Case Report

Three Cases of Previous Smokers with Rheumatoid Arthritis Who Did Not Respond to Tumor Necrosis Factor Inhibitors Were Treated Successfully with an Anti-Interleukin-6 Receptor Antibody

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Received 13 October 2014; Accepted 12 December 2014

Academic Editor: Suleyman Serdar Koca

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We report three cases of previous smokers who did not respond to TNF inhibitors but who responded successfully to an anti-interleukin-6 receptor antibody (tocilizumab [TCZ]). Case 1 is a 63-year-old woman whose smoking index was 200 and had been complaining of polyarthralgia since 1996. She started treatment with etanercept due to high disease activity, but her DAS28-CRP was 4.2. She was therefore switched to TCZ, which dramatically improved her symptoms; her DAS28-CRP had decreased to 2.1. Case 2 is a 64-year-old man whose smoking index was 1600 and had been complaining of polyarthralgia since 2006. Because his DAS28-CRP score increased over time to 5.9, etanercept and adalimumab were added sequentially, but he showed no response over the course of two years. The patient was therefore switched to TCZ, which dramatically improved his symptoms: his DAS28-CRP decreased to 2.7. Case 3 is a 48-year-old woman whose smoking index was 560 and had been complaining of pain in both knee joints since 2001. She was treated with adalimumab due to high disease activity but showed no response over the course of 1.5 years. The patient was therefore switched to TCZ, and her DAS28-CRP decreased to 1.8. An IL-6 blockade might be suitable for treating these 3 cases of previous smokers.

1. Introduction

Tumor necrosis factor (TNF) inhibitors represent an important advance in therapy for rheumatoid arthritis (RA). RA patients who smoke, however, are reported to be less likely to respond to treatment with TNF inhibitors [1–4]. This report presents three cases of smokers who did not respond to TNF inhibitors but who responded successfully to an anti-interleukin-6 receptor antibody (tocilizumab [TCZ]).

2. A Case Report

Case 1 is a 63-year-old woman whose smoking index was 200 (10 cigarettes/day × 20 years) (Table 1) and had been complaining of polyarthralgia since 1996. She could not take methotrexate due to the adverse effects of liver dysfunction and hair loss. During treatment for RA, she was able to quit smoking as per our instructions. Two years after her first visit, the lateral tibial condyle of her right knee joint collapsed. As a result, she underwent total knee arthroplasty. She started treatment with the TNF inhibitor etanercept due to high disease activity (Disease Activity Score assessing 28 joints with C-reactive protein [DAS28-CRP] was 4) 1.5 years after cessation of smoking but showed no response. Two years after starting this medication, her DAS28-CRP was 4.2 and her MMP-3 was 405 ng/mL. The patient was therefore switched to TCZ (8 mg/kg monthly), which dramatically improved her symptoms. Six months after switching to TCZ, her DAS28-CRP had decreased to less than 2.3 and her MMP-3 had decreased from 405 to less than 59.7 ng/mL (Figure 1). She has satisfied the Boolean-based definition for over 10 months after the cessation of the TCZ therapy. Recent radiograms of the involved joints show nonprogression.

Case 2 is a 64-year-old man whose smoking index was 1600 (40 cigarettes/day × 40 years) (Table 1) and had been complaining of polyarthralgia since 2006. He did not respond...
### Table 1: Characteristics of patients.

|                      | Case 1           | Case 2           | Case 3           |
|----------------------|------------------|------------------|------------------|
| **Sex**              | Female           | Male             | Female           |
| **Age (years)**      | 63               | 64               | 48               |
| **Disease duration (years)** | 12              | 6               | 8               |
| **Smoking index**    | 200 (10 cigarettes/day × 20 years) | 1600 (40 cigarettes/day × 40 years) | 560 (20 cigarettes/day × 28 years) |
| **2010 ACR/EULAR classification** | Satisfied | Satisfied | Satisfied |
| **Laboratory results** |                   |                   |                   |
| RF                   | 73.8 U/mL        | 60.0 U/mL        | 26.0 U/mL        |
| ACPA                 | 4.4 U/mL         | 150.0 U/mL       | 128.6 U/mL       |
| CRP                  | 2.9 mg/dL        | 1.5 mg/dL        | 0.07 mg/dL       |
| WBC                  | 11500/μL         | 8600/μL          | 12400/μL         |
| MMP-3                | 698.7 ng/mL      | 148.1 ng/mL      | 179.5 ng/mL      |
| Platelet             | 37.1 × 10^4/μL   | 35.0 × 10^4/μL   | 42.1 × 10^4/μL   |
| **Steinbrocker's roentgenographic classification** | Stage IV | Stage III | Stage III |
| **Functional status according to Steinbrocker's revised criteria** | Class II | Class II | Class II |
| **Previous treatment: type and dosage (duration in months)** | Etanercept 50 mg/week (26) | Adalimumab 40 mg/2 weeks (4) | Adalimumab 40 mg/2 weeks (4) |
|                     | Prednisolone 3 mg/day (62) | Methotrexate 8 mg/week (72) | Methotrexate 6 mg/week (72) |
|                     | Bucillamine 200 mg/day (52) | Prednisolone 5 mg/day (36) | Prednisolone 9 mg/day (36) |
|                     |                   | Bucillamine 200 mg/day (48) | Salazosulfapyridine 1000 mg/day |
|                     |                   | Gold sodium thiomalate | (6) |
|                     |                   | 10 mg/week (24) | MPM-3 |
|                     |                   | MIZORIBINE 150 mg/day (18) | 385.9 ng/mL |
| **Time (months) to remission of arthritis** | 11               | 16               | 1               |
| DAS28-CRP < 2.3      |                   |                   |                   |

