Effect of tumor necrosis factor inhibitors on rheumatoid arthritis-induced peripheral neuropathy

A cohort study**

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Abstract

In this historical cohort study, 236 patients with primary rheumatoid arthritis were treated with the tumor necrosis factor inhibitors, etanercept or infliximab (n = 80), or by conventional methods (n = 156). Results revealed that 11 patients developed varying types of peripheral neuropathy at 1–2 years post-treatment (mean 16 months). The incidence of peripheral neuropathy in the tumor necrosis factor inhibitors treatment group was 8.8% (7/80), which was significantly higher than the conventional treatment group (2.6%; 4/156). The relative risk of developing peripheral neuropathy in the tumor necrosis factor inhibitors treatment group was 3.41 (95% confidence interval: 1.03–11.31). Comparison of the tumor necrosis factor inhibitors revealed that etanercept and infliximab had no significant difference in terms of inducing peripheral neuropathy. Experimental findings indicate that tumor necrosis factor inhibitors may increase the risk of peripheral neuropathy.

Key Words: tumor necrosis factor inhibitors; adverse reactions; peripheral neuropathy; rheumatoid arthritis; cohort study; risk factors

Abbreviations: RA, rheumatoid arthritis; TNF, tumor necrosis factor; GBS, Guillain-Barré syndrome; MMN, multifocal motor neuropathy; CIDP, chronic inflammatory demyelinating polyradiculoneuropathy

INTRODUCTION

Tumor necrosis factor (TNF) inhibitors are important immunomodulators, which play a role in immune system development and T-cell-mediated tissue injury[1]. Such agents, especially etanercept (TNFα receptor II: IgG Fc Fusion Protein) and infliximab (monoclonal antibody against TNF-α), are widely used in China for rheumatoid arthritis (RA).

Although TNF inhibitors are generally well tolerated, there have been reports of adverse reactions, including local reactions, infections, congestive heart failure, malignancies, and autoimmune and neurological events[2]. The previous reports[3–5] suggest an etiological role for TNF inhibitors in the development of neurological disorders. Peripheral neuropathies associated with TNF inhibitor treatment include Guillain-Barré syndrome (GBS), multifocal motor neuropathy (MMN), chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), and axonal polyneuropathy[6]. The majority of previous studies regarding TNF inhibitor-induced peripheral neuropathies are limited to case reports, which cannot assess correlations between peripheral neuropathy and anti-TNF treatment systematically.

In this historical cohort study, we monitored the occurrence of peripheral neuropathy after TNF inhibitor treatment in RA patients. We sought to determine and describe the safety of using TNF inhibitors for RA by comparing the risk of developing peripheral neuropathy following treatment with the TNF inhibitors etanercept and infliximab.

RESULTS

Quantitative analysis of subjects

A total of 236 new-onset RA patients were divided into two groups according to the treatment: TNF inhibitors treatment group (n = 80) and conventional treatment group (n = 156). All RA patients were interviewed by a structured questionnaire after at least 1 year post-treatment and were involved in the analysis of results.

Baseline characteristics of subjects

The baseline characteristics of subjects in the two groups are shown in Table 1. There were no significant differences in the age, gender and disease duration between the two groups (P > 0.05).
The incidence of peripheral neuropathy after treatment

During the follow-up periods, 11 patients were diagnosed with four kinds of peripheral neuropathy (Table 2). The incidence of peripheral neuropathy in the TNF inhibitors treatment group was 8.8% (7/80), which was significantly higher than the conventional treatment group, which had an incidence of 2.6% (4/156; $\chi^2=4.55$, $P < 0.05$). The relative risk of developing peripheral neuropathy in the TNF inhibitors group was 3.41 (95% confidence interval: 1.03–11.31).

