Bennett and Scott in 1965 first described the involvement of autonomic nervous system in RA patients³. Later, several others have reported autonomic dysfunction in RA and other rheumatic diseases. But still the pathogenesis of ANS dysfunction in RA is poorly understood⁴⁻⁷.

In the present case, the patient had parasympathetic dysfunction in the absence of any autonomic symptoms and significant effects of tocilizumab were observed in inflammatory as well as autonomic function parameters. Though symptoms of autonomic dysfunction may be absent, nonspecific and extremely varied, diagnosis of ANS dysfunction is non invasive and is warranted in patients to prevent severe consequences including sudden death.

Vagus nerve is the major parasympathetic division of the autonomic nervous system providing constant and rapid regulation of organ function, including heart rate and gut motility. Previous results from clinical studies suggest that reduced vagus nerve activity occurs in subjects with chronic inflammatory diseases including SLE and RA^{5,9}. This hypothesis is supported by the observation that R-wave to R-wave interval variability (heart rate variability), is a marker of vagus nerve tone (that reflects parasympathetic activity) and was inversely related to levels of inflammatory markers (IL-6 and CRP) in the CARDIA (The Coronary Artery Risk Development in Young Adults) study of the evolution of risk factors in young adults¹⁶. A recent research study by David et al. also showed that cardiac autonomic imbalance, correlates with IL-6 concentrations in newly diagnosed diabetic patients¹⁷. In his review Tracey also points out a number of important clinical studies that show correlations between vagal nerve activity and inflammatory human diseases such as rheumatoid arthritis and lupus¹⁸. We assume that the improvement in autonomic function in the study subject may have resulted from the anti-inflammatory and immunological effects of tocilizumab on the CNS via the vagus nerve.

From the present case study results it appears that IL-6 inhibition with tocilizumab may also be efficacious in autonomic dysfunction of RA. It also supports the hypothesis that IL-6 may be involved in the reducing the vagus activity in RA resulting in parasympathetic autonomic dysfunction. A reduced vagal activity is likely to impair the cholinergic anti-inflammatory path-

way and conversely restoration of vagal activity improves this function. However, further study is required to prove the link between IL-6 inhibition and vagus nerve activity in RA patients.

In conclusion, we have reported a case of autonomic dysfunction in a patient with RA who was treated with tocilizumab. Although we were unable to investigate the mechanism of improvement of parasympathetic dysfunction, our findings indicate that IL-6 blockade with tocilizumab does have the potential to improve the vagus nerve mediated parasympathetic neuropathy and hence has the potential to restore cholinergic anti-inflammatory pathway in RA. Further clinical studies are needed to better evaluate the role of tocilizumab and other therapeutic molecules in the treatment of autonomic dysfunction associated with RA.

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