RF: rheumatoid factor; ACPA: anti-cyclic citrullinated peptide antibody; CRP: C-reactive protein; WBC: white blood cell count; MMP-3: matrix metalloproteinase-3.

Case 3 is a 48-year-old woman whose smoking index was 560 (20 cigarettes/day × 28 years) (Table 1) and had been complaining of pain in both knee joints since 2001. She was initially treated with a combination of prednisolone (10 mg/day) and methotrexate (8 mg/week) but did not respond to these medications despite the fact that she was simultaneously undergoing smoking cessation treatment. She was then switched to treatment with adalimumab (40 mg/2 weeks) due to high disease activity 2 months after she quit smoking but showed no response to the new medication over the course of 1.5 years. The patient was therefore switched to TCZ (8 mg/kg monthly), which dramatically improved her symptoms. After a single drip infusion of TCZ, her DAS28-CRP decreased to 1.8 and her MMP-3 decreased to 59.5 ng/mL (Figure 3). She has since satisfied the Boolean-based definition for 5 months. The latest radiographic examination of the involved joints showed no progression of bone erosion.

### 3. Discussion

Papadopoulos defined a previous smoker as a person who had stopped smoking for at least one year [5]. Cases 2 and 3 were treated with biologics in less than 3 months after smoking cessation; these two cases could therefore be considered current smokers. For case 1 who had smoked for 20 years, the influence of smoking was assumed to exist although etanercept was initiated 1.5 years after quitting smoking. It is said that even if quitting smoking can be achieved, it takes...
The three cases presented herein were effective for the treatment of RA in current and previous smokers [1–4]. It is reasonable to assume that TCZ was effective for her RA. A high DAS28-CRP (Disease Activity Score assessing 28 joints with C-reactive protein) was observed before the administration of TCZ. After a single drip infusion of TCZ, the DAS28-CRP decreased to 1.8. It is also refractory to anti-TNF agents, although the patients had stopped smoking before the administration of anti-TNF agents. The SAMURAI study demonstrated efficacy in patients with RA treated with TCZ monotherapy [8]. Patients with multidrug refractory adult onset Still’s disease (AOSD) were successfully treated with TCZ [9–13].

The relationship between cigarette smoking and the improved response to TCZ probably likely has several explanations. In terms of the relation between smoking and periodontitis, smoking is a major risk factor for periodontitis [14–16]. Sites from refractory patient with periodontitis produced significantly more IL-6 [17]. Fibroblasts from periodontal lesions in vitro produce greater amounts of IL-6 and IL-8 constitutively than healthy controls [18]. In periodontitis stroma, increased citrullinated protein presence (80%) was observed compared with control stroma (33%). Western blotting with monoclonal (F95) antibody to citrullinated proteins revealed the presence of similar citrullinated proteins in both periodontitis and RA-affected synovial tissue [19]. These three cases did not complain of oral problems. There are some reports on the relationship between IL-6 in the lungs and smoking. Higher IL-6 and exhaled carbon monoxide (CO) concentrations were found in the exhaled breath condensate of smokers than in that of nonsmokers. In addition, there was a correlation between IL-6 concentrations, number of cigarettes smoked per day, exhaled CO, leukotriene, and lung function [20]. In bronchoalveolar lavage (BAL), statistically greater concentrations of neutrophils, macrophages, IL-1 beta, IL-6, IL-8, and monocyte chemotactic protein-1 (MCP-1) were observed among smokers compared with nonsmokers [21]. Smoking increases peptidylarginine deiminase 2 enzyme expression in the human lungs and increases citrullination in BAL cells [22]. Snelgrove reported that cigarette smoke selectively inhibited leukotriene A(4) hydro-lase aminopeptidase activity, which led to the accumulation after the cessation of smoking.
of the neutrophil chemoattractant proline-glycine-proline and neutrophils, and made inflammation become chronic such as chronic obstructive pulmonary disease (COPD) and cystic fibrosis [23]. Cigarette smoke induces proinflammatory cytokines and chemokines, including IL-1 β, and IL-6 from synovial fibroblast-like cells (SFCs) [24]. And blood leukocytes, platelets, C-reactive protein (CRP), and fibrinogen were reported to be significantly high in smokers [25]. Mean platelet volume increased significantly with acute exposure to smoking [26]. IL-6 stimulates thrombopoiesis through thrombopoietin [27], and IL-6 activates platelets [28]. Boilard et al. surveyed the capacity of collagen-stimulated human platelet microparticles (MPs) to elicit a range of cytokines et al. [29]. Therefore, the positive feedback of IL-6 through fibroblast-like synoviocytes and platelets is formed in the human body. In this case report, cases 1 and 3 showed elevation of platelet count.