Table 2 Cases of peripheral neuropathy

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (year)</th>
<th>Gender</th>
<th>Treatment of rheumatoid arthritis</th>
<th>Type of peripheral neuropathy</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>55</td>
<td>Female</td>
<td>TNF inhibitors</td>
<td>MMN</td>
</tr>
<tr>
<td>2</td>
<td>47</td>
<td>Male</td>
<td>TNF inhibitors</td>
<td>MMN</td>
</tr>
<tr>
<td>3</td>
<td>42</td>
<td>Female</td>
<td>TNF inhibitors</td>
<td>CIDP</td>
</tr>
<tr>
<td>4</td>
<td>59</td>
<td>Male</td>
<td>TNF inhibitors</td>
<td>GBS</td>
</tr>
<tr>
<td>5</td>
<td>45</td>
<td>Male</td>
<td>TNF inhibitors</td>
<td>GBS</td>
</tr>
<tr>
<td>6</td>
<td>37</td>
<td>Male</td>
<td>TNF inhibitors</td>
<td>MMN</td>
</tr>
<tr>
<td>7</td>
<td>42</td>
<td>Female</td>
<td>TNF inhibitors</td>
<td>Axonal polyneuropathy</td>
</tr>
<tr>
<td>8</td>
<td>51</td>
<td>Female</td>
<td>Conventional methods</td>
<td>CIDP</td>
</tr>
<tr>
<td>9</td>
<td>36</td>
<td>Female</td>
<td>Conventional methods</td>
<td>MMN</td>
</tr>
<tr>
<td>10</td>
<td>45</td>
<td>Male</td>
<td>Conventional methods</td>
<td>CIDP</td>
</tr>
<tr>
<td>11</td>
<td>51</td>
<td>Female</td>
<td>Conventional methods</td>
<td>CIDP</td>
</tr>
</tbody>
</table>

TNF: Tumor necrosis factor; GBS: Guillain-Barré syndrome; MMN: multifocal motor neuropathy; CIDP: chronic inflammatory demyelinating polyradiculoneuropathy.

Comparison of peripheral neuropathy incidence between different TNF inhibitors

In the TNF inhibitors group, there was no significant difference in the incidence of peripheral neuropathy between the 52 patients treated with etanercept and the 28 patients treated with infliximab (9.6%, 5/52, vs. 7.1%, 2/28; $\chi^2=1.39$, respectively, $P > 0.05$), indicating that development of peripheral neuropathy was not dependent on the TNF inhibitor used.

DISCUSSION

TNF inhibitors are widely used as immunosuppressive agents in various medical conditions. By 2009, approximately one million patients were treated with anti-TNF agents[6], TNF inhibitors have been shown to be effective in treating rheumatologic disorders, such as RA and ankylosing spondylitis, psoriasis, and inflammatory bowel diseases[7–12]. However, peripheral neuropathies are relatively rare adverse events following anti-TNF therapy.

A 2008 review of peripheral neuropathies associated with TNF inhibitor therapy found 49 cases, encompassing GBS, MMN, CIDP, and axonal polyneuropathy[11]. All existing forms of demyelinating neuropathies, including GBS and MMN with conduction blocks, have been reported in patients receiving TNF inhibitors, especially infliximab, which is thought to be particularly immunogenic[13]. In 2006, Shin et al[14] reviewed the U.S. Food and Drug Administration database of post-marketing study commitments and found 15 patients with underlying inflammatory arthritic who developed GBS following administration of infliximab (nine cases), etanercept (five cases) or adalimumab (one case). After standard therapy, partial ($n = 9$) or complete ($n = 3$) resolution of GBS was observed in 12 of 13 patients with available follow-up. Despite the presence of antecedent events, including upper respiratory tract infections and flu-like illness in several patients, a causal relationship between anti-TNF therapy and GBS was suggested. In 2009, Lozeron et al[15] reported five additional patients who developed demyelinating neuropathies early (range 3–13 months, mean 8 months) after initiation of TNF inhibitor therapy. One patient had pure sensory neuropathy, and in the long term, some developed chronic demyelinating neuropathy[15]. CIDP can occur early or late during TNF inhibitor therapy[16–17]. Recently, a few cases of anti-TNF-induced axonal sensory and sensorimotor neuropathy and mononeuritis multiplex, including vasculitic neuropathy, have been reported[18–20]. One CIDP case was found in our study after a 15-month initiation of etanercept. Infliximab is believed to be responsible for the development of axonal neuropathy in at least two patients[21–22]. The time of onset (several days after infusion in one case and weeks after infusion in the other) argued against a direct toxic drug effect. Fairev et al[23] recently described a patient with severe acute axonal neuropathy following infliximab therapy. This patient presented with a proximal motor deficit of rapid onset in all four limbs, associated with areflexia and proprioceptive dysfunction. Nerve conduction studies and a nerve biopsy revealed neurogenic impairment without signs of demyelination. The role of TNF inhibitor therapy in the etiopathogenesis of...
Peripheral neuropathy remains to be elucidated. Both humoral and cellular immune systems are incriminated in the pathogenesis of peripheral neuropathy. Richez et al described two cases of CIDP presenting 4 and 17 months after etanercept and infliximab administration, respectively. The first case presented with serum anti-ganglioside M1 antibodies and the second with anti-ganglioside M2 antibodies. In addition, TNF antagonism may leave patients susceptible to viral infections that could secondarily induce neurological disorders.

