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Infliximab and etanercept have distinct actions but similar effects on cytokine profiles in rheumatoid arthritis

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ABSTRACT

Objective: Pro-inflammatory cytokines, especially TNFα, play a central role in the pathogenesis of rheumatoid arthritis (RA). The available TNF inhibitors are only slightly different from one another in terms of clinical efficacy, at least at the group level, but their structures and modes of action are not identical. Infliximab (IFX) and etanercept (ETN) differ in their ability to induce antibody-dependent cellular cytotoxicity and complement-dependent cytotoxicity, and in their ability to bind TNFβ. The purpose of our study was to elucidate the different cytokine pathways through which these two drugs enact their clinical efficacy.

Methods: Serum from 44 RA patients treated with IFX and 24 patients treated with ETN was studied. All patients had been given these biologics at identical dosages and intervals for one year. The concentrations of 11 inflammatory cytokines and their receptors (IL-1β, IL-2, IL-6, IL-6R, IL-8, IL-10, IL-12, TNFα, TNFβ, IFNγ, and GM-CSF) were measured at weeks 0, 22, and 54 using a high-sensitivity electro-chemiluminescence assay. Cytokine profiles were analyzed along with clinical efficacy.

Results: IL-6 was significantly decreased in the ETN + MTX and IFX + MTX groups, although not in the ETN-only group; this change was consistent with changes in disease activity. IFNγ was gradually increased only in the non-remission subgroup of the IFX group, and not at all in the ETN group. TNFβ increased after starting IFX regardless of clinical efficacy.

Conclusion: IL-6 inhibition is a pathway affected by both IFX and ETN. In addition, IFNγ increase is a distinctive feature of the inefficacy of IFX.

1. Introduction

Rheumatoid arthritis (RA) is an autoimmune disease characterized by chronic joint destruction. Pro-inflammatory cytokines are thought to be involved in its pathogenesis [1,2]. TNFα and IL-6 play particularly central roles, and biologics targeting them have high efficacy. Several TNF inhibitors are available for clinical use, including infliximab (IFX), etanercept (ETN), adalimumab, golimumab, and certolizumab pegol, and their clinical efficacies are similar, at least on a group level [3]. Accordingly, a widely used treatment guideline recommends all of them in the same line [4].

Yet the structures and modes of action of these TNF inhibitors are not the same: IFX, adalimumab, golimumab, and certolizumab pegol are monoclonal antibodies or their derivatives, while ETN is a fusion protein composed of a human IgG1 Fc fragment and two extracellular portions of TNF receptor 2. Anti-TNFα antibody, which has been particularly well-studied with regard to IFX and ADA, binds only to TNFα [5], and has antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). The peak serum concentrations of these drugs are higher than that of ETN [6]. ETN, on the other hand, binds to both TNFα

Abbreviations: RA, rheumatoid arthritis; IFX, infliximab; ETN, etanercept; ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytotoxicity; CCP, cyclic citrullinated peptide; RF, rheumatoid factor; MMP-3, matrix-metalloproteinase-3; DAS28-ESR, disease activity score in 28 joints based on the erythrocyte sedimentation rate; HAQ-DI, health assessment questionnaire-disability index; LDA, low disease activity; MDA, moderate disease activity; HDA, high disease activity; MTX, methotrexate; ΔmTSS, modified total sharp score/year.

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and TNFβ as a decoy receptor [7]. TNFβ is a pro-inflammatory cytokine, considered to have almost the same effect as TNFα [8].

Few reports to date have indicated the significance of TNFβ in RA. One paper reported a patient whose RA pathogenesis seemed to depend more on TNFβ than on TNFα [9], and another group showed that TNFβ as well as TNFα was expressed at the RA synovial membrane and that both of these were suppressed by ETN treatment [10]. The role of TNFβ in RA has not been elucidated in detail.

We have previously shown that the suppression of both TNFα and IL-6 is associated with better clinical response in IFX treatment [11]. Other groups have reported that ETN treatment reduces serum IL-6 [12–14], but there has been no direct comparison of these two TNF inhibitors in terms of cytokine profiles and clinical responses. We performed longitudinal measurements of serum proinflammatory cytokines in biologics-naïve RA patients, and analyzed the relationship between cytokine profile and clinical effectiveness.

2. Materials and methods

2.1. Patients and study protocol

Patients with RA refractory to non-biological disease modified anti-rheumatic-drugs who received ETN or IFX at the Saitama Medical Center were recruited for this study. A total of 68 patients who had stored serum samples from weeks 0, 22, and 54 of treatment and who agreed to participate in this study were enrolled. All patients met the American College of Rheumatology criteria for RA [15]. ETN was administered at 50 mg a week, and IFX was administered at 3 mg/kg weight every eight weeks after loading at weeks 0, 2, and 6. Because only ETN and IFX were approved as biologics for RA at that time, no patients changed their treatment during the 54-week study period.