Smoking is an established risk factor of RA and may cause prominent production of cytokines especially IL-6 (as described above). An IL-6 blockade might be suitable for treating these 3 cases. But this is a case report; however, further study of a large series of cases is required to determine the efficacy of an IL-6 blockade for patients with RA who smoke.

**Conflict of Interests**

The author declares that there is no conflict of interests regarding the publication of this paper.

**References**

[1] D. L. Mattey, A. Brownfield, and P. T. Dawes, “Relationship between pack-year history of smoking and response to tumor necrosis factor antagonists in patients with rheumatoid arthritis,” *Journal of Rheumatology*, vol. 36, no. 6, pp. 1180–1187, 2009.

[2] A. Abhishek, S. Butt, K. Gadsby, W. Zhang, and C. M. Deighton, “Anti-TNF-α agents are less effective for the treatment of rheumatoid arthritis in current smokers,” *Journal of Clinical Rheumatology*, vol. 16, no. 1, pp. 15–18, 2010.

[3] S. Saevarsdottir, S. Wedren, M. Seddighzadeh et al., “Patients with early rheumatoid arthritis who smoke are less likely to respond to treatment with methotrexate and tumor necrosis factor inhibitors: observations from the epidemiological investigation of rheumatoid arthritis and the Swedish rheumatology register cohorts,” *Arthritis and Rheumatism*, vol. 63, no. 1, pp. 26–36, 2011.

[4] M. K. Söderlin, I. F. Pettersson, and P. Geborek, “The effect of smoking on response and drug survival in rheumatoid arthritis patients treated with their first anti-TNF drug,” *Scandinavian Journal of Rheumatology*, vol. 41, no. 1, pp. 1–9, 2012.

[5] N. G. Papadopoulos, Y. Alamanos, P. V. Voulgaris, E. K. Epagelis, N. Tsifetaki, and A. A. Drosos, “Does cigarette smoking influence disease expression, activity and severity in early rheumatoid arthritis patients?” *Clinical and Experimental Rheumatology*, vol. 23, no. 6, pp. 861–866, 2005.

[6] S. Musich, S. D. Faruzzi, C. Liu, T. McDonald, D. Hirschland, and D. W. Edington, “Pattern of medical charges after quitting smoking among those with and without arthritis, allergies, or back pain,” *The American Journal of Health Promotion*, vol. 18, no. 2, pp. 133–142, 2003.

[7] E. W. Karlson, I. M. Lee, N. R. Cook, J. E. Buring, and C. H. Hennekens, “A retrospective cohort study of cigarette smoking and risk of rheumatoid arthritis in female health professionals,” *Arthritis & Rheumatism*, vol. 42, no. 5, pp. 910–917, 1999.

[8] N. Nishimoto, J. Hashimoto, N. Miyasaka et al., “Study of active controlled monotherapy for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab,” *Annals of the Rheumatic Diseases*, vol. 66, no. 9, pp. 1162–1167, 2007.

[9] M. de Bandt and B. Saint-Marcoux, “Tocilizumab for multirefractory adult-onset Still's disease,” *Annals of the Rheumatic Diseases*, vol. 68, no. 1, pp. 153–154, 2009.

[10] K. Matsumoto, T. Nagashima, S. Takatori et al., “Glucocorticoid and cyclosporine refractory adult onset Still's disease successfully treated with tocilizumab,” *Clinical Rheumatology*, vol. 28, no. 4, pp. 485–487, 2009.

[11] M. Yoshimura, J. Makiyama, T. Koga et al., “Successful treatment with tocilizumab in a patient with refractory adult-onset Still's disease (AOSD),” *Clinical and Experimental Rheumatology*, vol. 28, no. 1, pp. 141–142, 2010.

[12] K. Perdan-Pirkmajer, S. Praprotnik, and M. Tomšič, “A case of refractory adult-onset Still's disease successfully controlled with tocilizumab and a review of the literature,” *Clinical Rheumatology*, vol. 29, no. 12, pp. 1465–1467, 2010.