Previous reports addressing peripheral neuropathy related to TNF inhibitors are mostly limited to case reports. In the present study, we found that the incidence of peripheral neuropathy following treatment with TNF inhibitors was significantly higher than that in the conventional treatment group. Moreover, TNF inhibitors were associated with the development of peripheral neuropathy at least 1 year after treatment using our scientific historical cohort study. Both etanercept and infliximab induced peripheral neuropathy to a similar extent. In the seven cases that had been treated with TNF inhibitors, only one patient was observed to improve, and had mild symptoms after discontinuation of TNF inhibitors, while the others recovered after immunoglobulin therapy. This result was evidence that the prognosis of peripheral neuropathy associated with TNF inhibitors is poor. At the same time, this may be due to the short observation period after discontinuation of TNF inhibitors or the treatment of peripheral neuropathy. However, some physicians do not consider demyelinating neuropathies as autoimmune diseases induced by anti-TNF agents. Moreover, not all patients are affected by an underlying auto-immune disease. Therefore, this may reinforce the drug-induced autoimmune hypothesis. Recognition of neurological symptoms as an adverse treatment effect would aid accurate diagnosis and treatment.

Despite an increasing number of descriptions regarding peripheral neuropathy secondary to anti-TNF therapy, evidence has emerged mostly from uncontrolled studies, and definite conclusions cannot yet be drawn. More accurate studies are required to evaluate the real risk of peripheral neuropathy in RA patients receiving anti-TNF therapy.

**SUBJECTS AND METHODS**

**Design**  
A historical cohort study.

**Time and setting**  
The study was performed in the Department of Rheumatology and Immunology, Shengjing Hospital Affiliated to China Medical University, China from October to December 2011.

**Subjects**  
We selected RA patients who were hospitalized at the Department of Rheumatology and Immunology in Shengjing Hospital Affiliated to China Medical University from October 2009 to October 2010. All subjects were new-onset RA patients in accordance with the American College of Rheumatology 1987 Criteria for the Diagnosis (supplementary Table 1 online).

The patients who had nervous system symptoms before their therapy were eligible. We also excluded patients with combined nutritional, metabolic, and other autoimmune, nerve entrapment, and genetic diseases and food poisoning, which could lead to peripheral neuropathy. Patients treated with a combination therapy of TNF inhibitors and conventional methods were excluded, and patients treated with glucocorticoids were not included.

A total of 236 RA patients were included in this study. The mean age of the subjects was 49.6 ± 15.3 years (range 26–69 years) and the study population comprised 150 females and 86 males. The mean disease duration from symptom onset was 9.4 ± 3.3 weeks. All study subjects signed the informed consent form.

