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Original article

Higher body mass index and anti-drug antibodies predict the discontinuation of anti-TNF agents in Korean patients with axial spondyloarthritis

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ABSTRACT

Objective: The development of anti-drug antibodies against tumor necrosis factor inhibitors is a likely explanation for the failure of TNF-inhibitors in patients with spondyloarthritis. Our study determined the existence and clinical implications of ADAbs in axial spondyloarthritis patients.

Methods: According to the Assessment of SpondyloArthritis International Society classification criteria for axial spondyloarthritis, patients treated with adalimumab or infliximab were recruited consecutively. Serum samples were collected at enrollment to measure anti-drug antibodies and drug levels.

Results: Of 100 patients, the mean duration of current TNF inhibitor use was 22.3 ± 17.9 months. Anti-drug antibodies were detected in 5 of 72 adalimumab users compared to 5 of 28 infliximab users (6.9% vs. 17.9%). Anti-drug antibodies-positive patients had a significantly higher body mass index than anti-drug antibodies-negative patients among both adalimumab (28.4 ± 5.9 kg/m^2 vs. 24.3 ± 2.9 kg/m^2, respectively, $p = 0.01$) and infliximab users (25.9 ± 2.8 kg/m^2 vs. 22.6 ± 2.8 kg/m^2, respectively, $p = 0.02$). During the median 15-month follow-up period, drug discontinuation occurred more frequently in the anti-drug antibodies-positive group than the anti-drug antibodies-negative group (30.0% vs. 6.5%, respectively, $p = 0.04$). In logistic regression, anti-drug antibodies positivity (OR = 5.85, 95% CI 1.19–28.61, $p = 0.029$) and body mass index (OR = 4.35, 95% CI 1.01–18.69, $p = 0.048$) were associated with a greater risk of stopping TNF inhibitor treatment.

Conclusions: Our result suggests that the presence of anti-drug antibodies against adalimumab and infliximab as well as a higher body mass index can predict subsequent drug discontinuation in axial spondyloarthritis patients.

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O maior índice de massa corporal e a presença de anticorpos antifármacos predizem a interrupção no uso de agentes anti-TNF em pacientes sul-coreanos com espondiloartrite axial

Palavras-chave:
Adalimumabe
Anticorpos antifármacos
Espondiloartrite axial
Infliximabe
Inibidores da necrose tumoral

RESUMO

Objetivo: O desenvolvimento de anticorpos antifármacos (ADAb) contra o fator de necrose tumoral (TNF) é uma explicação provável para a falha dos anti-TNF em pacientes com espondiloartrites (EspA). O presente estudo determinou a presença e as implicações clínicas dos ADAb em pacientes com EspA axiais.

Métodos: De acordo com os critérios de classificação para EspA axial da *Assessment of SpondyloArthritis International Society*, recrutaram-se consecutivamente pacientes tratados com adalimumabe ou infliximabe. Coletaram-se amostras de soro no momento da entrada no estudo para medir os níveis de ADAb e de fármaco.

Resultados: Dos 100 pacientes, a duração média de uso dos anti-TNF atuais foi de 22,3 ± 17,9 meses. Os ADAb foram detectados em cinco de 72 pacientes em uso de adalimumabe, em comparação com cinco de 28 usuários de infliximabe (6,9% *vs.* 17,9%). Os pacientes ADAb-positivos tinham um índice de massa corporal maior do que aqueles ADAb-negativos, tanto entre indivíduos em uso de adalimumabe (28,4 ± 5,9 kg/m^2 *vs.* 24,3 ± 2,9 kg/m^2, respectivamente, p = 0,01) quanto de infliximabe (25,9 ± 2,8 kg/m^2 *vs.* 22,6 ± 2,8 kg/m^2 respectivamente, p = 0,02). Durante o período médio de seguimento de 15 meses, a suspensão do fármaco ocorreu com maior frequência no grupo ADAb-positivo do que no grupo ADAb-negativo (30,0% *vs.* 6,5%, respectivamente, p = 0,04). Na regressão logística, a positividade no ADAb (OR = 5,85, IC 95% 1,19 a 28,61, p = 0,029) e o IMC (OR = 4,35, IC 95% 1,01 a 18,69, p = 0,048) esteve associada a um maior risco de interromper o tratamento com anti-TNF.

Conclusões: Os resultados do presente estudo sugerem que a presença de ADAb contra o adalimumabe e o infliximabe, bem como um IMC mais alto, pode predizer a subsequente interrupção do fármaco em pacientes com EspA axial.

Introduction

The advent of tumor necrosis factor (TNF) inhibitors represented a breakthrough in the management of chronic inflammatory diseases such as rheumatoid arthritis (RA), spondyloarthritis (SpA), psoriasis, and inflammatory bowel disease (IBD). Not only ankylosing spondylitis (AS), but also the non-radiographic form of axial SpA have benefitted from these drugs with response rates of 60–70%.[1–3] Regardless, a considerable proportion of SpA patients fail to respond ab initio (primary failure), or the inhibitors lose their efficacy over time despite an initial good response (secondary failure).[4,5] Some patients may also need to discontinue TNF inhibitor treatment due to significant adverse events.[6]

Recently, immunogenicity has been implicated as a primary cause of response failure, because all biologics, including TNF inhibitors, have immunogenic potential. The development of anti-drug antibodies (ADAbs) leads to low or undetectable drug levels, resulting in the failure or loss of efficacy of the drug and adverse events; this phenomenon has been well documented in patients with RA and Crohn's disease (CD).[7,8] To date, ADAbs have been detected against infliximab (IFX), adalimumab (ADL), and golimumab (GLM) in SpA patients and there are several reports about the associations of these ADAbs with clinical response.[9] In addition to ADAbs, there are other factors that affect the pharmacokinetics of TNF inhibitors, such as concomitant use of disease-modifying antirheumatic drugs (DMARDs), especially methotrexate, the degree of systemic inflammation (e.g., serum albumin, C-reactive protein, and TNF burden), body weight, and gender.[10] Historically, in the meantime, ADAbs against IFX were more often observed in RA patients compared to AS patients. It was thought to be higher doses of IFX used in axial SpA patients.[11] Established combination therapy with biologic agent and immunomodulators has also been described to prevent the development of ADAbs in patients with RA and CD as well.[12,13] With respect to DMARDs, there is no solid evidence to support their use in axial SpA.

Previous studies of ADAbs in SpA patients have focused mostly on the incidence of ADAbs and their effects in western populations. We undertook the present study to investigate whether ADAbs exist in Korean patients with axial SpA and the clinical significance of this. Additionally, we investigated whether factors such as body weight and smoking affected ADAb levels in Korean SpA patients.

Methods

Study design and patients

This study was performed in an ambispective observational manner. From May 2012 to April 2013, a total of 100 axial

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