[13] J. Rech, M. Ronneberger, M. Englbrecth et al., “Successful treatment of adult-onset Still's disease refractory to TNF and IL-1 blockade by IL-6 receptor blockade,” *Annals of the Rheumatic Diseases*, vol. 70, no. 2, pp. 390–392, 2011.

[14] S. L. Tomar and S. Asma, “Smoking-attributable periodontitis in the United States: findings from NHANES III,” *Journal of Periodontology*, vol. 71, no. 5, pp. 743–751, 2000.

[15] B. H. Mullally, “The influence of tobacco smoking on the onset of periodontitis in young persons,” *Tobacco Induced Diseases*, vol. 15, no. 2, pp. 53–65, 2004.

[16] Y. Yamamoto, N. Nishida, M. Tanaka et al., “Association between passive and active smoking evaluated by salivary cotinine and periodontitis,” *Journal of Clinical Periodontology*, vol. 32, no. 10, pp. 1041–1046, 2005.

[17] R. A. Reinhardt, M. P. Masada, W. B. Kaldahl et al., “Gingival fluid IL-1 and IL-6 levels in refractory periodontitis,” *Journal of Clinical Periodontology*, vol. 20, no. 3, pp. 225–231, 1993.

[18] A. I. Dongari-Bagtzoglou and J. L. Ebersole, “Increased presence of interleukin-6 (IL-6) and IL-8 secreting fibroblast subpopulations in adult periodontitis,” *Journal of Periodontology*, vol. 69, no. 8, pp. 899–910, 1998.

[19] W. Nesse, J. Westra, J. E. van der Wal et al., “The periodontium of periodontitis patients contains citrullinated proteins which may play a role in ACPA (anti-citrullinated protein antibody) formation,” *Journal of Clinical Periodontology*, vol. 39, no. 7, pp. 599–607, 2012.

[20] G. E. Carpagnano, S. A. Kharitonov, M. P. Foschino-Barbaro, O. Resta, E. Gramiccioni, and P. J. Barnes, “Increase inflammatory markers in the exhaled breath condensate of cigarette smokers,” *The European Respiratory Journal*, vol. 21, no. 4, pp. 589–593, 2003.
[21] W. G. Kuschner, A. D’Alessandro, H. Wong, and P. D. Blanc, "Dose-dependent cigarette smoking-related inflammatory responses in healthy adults," *European Respiratory Journal*, vol. 9, no. 10, pp. 1989–1994, 1996.

[22] D. Makrygiannakis, M. Hermansson, A.-K. Ulfgren et al., "Smoking increases peptidylarginine deiminase 2 enzyme expression in human lungs and increases citrullination in BAL cells," *Annals of the Rheumatic Diseases*, vol. 67, no. 10, pp. 1488–1492, 2008.

[23] R. J. Snelgrove, P. L. Jackson, M. T. Hardison et al., "A critical role for LTA4H in limiting chronic pulmonary neutrophilic inflammation," *Science*, vol. 330, no. 6000, pp. 90–94, 2010.

[24] M. Shizu, Y. Itoh, R. Sunahara et al., "Cigarette smoke condensate upregulates the gene and protein expression of proinflammatory cytokines in human fibroblast-like synoviocyte line," *Journal of Interferon and Cytokine Research*, vol. 28, no. 8, pp. 509–521, 2007.

[25] H. Yasue, N. Hirai, Y. Mizuno et al., "Low-grade inflammation, thrombogenicity, and atherogenic lipid profile in cigarette smokers," *Circulation Journal*, vol. 70, no. 1, pp. 8–13, 2006.

[26] M. Yarlioglues, I. Ardic, O. Dogdu et al., "The acute effects of passive smoking on mean platelet volume in healthy volunteers," *Angiology*, vol. 63, no. 5, pp. 353–357, 2012.

[27] A. Kaser, G. Brandacher, W. Steurer et al., "Interleukin-6 stimulates thrombopoiesis through thrombopoietin: role in inflammatory thrombocytosis," *Blood*, vol. 98, no. 9, pp. 2720–2725, 2001.

[28] L. Oleksowicz, Z. Mrowiec, D. Zuckerman, R. Isaacs, J. Dutcher, and E. Puszkin, "Platelet activation induced by interleukin-6: evidence for a mechanism involving arachidonic acid metabolism," *Thrombosis and Haemostasis*, vol. 72, no. 2, pp. 302–308, 1994.

[29] E. Boilard, P. A. Nigrovic, K. Larabee et al., "Platelets amplify inflammation in arthritis via collagen-dependent microparticle production," *Science*, vol. 327, no. 5965, pp. 580–583, 2010.