**Methods**

**Drug interventions**

In the TNF inhibitors treatment group, 52 cases were treated with etanercept (25 mg; Shanghai Pharmaceutical (Group) Co., Ltd., Shanghai, China) twice per week, and 28 with infliximab (200 mg; CILAG AG, Schaffhausen, Swiss) twice per month. The conventional treatment methods mainly consisted of non-steroidal anti-inflammatory drugs and other disease-modifying anti-rheumatic drugs, such as leflunomide (Huitian, Sanming, Fujian, China), methotrexate (Sinepharm, Shanghai, China), and chloroquine (Zhongxi Pharm, Shanghai, China). Most of the patients received a combination therapy including at least two kinds of the above drugs. All subjects were not given preventive treatments for peripheral neuropathy, such as neurotrophic treatment.

**Incidence and intervention of peripheral neuropathy during follow-ups**

Peripheral neuropathy-associated information, particularly nervous system symptoms, was obtained in October 2011, at least 1 year after their treatment, and the mean duration was 16 months. Eleven patients who presented with significant nervous system symptoms, such as arm or leg weakness, weak tendon reflexes, abnormal sensation, and positive findings from neurophysiological examinations or nerve biopsy were diagnosed with four kinds of peripheral neuropathy as follows: (1) Four patients were diagnosed with CIDP: they all showed significant sensorimotor dysfunction, neurophysiological examination showed decreased nerve conduction velocity and prolonged distal motor
latency and partial motor nerve conduction block or disappearance of F-wave, and nerve biopsy from one patient revealed demyelination. (2) The other four patients were diagnosed with MMN; they manifested as upper limb weakness, neurophysiological examination showed multifocal motor conduction block and prolonged F-wave latency. (3) Two of the patients were diagnosed with GBS: they had rapid onset, one showed motor neuron disorder and the other one showed sensory nerve disorder, neurophysiological examination showed decreased nerve conduction velocity. (4) The remaining patient was diagnosed with axonal polyneuropathy: he showed flaccid paralysis of the limbs, and neurophysiological examination showed decreased nerve conduction velocity.

Seven of the eleven cases had been treated with TNF inhibitors, one patient with mild symptoms gradually improved after discontinuation of TNF inhibitors, and recovered after immunoglobulin (Green Cross China, Huainan, Anhui Province, China) therapy. The remaining nine cases, including four patients treated with conventional methods, had no significant disease remission after discontinuation of RA therapy and appropriate treatment. The average duration was 2 months from discontinuation of TNF inhibitors or the treatment of peripheral neuropathy to the end of our study. The following tests were normal or negative in the study population: creatinine, glucose, hepatic function tests, thyroid function tests, vitamin B12, serum immunoelectrophoresis, human immunodeficiency virus antibody and syphilis serology.

Data source

The patient’s medical records were collected using the Hospital Information System of Shengjing Hospital, China, involving the detailed treatment information on the type and dose of drugs during hospitalization. Patients were interviewed by three trained investigators, using a structured questionnaire during October 2011. The survey sought to ascertain nervous system symptoms after treatment and the duration from initiation of the treatment to the emergence of symptoms, as well as detailed diagnostic and treatment information of peripheral neuropathy such as the result of neurophysiological examination, nerve biopsy and treatment prognosis.

Statistical analysis

Data analyses were performed with SPSS 17.0 statistical software (SPSS, Chicago, IL, USA). The associations between the treatment with TNF inhibitors and the risk of peripheral neuropathy were analyzed by Pearson’s chi-square test to estimate the relative risk and 95% confidence intervals. The comparison between etanercept and infliximab was conducted by the same method. The descriptive variables were expressed as mean ± SD. A P value less than 0.05 was considered statistically significant.

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Author contributions: Naizhi Wang was responsible for the study proposal, design, operation, data acquisition, and wrote the manuscript. Ning Zhang was responsible for funding and validation of the study, and also serves as the corresponding author. Yingying Guo, Lili Yang, Wenyi Fu, Yanbing Xu, Linxin Hou, and Shuai Zhao participated in study implementation.

Conflicts of interest: None declared.

Ethical approval: This study was approved by the Ethics Committee of China Medical University in China.

Supplementary information: Supplementary data associated with this article can be found, in the online version, by visiting www.nrronline.org, and entering Vol. 7, No. 11, 2012 item after selecting the “NRR Current Issue” button on the page.

REFERENCES


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