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CONCISE COMMUNICATION

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Anti-adalimumab antibodies in rheumatoid arthritis patients are associated with interleukin-10 gene polymorphisms

Inadequate response to tumor necrosis factor α (TNFα)–blocking therapy in rheumatoid arthritis (RA) may result from the formation of antibodies against these drugs (1). Previous studies have shown that polymorphisms in the promoter region of the gene for interleukin-10 (IL-10), a cytokine with a key role in antibody formation, are associated with the formation of antibodies that inhibit recombinant factor VIII (FVIII) in hemophilia (2) and with the development of autoantibodies against nicotinic acetylcholine receptor (nAChR) in myasthenia gravis (MG) (3). We hypothesized that polymorphisms in *IL10* are also associated with the formation of antibodies against anti-TNFα agents.

To test this hypothesis, the presence of anti-adalimumab antibodies was determined in a prospective study of 192 white patients with RA according to the criteria of the American College of Rheumatology (formerly, the American Rheumatism Association) (4). Patients had been treated with adalimumab (40 mg subcutaneously/every other week) in combination with methotrexate (mean dosage 20 mg/week), and the presence of antibodies was determined 28 weeks after initiation of treatment with adalimumab (1). Three single-nucleotide polymorphisms (SNPs) in the promoter region of the IL-10 gene (rs1800871 at −819, rs1800896 at −1082, and rs6703630 at −2849) were typed using TaqMan technology (Applied Biosystems, Foster City, CA), and odds ratios (ORs) and 95% confidence intervals (95% CIs) were calculated. The study was approved by the local Medical Ethics Committee.

Anti-adalimumab antibodies were present in 25 of the 192 patients (13%) and were associated with nonresponse according to the European League Against Rheumatism criteria (5) after 28 weeks of treatment with adalimumab (OR 4.05 [95% CI 1.69–9.73], $P = 0.001$) (43 of the patients [22%] did not exhibit treatment response). Furthermore, the −1082 AA genotype was strongly associated with a significantly lower frequency of anti-adalimumab antibodies (OR 0.05 [95% CI 0.003–0.86], $P = 0.001$) (Table 1). However, we did not find an association between the AA genotype and response to adalimumab ($P = 0.35$).

Four haplotypes were inferred using Phase 2.0 (http://www.stat.washington.edu/stephens/software.html) with an average probability of certainty in haplotype inference of 99%. Carriage of the GAT haplotype (alleles at positions −2849, −1082, and −819) showed a significant negative association with anti-adalimumab antibodies ($P = 0.004$), and carriage of the AGC haplotype showed a positive association with anti-adalimumab antibodies ($P = 0.041$). Unlike haplotype GAC ($P = 0.860$), a positive trend toward carriage of haplotype GGC was found ($P = 0.063$). Based on microsatellite SNP haplotypes reported in a Dutch population (6), our observations are consistent with the reported association of the G8 microsatellite allele with formation of antibodies to recombinant FVIII in hemophilia (2) and to nAChR in MG (3).

Table 1. *IL10* promoter polymorphisms and anti-adalimumab antibodies in the 192 rheumatoid arthritis study patients*

SNP, genotype	Anti-adalimumab antibodies: No. (%) negative (n = 167)	Anti-adalimumab antibodies: No. (%) positive (n = 25)	OR (95% CI)	*P*
−2849				
AA or GA	78 (47)	17 (68)		
GG	89 (53)	8 (32)	0.41 (0.17–1.01)	0.05
−1082				
GG or GA	121 (73)	25 (100)		
AA	46 (28)	0 (0)	0.05 (0.003–0.86)	0.001
−819				
TT or TC	77 (46)	4 (16)		
CC	90 (54)	21 (84)	4.49 (1.48–13.65)	0.004

* SNP = single-nucleotide polymorphism; OR = odds ratio; 95% CI = 95% confidence interval.

In conclusion, our results indicate that *IL10* polymorphisms are associated with increased formation of antibodies against adalimumab in RA patients. Additional studies utilizing larger groups of patients are needed to confirm our findings.

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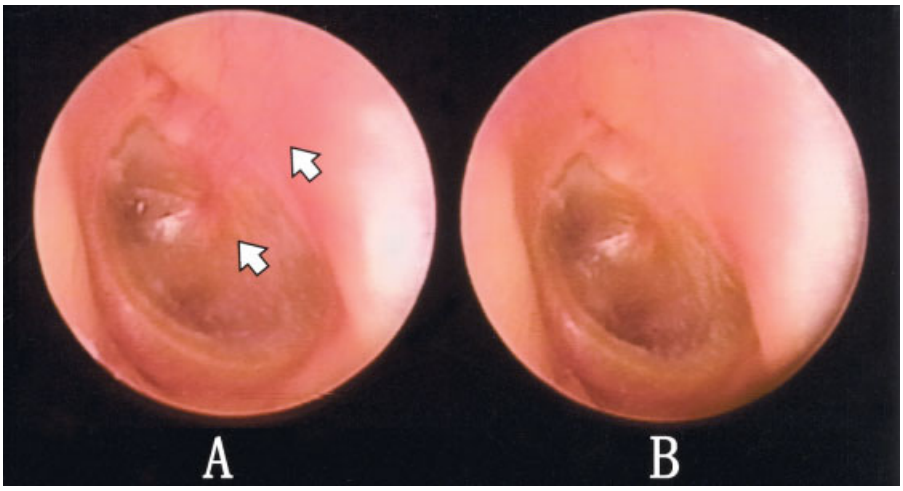
Clinical Images: Otalgia, an unusual complication of Sjögren's syndrome



The patient, a 54-year-old woman with Sjögren's syndrome with sicca symptoms, peripheral neuropathy, and somatic patchydyshidrosis, developed otalgia in her left ear. The leukocyte count, C-reactive protein level, and erythrocyte sedimentation rate were all normal, and the patient was negative for antinuclear, anticardiolipin, antineutrophil cytoplasmic, and anti–type II collagen antibodies. The left auricle was painful but not inflamed. However, reddening and dilated capillaries in the left auditory meatus and eardrum were found (**A**) (**arrows**), resulting in otitis externa and myringitis. Steroid therapy relieved the pain, as well as the otitis externa and myringitis (**B**) to some extent, and the associated sensorineural hearing loss also resolved. Over the last several years, the patient's otalgia has recurred in cycles that have paralleled the worsening and improvement of the symptoms and signs of her Sjögren's syndrome, but systemic inflammation has not occurred.

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