2.2. Laboratory test values and serum cytokine measurement

The concentrations of 11 inflammatory cytokines and their receptors (IL-1β, IL-2, IL-6, IL-6R, IL-8, IL-10, IL-12, TNFα, TNFβ, IFNγ, and GM-CSF) were measured at weeks 0, 22, and 54 by high-sensitivity electro-chemiluminescence assay using a SECTOR Imager 2400 (Meso Scale Discovery, Rockville, MD, USA) according to the manufacturer's instructions. The lower detection limits are shown in Table 2. Immunoglobulin Inhibiting Reagent (Bioreclamation, Westbury, NY, USA) was added to sera prior to this measurement in order to avoid interference from the patients' rheumatoid factors [16]. Antibody against cyclic citrullinated peptide (CCP) was measured by ELISA. Rheumatoid factor (RF) and matrix-metalloproteinase-3 (MMP-3) were measured by means of the latex agglutination test.

2.3. Evaluation of disease activity

Disease activity was assessed using the Disease Activity Score in 28 Joints based on the Erythrocyte Sedimentation Rate (DAS28-ESR). The cut-off values for DAS28-ESR were as follows: remission, less than 2.6; low disease activity (LDA), 2.6 or greater to less than 3.2; moderate disease activity (MDA), 3.2 or greater to 5.1 or less; high disease activity (HDA), greater than 5.1 [17]. Joint destruction was assessed based on changes in modified Sharp score [18], which is the average score of two independent readers.

2.4. Statistical analysis

The Kruskal–Wallis H-test and the chi square test were used to examine differences in baseline parameters and changes in disease activity between the ETN and IFX group. The Wilcoxon signed-rank test was used to examine changes in serum cytokine concentrations. We considered a P value < 0.05 to be significant (JMP 11, SAS Institute, Inc., Cary, NC, USA).

2.5. Study approval

This study was approved by the Institutional Review Board of Keio University School of Medicine and Saitama Medical Center, and conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all individuals.

3. Results

3.1. Patients' backgrounds and clinical responses

Patients' baseline characteristics are shown in Table 1. Because ETN-treated patients showed different clinical and radiological responses depending on whether they were simultaneously treated with methotrexate (MTX), we divided the ETN group into an ETN-only subgroup and an ETN + MTX subgroup. As all patients in the IFX group were simultaneously treated with MTX, this group is referred to as the IFX + MTX group. There were no significant differences in the baseline characteristics of the patient groups with the exception of MTX dose.

Fig. 1A shows disease activity at weeks 0, 22, and 54 in each group. The incidence of remission at week 54 was significantly lower in the ETN-only group than in the ETN + MTX group. There was no significant difference in disease activity between the ETN + MTX and IFX + MTX groups. Although one patient was categorized remission by DAS28-ESR in ETN + MTX group at week 0, partly due to low ESR, other indicaters, such as DAS28-CRP, showed residual disease activity, ETN was administered. Fig. 1B shows the cumulative probability scores of progression of the modified total Sharp score/year (ΔmTSS) in the three groups. Radiological remission was achieved in 40.0%, 64.3%, and 72.7% of patients in the ETN-only, ETN + MTX, and IFX + MTX groups, respectively.

3.2. Changes in serum cytokine concentrations after ETN and IFX treatment

Table 2 shows disease activity and serum cytokine concentrations at weeks 0, 22, and 54. At baseline, the only significant difference between the ETN + MTX group and the IFX + MTX group was that TNFα was significantly lower in the ETN + MTX group.

Table 1
Patients' baseline characteristics.

	ETN only $n = 10$	ETN + MTX $n = 14$	IFX + MTX $n = 44$
Age, years	64 (53–68)	56 (40–59)	61 (54–65)
Female, n (%)	7 (70)	11 (79)	34 (77)
Disease duration, months	150 (36–297)	56 (18–102)	75 (23–172)
RF positive, n (%)	8 (80)	12 (86)	34 (77)
ACPA positive, n (%)	9 (90)	14 (100)	38 (86)
MTX use, (%)	0	100	100
MTX dose*, mg/week	0 (0–0)	8 (6–8)	8 (8–8)
DAS28-ESR	5.2 (4.4–6.9)	5.4 (4.8–5.7)	5.3 (4.2–6.0)
CRP, mg/dl	2.9 (1.1–4.3)	1.9 (0.9–3.4)	1.1 (0.3–3.2)
ESR, mm/h	58 (40–77)	59 (27–63)	40 (23–63)
MMP-3, ng/ml	139 (75–347)	260 (99–364)	140 (83–263)
HAQ-DI	1.3 (1.0–1.8)	0.9 (0.5–1.3)	1.0 (0.4–1.8)

Values are medians and IQR. HAQ-DI, health assessment questionnaire-disability index.

* $P < 0.0001$ by Kruskal–Wallis test.

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